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EDITORIAL

Advancing Diabetes Equity through Health Policy Advocacy

Neelesh Kapoor[1*], Amit Gupta[2]

As per International Diabetes Federation estimates, the world diabetic population is expected to reach 643 million by 2030 and 783 million by 2045.[1] The global rise in diabetes cases has underscored the urgent need to address the inequities that persist in diabetes care. As per the World Health Organization, "health equity" has been defined as "the absence of unfair, avoidable, or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, geographically, or by other dimensions of inequality (e.g., sex, gender, ethnicity, disability, or sexual orientation)."[2]

The absence of avoidable and unjust differences in health outcomes remains a pivotal goal in improving the lives of people with diabetes. The fight for diabetes equity must confront supply-side barriers related to accessibility, availability, and affordability of healthcare services, which disproportionately affect marginalized groups. In this regard, health policy advocacy has emerged as a powerful tool for clinicians, patient groups, and civil society members to bridge these gaps and work toward equitable healthcare.[3]

Diabetes Inequity Crisis

Diabetes disparities span several demographic and socioeconomic dimensions, with rural populations, low-income groups, and ethnic minorities often bearing a disproportionate burden of the disease.[4] These groups face significant barriers to access, including inadequate availability of healthcare infrastructure, financial constraints, and a lack of culturally competent care. The consequences of these disparities are seen in unequal health outcomes, with marginalized populations often experiencing higher rates of complications and mortality.[5]

Role of Health Policy Advocacy

Health policy advocacy offers a pathway to address these systemic challenges by influencing decision-makers and shaping healthcare policies that reflect the needs of diverse populations. Advocacy promotes equitable access to diabetes management services, enhances the quality of care, and shapes national health priorities. Through direct lobbying, grassroots campaigns, and strategic use of media, advocates can push for policies that prioritize underserved populations and aim to rectify disparities in care delivery.[6]

Central to effective advocacy is the engagement of key stakeholders, including government bodies, healthcare professionals, nongovernmental organizations (NGOs), and the public. Governments play a critical role in enacting and enforcing policies that ensure equitable care, while healthcare professionals bring frontline insights and evidence to policy discussions. NGOs often serve as vital intermediaries, translating community needs into actionable policy proposals. Meanwhile, patients and the public contribute personal experiences that humanize policy debates and amplify the call for equity.

Achieving Health Equity in Diabetes Care

To achieve diabetes equity, advocacy efforts must address the "3 As": availability, accessibility, and affordability. Expanding health insurance coverage is crucial, particularly for low-income individuals, to ensure access to preventive care, screenings, and essential medications, especially insulin.[7] Furthermore, increasing funding for diabetes research will not only help develop new treatments but also provide targeted interventions to underserved populations. Policies that address social determinants of health—such as housing, food security, and education—are equally vital in creating an environment that supports comprehensive diabetes management.

Another critical aspect of health equity is promoting cultural competence among healthcare providers. By fostering a healthcare system that is responsive to the cultural and linguistic needs of diverse populations, we can ensure that care is not only accessible but also respectful and effective. Clinicians play a pivotal role in this process by using their clinical data to identify gaps in care, advocating for necessary policy changes, and sharing patient stories to humanize the advocacy effort.[8]

Overcoming Challenges in Advocacy

While the path to health equity is clear, advocacy efforts often face resistance from political interests, resource limitations, and miscommunication between stakeholders. Overcoming these challenges requires perseverance, collaboration, and a data-driven approach. Clinicians, with their access to real-world patient data, are uniquely positioned to highlight disparities in care and advocate for evidence-based solutions. Through collaboration with NGOs, mentorship of future advocates, and direct engagement with policymakers, healthcare professionals can lead the charge in creating sustainable, long-term improvements in diabetes care.[9,10]

Conclusion

The journey to achieving diabetes equity is a multifaceted one, requiring concerted efforts across policy, clinical practice, and community engagement. By prioritizing health equity, clinicians, policymakers, and advocates can work together to ensure that diabetes care is not only accessible but also equitable for all. The fight for diabetes equity is not just a medical or policy challenge—it is a moral imperative, as health equity is a fundamental human right.[11]

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OBITUARY

Padma Shree Dr Gurmukh Sajanmal Sainani

28.03.1931–03.12.2024

A Pillar of Strength Whose Legacy We Celebrate

In Memoriam

Prof Dr GS Sainani, Past President of the Association of Physicians of India, Past Dean Indian College of Physicians, former Editor of The Journal of the Association of Physicians of India and Editor-in-chief of API Textbook of Medicine.

The Association of Physicians of India and the medical community mourn the passing of Prof Dr GS Sainani, Past President of the Association of Physicians of India, Past Dean Indian College of Physicians, former Editor of The Journal of the Association of Physicians of India and Editor-in-chief of API Textbook of Medicine, who left for heavenly abode on 4th December 2024.

Dr GS Sainani was a towering figure in the field of medicine, known not only for his clinical acumen and scholarly contributions but also for his visionary leadership and dedication to the advancement of medical science.

During their tenure as President of the Association of Physicians of India in 1982, Prof Dr GS Sainani championed numerous initiatives aimed at fostering medical education, research, and collaboration among healthcare professionals. His efforts strengthened our association's foundations and extended its reach, leaving a legacy of growth and innovation.

As an Editor of the Journal of the Association of Physicians of India from 1982 to 1988, Prof Dr GS Sainani upheld the highest standards of editorial excellence, ensuring the dissemination of quality research that continues to inspire medical professionals worldwide even today.

Prof Dr GS Sainani's contributions to Medicine are unsurpassable. He worked tirelessly for the Association of Physicians of India for the last 4 decades in various capacities- President, API 1982, Dean ICP 1992, Hon. Editor JAPI from 1982 to 1988 and Editor-in-Chief of 5th and 6th editions of the prestigious API Textbook of Medicine. He started the Dr GS Sainani Oration in 2004 onwards. We remember as a dedicated leader a respected editor, and a compassionate physician whose work touched countless lives. His commitment to excellence and unwavering service to the profession will remain an enduring in inspiration to all of us. Beyond his professional accomplishments, he was a mentor, a role model, and a source of encouragement to colleagues and younger generations colleagues in medicine.

In recognition of his work, Prof GS Sainani received the prestigious "Padma Shri" – the fourth highest civilian award from the Government of India in 2000.

On behalf of the Association of Physicians of India and the editorial board of The Journal of the Association of India, we extend our deepest condolences to Prof Dr GS Sainani's family, friends, and all those who had the honor of working alongside them.

May his memory and legacy live on through the work he loved and nurtured.

Prof Dr Mangesh Tiwaskar
Editor-in-Chief, JAPI

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ORIGINAL ARTICLE

A Retrospective Analysis of Factors Influencing Maintenance Hemodialysis Adequacy: A Single-center Study in Eastern India

Dilip Pahari[1*], Abhishek Kumar[2]

Received: 24 June 2023; *Accepted:* 27 July 2023

Abstract

Objective: Quality of life in maintenance hemodialysis (MHD) patients is dependent on adequate hemodialysis. Kt/V, which gauges urea clearance, serves as the standard metric for assessing the effectiveness of MHD. According to the 2006 guidelines from the NKF-KDOQI, a spKt/V exceeding 1.2 or a urea reduction ratio (URR) of 65% is advised for maintenance hemodialysis conducted three times weekly. This study was aimed at determining the adequate hemodialysis sessions and their associated factors for patients undergoing maintenance hemodialysis sessions at our center.

Materials and methods: The study was conducted over a 1-year period at Medica Hospital in Kolkata, focusing on patients receiving maintenance hemodialysis three times per week. Kt/V levels were assessed using the Online Clearance Monitoring (OCM) technique.

Results: The study included 251 participants, consisting of 170 (67.72%) men and 81 (32.28%) women, with a mean age of 59.09 ± 13.00 years. Diabetes was the most frequently observed underlying condition, affecting 138 patients (55.4%), while fistula was the predominant type of vascular access, utilized in 198 patients (79%). Hemodialysis adequacy was achieved in 81.08% of MHD sessions. Patients on high-flux dialyzers achieved a higher average Kt/V compared to patients on low-flux dialyzers. Dialyzer clotting was associated with a decline in Kt/V. The study found that MHD adequacy was inversely related to both age and predialysis systolic blood pressure, while it showed a direct correlation with the duration of hemodialysis. Additionally, females attained higher Kt/V values compared to males. Logistic regression analysis identified male gender and blood flow as independent determinants of hemodialysis adequacy.

Conclusion: MHD adequacy is determined by a combination of factors rather than a single variable. Our findings indicate that achieving MHD adequacy requires a combination of sufficient treatment duration, appropriate rate of blood flow, effective anticoagulation for prevention of clotting, stable blood pressure management, and the use of hemodialyzers with a surface area exceeding 1.2 m^2.

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Introduction

The quality of life with end-stage kidney disease on maintenance hemodialysis depends upon consistent and efficient removal of uremic toxins. These toxins include a variety of small and medium-sized molecules, but the evaluation of removal efficiency during hemodialysis predominantly focuses on urea measurements. Kt/V, a widely adopted measure of hemodialysis adequacy based on urea clearance, was developed by Gotch and Sargent using *post hoc* analysis of NCDS data.[1] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) 2006 recommends a spKt/V greater than 1.2 or a urea reduction ratio (URR) of 65% for maintenance hemodialysis per session with a three-times-per-week regimen. These figures represent the minimum requirements rather than target goals, which are set at 1.4 for spKt/V and 70% for URR.[2–5] Several elements can impact the Kt/V-determined dialysis dose, such as the rate of blood flow, dialysate circulation, interruptions during treatment (e.g., low blood pressure or clotting), the effectiveness of vascular access (including issues like stenosis or recirculation), as well as the needle dimensions, insertion technique, and specific dialyzer features.[5] Numerous studies have indicated that inadequate hemodialysis dosage over multiple sessions is associated with higher mortality rates, particularly among females.[6–11]

There have been no previous studies assessing the adequacy of hemodialysis in Eastern India. This study focused on analyzing hemodialysis adequacy and the factors influencing it among patients receiving chronic treatment at Medica Hospital in Kolkata.

The results of this study will offer valuable feedback to dialysis centers across India, aiding in the enhancement of dialysis services nationwide. Additionally, this study aims to raise awareness among dialysis centers that are not currently assessing hemodialysis adequacy for their patients.

Materials and Methods

This year-long longitudinal study took place at Medica Hospital in Kolkata, with data collection spanning from 1st May 2021 to 30th April 2022. Our subject population consisted of all consenting adults aged 18 and older who were undergoing chronic hemodialysis and had completed a minimum of 72 maintenance hemodialysis sessions at Medica Hospital. The observation phase commenced following an initial 12-week dialysis period at our center. We examined the flow sheets of each treatment to assess hemodialysis adequacy.

Kt/V was assessed using online clearance monitoring (OCM). The analysis of dialysate UV absorption curves over time shows the effect on blood, and the early and late UV absorption ratio shows the pre- and postdialysis BUN. From UV analysis of the spent dialysate, the Kt of a treatment can be computed in real time. The dialysis machine estimated total body water, assumed to be equivalent to the urea distribution volume, using Watson et al.'s[12] empirical formula, for both men and women.

Statistical Analysis

Measures of central tendency were represented by the mean and standard deviation. The relationship between dialysis dose and various predictor variables was examined using univariate analysis through *t*-tests or analysis of variance (ANOVA). With 251 observations, the sample size was finite. Statistical Package for the Social Sciences (SPSS) 26 software was employed for data analysis, and multivariate binary logistic regression was conducted to identify independent predictors of Kt/V.

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Results

The study included 251 participants, consisting of 170 (67.72%) men and 81 (32.28%) women, with a mean age of 59.09 ± 13.00 years. Diabetes was the most prevalent underlying condition, affecting 138 patients (55.4%), while fistula was the most commonly used type of vascular access, seen in 198 patients (79%). A total of 28,775 hemodialysis sessions were analyzed over the course of one year, with the adequacy results presented in Table 1.

Pearson's correlation analysis indicated an inverse association between hemodialysis adequacy and both age (R = –0.19, p = 0.002505) and predialysis systolic blood pressure (p = 0.02), while a direct correlation was observed with the duration of hemodialysis in months (p = 0.02). A t-test comparing hemodialysis adequacy between genders revealed a significant difference (t-value = –9.48199, p < 0.00001), with females achieving a mean Kt/V of 1.55 compared to 1.35 for males.

We compared the mean blood flow of hemodialysis sessions with spKt/V >1.2 with hemodialysis sessions with spKt/V <1.2 and found a statistically significant difference in the mean blood flow between inadequate and adequate hemodialysis sessions, as shown in Table 2.

We reviewed each hemodialysis session flow sheet to ascertain the presence or absence of potential barriers to hemodialysis. The lowest systolic blood pressure was noted in each session, and sessions were classified into various groups based on the lowest systolic blood pressure during the session. The mean Kt/V was derived, as shown in Table 3.

Analysis of variance testing revealed a statistically significant difference in mean Kt/V across groups categorized by the lowest systolic blood pressure during hemodialysis sessions, as detailed in Table 2 (p-value: 0.00). Sessions with lower mean systolic blood pressure exhibited a comparatively higher mean Kt/V than those with higher mean systolic pressure. Additionally, the mean Kt/V was greater for patients using high-flux dialyzers compared to those using low-flux dialyzers, as demonstrated in Table 4.

Patients using low-flux dialyzers were further analyzed based on the effective surface area of the dialyzer, as detailed in Table 5, while those using high-flux dialyzers were similarly assessed, as shown in Table 6. Each hemodialysis session was evaluated for dialyzer clotting, which was linked to a reduction in Kt/V, as depicted in Table 7. No significant correlation was observed between the direction of the arteriovenous needle (for fistula cases) or the shift timing of the hemodialysis personnel and the adequacy of hemodialysis (p = 0.70). A multivariate binomial logistic regression was conducted to identify determinants of Kt/V, categorizing mean Kt/V values above 1.2 as adequate and below 1.2 as inadequate, as shown in Table 8. The analysis identified blood flow and male gender as independent factors affecting hemodialysis adequacy among patients undergoing chronic hemodialysis at Medica Super Specialty Hospital, Kolkata.

Table 1: Adequacy of hemodialysis (the mean Kt/V was 1.40 ± 0.16)

Sessions with spKT/V >1.2	*Sessions with spKT/V <1.2*
23,329 sessions (81.08%)	5,446 sessions (18.92%)
Patients with mean KT/V >1.2	Patients with mean KT/V <1.2
226 (90.03%)	25 (9.96%)

Table 2: Comparison between mean blood flow in the two groups

Mean blood flow ± SD (mL/minute) (n = 23,329) HD session with spKT/V >1.2	*Mean blood flow ± SD (mL/minute) (n = 5,446) HD session with spKT/V <1.2*	*t-test p-value*
340 ± 60	280 ± 48	0.0001

Table 3: Stratification based on lowest SBP

Lowest SBP in HD session	*Number of HD session*	*Mean ± SD (KT/V)*
<90 mm Hg	4,200	1.42 ± 0.24
90–110 mm Hg	4,175	1.36 ± 0.22
110–130 mm Hg	8,900	1.34 ± 0.36
>130 mm Hg	1,1500	1.38 ± 0.34

Table 4: Comparison between high and low flux dialyzer

Mean KT/V ± SD Low flux dialyzer	*Mean KT/V ± SD High flux dialyzer*	*Student's t-test p-value*
1.39 ± 0.16	1.47 ± 0.19	0.001

Table 5: Comparison based on effective surface area of low flux dialyzer

Mean KT/V ± SD Low flux dialyzer with 1.3–1.4 m^2 surface area	*Mean KT/V ± SD Low flux dialyzer with 1.7–1.8 m^2 surface area*	*Student's t-test p-value*
1.38 ± 0.16 (n = 131)	1.42 ± 0.18 (n = 35)	0.20

Table 6: Comparison based on effective surface area of high flux dialyzer

Mean KT/V ± SD High flux dialyzer with 1.3–1.4 m^2 surface area	*Mean KT/V ± SD High flux dialyzer with 1.7–1.8 m^2 surface area*	*Student t-test p-value*
1.46 ± 0.20 (n = 47)	1.48 ± 0.18 (n = 38)	0.63

Table 7: Dialyzer clotting and KT/V

Dialyser	*Number of HD session*	*Mean ± SD(KT/V)*	*Student's t-test*
Clotting noted in HD session	290	1.08 ± 0.28	p-value = 0.0001
No evidence of clotting	28,485	1.34 ± 0.36	

Table 8: Multivariate binomial logistic regression analysis

Predictor	*Odds ratio*	*CI (5–95%)*	*p-value*
Bloodflow (mL/minute)	1.027	1.010–1.044	**0.002**
Number of HD session	0.995	0.981–1.009	0.475
Male gender	13.940	1.806–107.618	**0.012**
Age	1.011	0.977–1.046	0.525
Dialyzer type	1.27	0.463–3.491	0.641

Bold values indicate statistical significance at p-value <0.05

Discussion

Despite its known limitations of inability to assess adequacy of hemodialysis in terms of fluid removal and middle molecule clearance, single pool Kt/V remains an index for assessment of small molecule clearance and an effective measure of adequacy of hemodialysis.[13] Our study, a year-long longitudinal analysis, examined the prevalence of inadequate dialysis and its related factors. The average Kt/V in this study was 1.42 ± 0.18. About 10% of patients had a mean Kt/V below 1.2, compared to rates ranging from 5 to 17% in countries like Canada, Europe, Japan, and the United States.[14] One of the significant predictors associated with the adequacy of hemodialysis is treatment time.[15] In our center, a uniform treatment time of 240 minutes (4

hours) was given, and we achieved adequacy in 81.08% of the studied hemodialysis sessions, comparable to the adequacy achieved in developed countries. Men were more prone to experiencing inadequate hemodialysis compared to women. This finding aligns with previous studies, which reported that men were three times more likely to have inadequate hemodialysis than women.[16] The study also reported that patients using low-flux hemodialyzers with a surface area under 1.4 m^2 received a significantly lower dialysis dose compared to those using high-flux dialyzers with a surface area of 1.4 m^2 or larger. These findings are consistent with earlier studies by Stivelman et al.[17] and Pascual et al.,[18] which reported similar results regarding membrane size and clearance rates. A study conducted in Bangladesh reported similar results, indicating that increasing the dialyzer membrane surface area from 1.2 to 1.3 m^2 enhanced hemodialysis adequacy by 19.7%, as measured by Kt/V criteria.[19] Interestingly, lower blood pressure was linked to a higher dialysis dose rather than a lower one. This outcome aligns with the findings of Panagoutsos et al.,[20,21] who observed that reduced blood pressure correlates with increased dialysis dosage. However, McGregor et al.[22] found no significant relationship between dialysis dose (Kt/V) and blood pressure.

The logistic regression analysis showed blood flow and gender as independent factors associated with hemodialysis adequacy. This aligns with past studies that reported blood flow as a predictor of adequacy of hemodialysis.[23–26] Conversely, our findings differed from those of Ghali and Malik,[27] who reported that increasing blood flow rate (BFR) had no significant impact on hemodialysis adequacy.

In conclusion, adequacy is not dependent on one variable alone, but rather it is a function of different factors. Our study examined various predictor variables associated with hemodialysis. Our study demonstrated that achieving maintenance hemodialysis adequacy depends on factors such as optimal treatment duration, sufficient blood flow rate, proper anticoagulation to prevent dialyzer clotting, effective blood pressure management, and the use of hemodialyzers with a surface area greater than 1.2 m^2. The study's strengths included the evaluation of multiple factors related to hemodialysis adequacy. However, it had some limitations, being a single-center study, and did not account for confounding variables like albumin levels, inflammatory markers (CRP and ferritin), residual kidney function, and other comorbidities unrelated to CKD.

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ORIGINAL ARTICLE

A Clinical Study to Evaluate the Anti-inflammatory Effect of Lactoferrin + Disodium Guanosine Monophosphate Therapy in the Patients with Chronic Kidney Disease

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Abstract

Introduction: India is impacted by the increasing burden of chronic kidney disease (CKD) and end-stage renal disease (ESRD), necessitating efficient management and therapy. CKD is characterized by elevated levels of inflammatory biomarkers, specifically IL-1β, IL-1RA, IL-6, TNF-α, TGF-β, and fibrinogen. The aim of this research is to determine the antiinflammatory effects of lactoferrin + disodium guanosine monophosphate therapy in CKD patients. The objective of this study is to examine the efficacy of this therapy versus conservative CKD management alone in reducing inflammation. This study intends to examine the possible benefits of study drug in treating inflammation associated with CKD by analyzing its effect on inflammatory markers including IL-6 and TNF-α.

Methods: This randomized, open-label, parallel group, two-arm clinical study, comprising of 40 patients with CKD, with 20 patients in each group. The groups were well-matched in terms of demographic characteristics. Conception, screening, randomization, and follow-up visits including physical examinations, laboratory investigations, and medication dispensation were all carried out over a 29-week period. Creatinine clearance, estimated glomerular filtration rate (eGFR), estimated urine urea nitrogen, and inflammatory markers (IL-6, IL-10, TNF-α, CRP) were analyzed at time of screening and at 3 and 6-month postrandomization.

Results: The study found a significant decrease in inflammatory markers, including TNF-α, IL-6, and IL-10, in the group receiving study drug, indicating its potential as an antiinflammatory intervention for managing CKD. Secondary endpoints, including hemoglobin (Hb) and e-GFR levels, showed nonsignificant improvements in the study group compared to the control group. No significant adverse events were reported during the study.

Conclusion: The study highlights the potential antiinflammatory effects of the lactoferrin + disodium guanosine monophosphate therapy in individuals with CKD. The findings suggest that study drug may be a viable intervention for managing inflammation in CKD patients. Further research is needed to validate these results and explore its long-term effects in CKD management.

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Introduction

Chronic kidney disease (CKD) is a slowly progressive condition that impacts over 10% of the global population, which is equivalent to >800 million people.[1] The global public health challenge of kidney failure is marked by rising incidence and prevalence rates, substantial costs, and unfavorable outcomes.[2] CKD has been identified as a noteworthy public health issue owing to its healthcare and economic implications, particularly in countries with substantial populations like India. Additionally, >1,00,000 new patients are enrolled in renal replacement programs each year.

Chronic kidney disease is defined as the presence of damage to the kidneys or a sustained reduction in the glomerular filtration rate (GFR) to <60 mL/minute/1.73 m^2 for at least 3 months.[3] The progressive decline in GFR occurs as a result of irreversible sclerosis of nephrons, which happens when the functional renal mass is reduced to a certain threshold due to the loss of nephrons.[4] The staging of CKD is determined by the degree of impairment in kidney function, which spans from stage I (kidney damage with normal or elevated GFR) to stage V (kidney failure with GFR <15 mL/minute/1.73 m^2 or dialysis).

Inflammation and CKD exhibit a strong association with heightened cardiovascular morbidity and mortality. Studies have indicated that individuals diagnosed with CKD exhibit elevated concentrations of inflammatory markers, including C-reactive protein (CRP), which is associated with an augmented likelihood of cardiovascular complications.[5] Elevated levels of inflammatory biomarkers, specifically IL-1β, IL-1RA, IL-6, TNF-α, TGF-β, and fibrinogen, were observed in individuals with CKD who exhibited reduced renal function.[6] The concentrations of coagulation factors, including fibrinogen and factor VIII, also exhibit an upward trend as CKD advances. These data emphasize the complicated link between inflammation, coagulation variables, and cardiovascular risk in CKD patients.[7]

The management of CKD involves a multidisciplinary approach focusing on slowing the progression of the disease, controlling associated risk factors, and addressing complications. The implementation of conservative management strategies is a common approach that involves making lifestyle modifications, such as adhering to a specific diet, engaging in regular physical activity, and managing body weight. Additionally, effective control of underlying conditions like diabetes and hypertension is crucial in preventing further kidney damage.

Lactoferrin has been found to exhibit antibacterial, antiviral, antioxidant, and antiinflammatory properties.[8] Prior studies have demonstrated that lactoferrin (LF), a protein that binds to iron and is present in neutrophils and bodily fluids, exhibits protective characteristics against oxidative stress caused by excessive release of cytokines, specifically IL-6 and TNF-α. These cytokines have been linked to significant tissue necrosis. The role of lactoferrin in the maturation and regulation of immune system function, as well as its capacity to sequester free iron, enhances its acknowledged defensive capabilities.[9] Having strong antiinflammatory properties makes it a suitable candidate to test in

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inflammatory milieu of CKD. In literature, there is some evidence of role of lactoferrin in both aseptic and septic inflammation.[10] It also plays a crucial role in balancing ups and downs of inflammation due to microbial infections in gut and respiratory tract.[11] However, its role in inflammation of CKD is less well studied. The primary aim of this study was to explore the possible antiinflammatory properties of lactoferrin and guanosine monophosphate (GMP) in the setting of CKD.

The objective of this study was to evaluate the antiinflammatory impact of lactoferrin and GMP plus conservative therapy in comparison to conservative therapy alone in patients with CKD. The investigations consisted of a series of physical examinations, assessments of vital signs, electrocardiogram (ECG), laboratory testing including Hb, ESR, e-GFR, and inflammatory markers, and the administration of study medication. Alterations in inflammatory markers (IL6, IL10, TNF-α, CRP), and improvements in Hb and estimated GFR (eGFR) were the primary and secondary objectives, respectively.

Methods

Study Design

This study used an open-label, randomized, parallel-group design, consisting of two treatment arms. In study arm, lactoferrin and GMP were used in conjunction with conservative CKD management, as compared to conservative CKD management alone in control arm. A cohort of 40 individuals diagnosed with CKD were recruited and allocated randomly in a 1:1 ratio (20 patients in test group and 20 in control group, respectively).

Inclusion criteria: All CKD (defined as having reduced eGFR <60 mL/minute or albuminuria >300 mg/day for >3 months) patients above age of 18 years were included in study.

Exclusion criteria: Those having any signs of active infection (signs of systemic inflammatory response syndrome) or having systemic inflammatory disease were excluded from study.

Randomization Procedure

The randomization schedule was generated using SAS® statistical software to ensure the treatment's integrity.

Formulation Details

In the test group, patients were administered combination of lactoferrin at a dosage of 100 mg and GMP at a dosage of 10 mg. In the control group, patients with CKD were exclusively administered conservative CKD management therapy. Both groups received the conventional medication as per current standard of care.

Study Visit Schedule

The study consisted of the following visits:

- Visit 1: screening visit (up to 4 weeks before randomization).
- Visit 2: randomization/baseline visit (day 1).
- Visit 3: week 12 (±4 days).
- Visit 4: week 24 (±7 days)/end of the treatment.

Safety follow-up: 1 week (±2 days) after the end of treatment (telephonically).

Study Investigations

Several evaluations were conducted during the study visits, including a comprehensive physical examination, documentation of vital signs, and laboratory analyses. The primary laboratory analyses consisted of measuring creatinine clearance, calculating e-GFR from creatinine-based equation (CKD-EPI equation), measuring urinary urea nitrogen levels through a 24-hour urine collection, and measuring inflammatory markers such as IL-6, IL-10, TNF-α, and CRP.

Endpoints

The primary endpoints of the study involved evaluating the alterations in inflammatory markers, specifically IL-6, IL-10, TNF-α, and CRP. Secondary endpoints included the assessment of improvements in Hb levels and the e-GFR.

Safety Analysis

A safety assessment was conducted on the patients who received a minimum of one dose of the experimental drug. Adverse events were documented, classified, and examined in accordance with their severity, frequency, and their association with the experimental drug. The analysis also encompassed the examination of clinical significance in safety laboratory measures before and after treatment.

Efficacy Analysis

The efficacy analysis consisted of the evaluation of various parameters, such as the estimation of creatinine clearance, e-GFR, urinary urea nitrogen estimation, and the measurement of inflammatory markers (IL-6, IL-10, TNF-α, CRP). These assessments were conducted to assess the potential antiinflammatory effect of study drug.

Statistical Methods

SAS® version 9.4 was used for the statistical analysis. All tests were subjected to statistical analysis at a significance level of 5% (p-value <0.05). Descriptive statistics were used to examine the data, and appropriate statistical tests were performed to establish statistical significance. Appropriate graphical displays for different types of data were generated for analysis data set. Analysis populations were categorized as safety population, modified intent-to-treat (mITT), and per-protocol population (PP). The PP population was used for efficacy analysis while safety analysis was based on safety population only. Adverse event incidences were summarized using the MedDRA dictionary by treatment group, body system, severity, frequency, and relationship to study treatment.

Results

Descriptive statistics were employed to compile the demographic and baseline characteristics of the subject, including age, height, weight, and gender as shown in Table1. In terms of age, body mass index, and other demographic factors, there were

Table 1: Descriptive analysis of demographic data

Statistics	*Test group (N = 20)*	*Control group (N = 20)*	*Overall (N = 40)*
Age (years)			
Mean (SD)	45.45 (13.14)	46.60 (10.93)	46.03 (11.94)
Min, max	18, 65	31, 68	18, 68
Height (cm)			
Mean (SD)	166.99 (7.82)	167.80 (7.78)	167.40 (7.71)
Min, max	150, 178	152, 183	150, 183
Weight (kg)			
Mean (SD)	69.04 (9.19)	68.12 (14.10)	68.58 (11.75)
Min, max	54, 83.7	46.5, 107	46.5, 107
Race *n* (%)			
Asian	20 (100.0)	20 (100.0)	40 (100.00)
Ethnicity *n* (%)			
Not Hispanic or Latino	20 (100.0)	20 (100.0)	40 (100.00)

no significant differences between the two groups. Out of the total recruited patients, 20 individuals were assigned to test group, consisting of 16 males and 4 females, while 20 individuals were allocated to control group, comprising 17 males and 3 females. All patients were of Asian background. The participant's average age was 46.03 years, with test group exhibiting a slightly lower average age of 45.45 years compared to the average age of 46.60 years observed in control group. The average weight was 68.58 kg, with test group averaging 69.04 kg and control group averaging 68.12 kg.

Regarding the medical and surgical history, all patients had CKD as an inclusion criterion. Furthermore, they presented with various comorbidities, including diabetes mellitus, hypertension, hypothyroidism, cerebrovascular disease dilated cardiomyopathy and systemic lupus erythematosus (SLE). Detailed information regarding the medical and surgical history is shown in Figure 1.

Baseline Investigations

Urine pregnancy tests were conducted in female participants and all yielded negative results for pregnancy. Subsequent to screening and randomization physical examination was carried out during visit 3 and visit 4, detecting no clinically significant abnormalities. However, standard 12-lead ECG evaluations at screening during visit 3 and end of the study visit showed normal or nonclinically significant abnormal results, with no significant differences between the groups. Similarly, vital signs, including pulse rate, respiratory rate, and body temperature, recorded at screening, randomization, visit 3 and visit 4 remained within the normal range for both test group and control group throughout the study period. Although there were slight abnormalities in systolic and diastolic blood pressure readings, these deviations were not clinically significant in either group. Overall, the study patients exhibited stable vital signs and no concerning findings in the physical examinations or ECG evaluations.

Primary Endpoint

Assessments were carried out at the screening and randomization visits, as well as visits 3 and 4, for both test group and control group. The findings of the study suggest a significant reduction in inflammatory markers within the test group from the start to the end of the research ($p < 0.05$). The study observed a significant decrease in TNF-α, IL-6, and IL-10 levels in test group (Fig. 2) compared to control group. The reduction in these cytokine levels was approximately twice as much in test group as in control group. The findings indicate that lactoferrin and GMP administration may result in a significant reduction of inflammatory markers in patients with CKD.

Secondary Endpoints

During the screening visits 3 and 4 (end of the study visit), Hb and serum creatinine were measured and eGFR calculated from serum creatinine. The findings revealed that patients in test group exhibited a statistically nonsignificant increase in mean Hb level and mean eGFR ($p > 0.05$) (Fig. 3), while patients in control group showed a reduction in mean Hb levels and mean eGFR.

Adverse Events

In total, 35 treatment-emergent adverse events (AEs) were reported during the study, with 17 events reported in test group and 18 events reported in control group. All events were of mild severity. All treatment-emergent adverse events (TEAEs) were deemed to have probable or likely causality with the treatment administered and were resolved without any interruption in the study treatment. It is highly improbable that AEs and investigational medicinal products

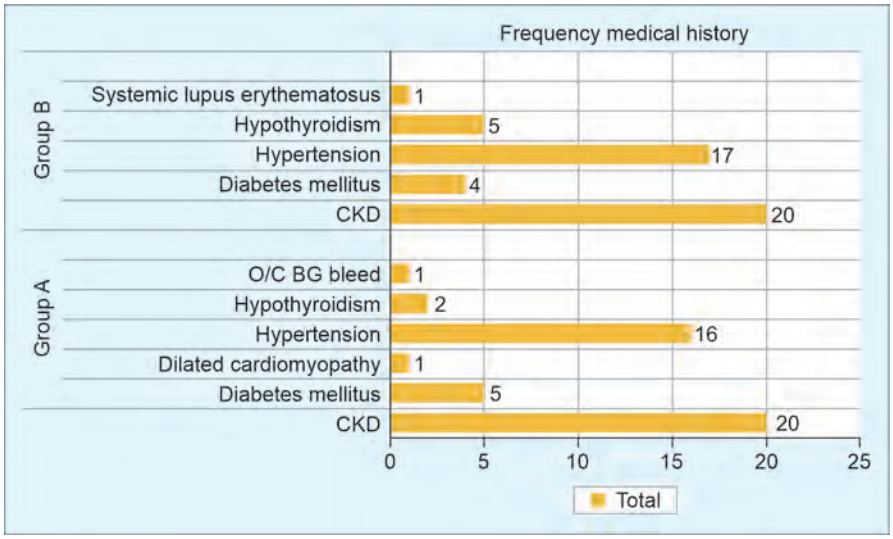

Fig. 1: Medical history representation in both groups

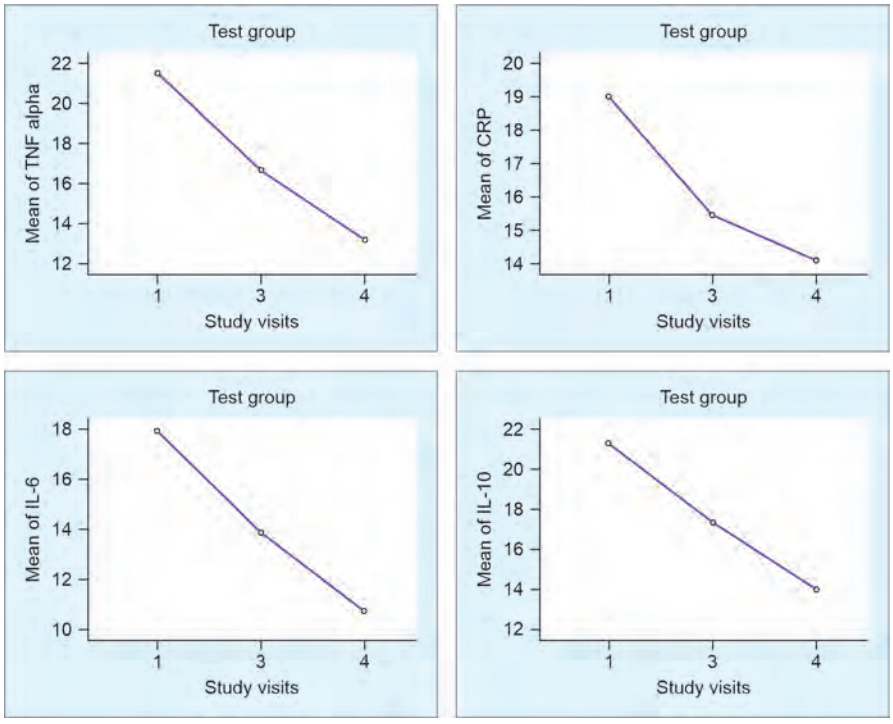

Fig. 2: Change in inflammatory markers in test group

(IMP) are causally related to one another. All observed negative occurrences were classified as treatment-emergent AEs and exhibited a probable causal relationship with the standard treatment for CKD. There was no correlation between the unfavorable incidents and the investigational substance used in the study (Table 2). No significant AEs were reported during the course of the study.

Discussion and Conclusion

Chronic kidney disease is a widespread health concern on a global scale, with an estimated prevalence of around 10% of the world's population.[1] The prevalent main etiologies of CKD comprise diabetes, hypertension, and glomerulonephritis.[1] Despite the high burden of CKD, there are limited options available for slowing down the progression of the disease. Current treatments primarily focus on managing underlying causes and symptoms, such as blood pressure control, dietary modifications, and medications like angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs).

Chronic kidney disease is marked by inflammation, which worsens health outcomes. Inflammatory markers like IL6, IL10, TNF-α, and CRP indicate CKD progression and cardiovascular risk. Studies have demonstrated significant involvement of inflammation and oxidative stress in the advancement of CKD.[12] Chronic inflammation is a common occurrence among patients with CKD, and its intensity tends to increase with the progression of renal dysfunction.[13,14] While inflammation serves as a defense mechanism against infections, unregulated inflammation can lead to deleterious effects, including excessive cytokine production and an increase in proinflammatory mediators. Therefore, the treatment of inflammation is of paramount importance in managing the uremic syndrome associated with CKD.[13]

Interestingly, although the management of CKD typically involves assessing parameters like Hb, eGFR, creatinine clearance, and urinary urea nitrogen, the evaluation of inflammatory markers is often overlooked. This study aimed to address this gap and evaluate the antiinflammatory effect of lactoferrin and GMP in CKD patients who were already receiving conservative management therapy.

The primary endpoint of this study was the change in inflammatory markers, including IL-6, IL-10, TNF-α, and CRP. The results demonstrated a statistically significant reduction in these inflammatory markers from baseline to the end of the study in test group compared to control group. One group also had a patient with SLE, which is itself a systemic inflammatory condition; however, this patient was in complete remission during inclusion in study period.

In addition, the study investigated secondary outcomes, including monitoring of Hb levels and estimated eGFR. Importantly, no clinically relevant findings were observed in either group regarding Hb levels and eGFR. Test group showed a nonsignificant increase in mean Hb levels and mean eGFR, the control group demonstrated a decrease in the mean values of both eGFR and Hb levels, although these differences were not statistically significant ($p > 0.05$). In this study, we did not measure baseline serum iron and ferritin levels. Serum ferritin is both inflammatory marker as well as measure of iron stores, no meaningful conclusion could have been drawn from effect of ferritin level on change in hemoglobin level in setting of inflammation.

Additionally, the study examined other aspects such as demographic details, medical and surgical history, vital signs, physical examination, urine pregnancy tests, ECG evaluation, creatinine clearance, urinary urea nitrogen estimation, and AEs. These evaluations provided comprehensive insights into the patients' characteristics, safety, and overall well-being throughout the study. Notably, the study reported a low number of TEAEs in both test group and control group, with all TEAEs being mild and resolved without any interruption in study treatment.

Overall, the findings of this study highlight the potential benefits of lactoferrin and GMP in reducing inflammation and their safety profile in CKD patients. The significant reduction in inflammatory markers observed in the test group suggests that lactoferrin and GMP hold promise as a novel therapeutic approach for managing inflammation in CKD. Despite observing enhancements in Hb levels and estimated eGFR, these changes did not attain statistical significance.

The study's findings regarding the potential effects of lactoferrin and GMP on inflammation reduction and their demonstrated safety profile have substantial

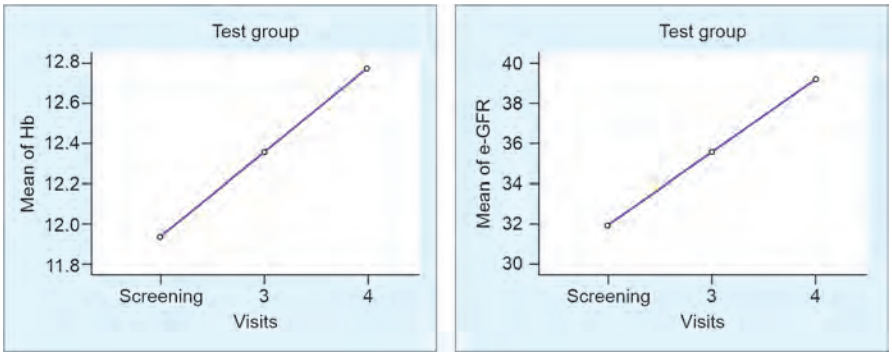

Fig. 3: Mean change in lab parameters (Hb and eGFR) over test group

Table 2: Organ system-based categorization of TEAEs based on severity and association with study drug and a summary of TEAEs

Categorization of TEAEs over the parameter of severity and relatedness with study drug			
	Test group (N = 20) n (%)	*Control group (N = 20) n (%)*	*Overall (N = 40) n (%)*
All TEAEs	17 (85.0)	18 (90.0)	35 (87.5)
TEAE related to study drug			
Probable/likely	17 (85.0)	18 (90.0)	35 (87.5)
Severity of TEAEs			
Mild	17 (85.0)	18 (90.0)	35 (87.5)
Summary of treatment emergent AEs			
AEs			
Cough	3 (15.0)	4 (20.0)	7 (17.5)
Fever	2 (10.0)	4 (20.0)	6 (15.0)
Headache	2 (10.0)	4 (20.0)	6 (15.0)
Itching	3 (15.0)	2 (10.0)	5 (12.5)
Sore throat	7 (35.0)	4 (20.0)	11 (27.5)

implications for the management of CKD. A study conducted on a larger population sample and spanning a longer duration would yield more comprehensive data on the long-term effects and advantages of the subject drug. This would not only serve to validate the observed enhancements in Hb levels and eGFR, but also provide insight into whether these alterations result in significant clinical outcomes and enhanced patient welfare. Major limitation of our study appears to be small sample size. Secondly, we did not measure serum iron and ferritin levels, later being an acute phase reactant may have implications in interpreting study results.

The findings of this study would not only contribute to our comprehension of its therapeutic capacity in CKD, but also furnish healthcare practitioners and researchers with significant inputs for making well-informed choices regarding its application in clinical settings. In order to advance patient care and enhance the quality of life for individuals with CKD, it is imperative to conduct a comprehensive and rigorous study on the effectiveness and safety of lactoferrin and GMP in managing this condition.

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ORIGINAL ARTICLE

An Observational Study of the Incidence and Risk Factors of Multivessel Coronary Artery Disease in Patients with Acute Coronary Syndrome Presenting at a Tertiary Care Hospital India

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Abstract

Objectives: To study the clinical and demographic characteristics of the patients with symptomatic acute coronary syndrome (ACS). To determine the outcomes in terms of single-vessel disease (SVD), double-vessel disease (DVD), and triple-vessel disease (TVD) among the patients. To determine the risk factors of TVD.

Methods: A prospective observational study was conducted on 111 patients with ACS. Demographic and clinical profiles of the patients were noted. Patients with unstable angina (UA) and asymptomatic patients were excluded from the study. Outcomes were noted in terms of the involvement of the number of coronary vessels and the risk factors of TVD.

Results: The mean age of the patients was 55.7 ± 13.7 years, with 75.68% males and 24.32% females. Chest pain was the most common symptom in 69 (62.16%) cases. SVD, DVD, and TVD were seen in 64 (42.30%), 17 (23.40%), and 30 (34.20%) patients, with the most common vessel involved being the left anterior descending (LAD) artery. Fatigue was predominantly found in SVD, chest pain was predominantly found in DVD, and shortness of breath was the most common symptom in TVD, with a *p*-value of 0.049. Univariate logistic regression showed that none of the factors among age, gender, comorbidities, and family history were significant independent risk factors for TVD.

Conclusion: It can be concluded that ACS patients are predominantly elderly males with comorbidities like diabetes, hypertension, a family history of heart disease, and dyslipidemia. The LAD was the most commonly involved coronary artery in ACS. The occurrence of SVD surpassed DVD and TVD among ACS patients. None of the risk factors was significantly associated with TVD independently.

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Introduction

Coronary artery disease (CAD) stands as the primary cause of mortality and morbidity globally, with acute coronary syndrome (ACS), comprising ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA), representing the leading causes of death in CAD patients.[1] NSTE-ACS accounts for about two-thirds of ACS cases, with the remainder being STEMI.[2]

The clinical symptoms of ACS include pain radiating to the neck, jaw, shoulders, back, or one or both arms. The pain may also be characterized as indigestion or heartburn, accompanied by nausea and/or vomiting. Additional symptoms may include shortness of breath, weakness, dizziness, lightheadedness, or even loss of consciousness.[3]

The diagnosis of ACS depends on a combination of clinical presentation, electrocardiogram (ECG) findings, and biochemical markers indicating myocardial injury. The initial crucial step in evaluating a patient with suspected ACS is determining whether there are diagnostic ST-segment elevations on the 12-lead ECG. The diagnosis of NSTE-ACS has advanced notably with the introduction of high-sensitivity troponin (hsTn) assays. Additional diagnostic tools like echocardiography or cardiac MRI aid in identifying regional wall motion abnormalities (RWMA) and other signs of myocardial ischemia in patients suspected of having ACS.[4,5]

The introduction of a wide array of invasive and noninvasive therapeutic approaches has notably decreased ACS-related mortality in developed nations over the last 2 decades. However, mortality rates among Indians continue to remain high despite these advancements,[6] with in-hospital mortality rates among STEMI patients reported as 8.9%, and in NSTE-ACS patients as 4.5% in a study conducted in North India.[7]

Patients who have multivessel coronary artery disease (MVD), characterized by ≥50% narrowing in two or more major epicardial vessels, experience a poorer prognosis among those presenting with ACS, in contrast to individuals with only one-vessel disease.[8] Thus, it remains essential to determine the incidence and clinical findings in relation to triple-vessel disease (TVD) in comparison to single-vessel disease (SVD) or double-vessel disease (DVD). Not many studies have been conducted in this regard.[9–12]

Thus, we conducted this study to determine the incidence of TVD, its association with clinical characteristics of the patients, and the risk factors of TVD.

Methods

The present prospective observational study was done at a tertiary care center in the department of general medicine over a period of 18 months from July 2022 until December 2023. Institutional Ethical clearance was obtained for the study (01/29/JUN/CHWC/2022, dated 29 June 2022).

Inclusion Criteria

All patients attending OPD or IPD, irrespective of their age and sex, presenting with clinical

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features of ACS, which included typical ECG changes suggestive of ACS and elevated cardiac biomarkers.

Exclusion Criteria

Patients not willing to participate and those with UA and asymptomatic conditions were excluded.

Sample Size

According to a systematic review conducted by Rao et al.,[13] the prevalence of CAD was found to be 2.5–12.6% in urban regions and 1.4–4.6% in rural areas. Based on this, using the formula $N = Za^2pq/d^2$, the minimum sample size needed was 111.

After taking a written informed consent from the patients, the study patients were enrolled. Complete history was taken, and clinical examination was done. The sociodemographic history (age, gender), family history, smoking history, and past history, as well as comorbidities like diabetes mellitus, hypertension, and dyslipidemia, were recorded.

The patients were evaluated with ECG, cardiac biomarkers (CKMB, TROP-T), and diagnosis was established by 2-dimensional echocardiography (2D echo) and angiography. After initial evaluation in a sample of 108 patients, the correlation of clinical presentation, ECG changes, and 2D echo findings with coronary angiography was analyzed. The vessel involved and the type of vessel disease, whether single vessel disease, double vessel disease, or triple vessel disease, were recorded, and the factors affecting it were assessed.

Statistical Analysis

Mean and standard deviation were used to present quantitative data. Unpaired *t*-test was used to compare the study groups based on the normality test findings. A frequency and percentage table was used to present qualitative data. The Fisher test, the Student's *t*-test, and the Chi-squared test were used to evaluate the association between the study groups. A *p*-value of <0.05 was considered significant. For statistical analysis, the appropriate statistical software was utilized, that is, Statistical Package for the Social Sciences (SPSS) ver. 24, IBM manufacturer, Chicago, USA.

Results

The mean age of the study subjects was 55.7 ± 13.7 years, with 84 (75.68%) individuals being male and 27 (24.32%) being female. Of the total participants, 8 (7.20%) were current smokers, 28 (25.20%) had diabetes mellitus, 28 (25.20%) had hypertension, 24 (21.60%) had dyslipidemia, and 23 (20.70%) had a family history of CAD (Table 1).

Among the symptoms, chest pain was reported in 69 (62.16%) cases, shortness of breath was noted in 16 (14.41%) cases, fatigue in 14 (12.61%) cases, palpitations in 10 (9.01%) cases, and syncope was reported in 2 (1.80%) cases (Fig. 1).

Single-vessel disease, DVD, and TVD were seen in 64 (42.30%), 17 (23.40%), and 30 (34.20%) patients, respectively. In cases of SVD, the commonest vessel involved was left anterior descending (LAD) in 54 (84.38%) cases, while right coronary artery (RCA) was involved in 39 (60.94%) cases, and right circumflex artery (RCX) was involved in 21 (32.81%) cases. In DVD, the commonest vessel involved was LAD in 14 (82.35%) cases, while RCA was affected in 7 (41.18%) cases, and RCX was involved in 2 (11.76%) cases. The mean percentage of blockage in CAD was 83.95 ± 9.24. On 2D echo, the mean left ventricular ejection fraction (LVEF) was 35.42 ± 11.85. RWMA was absent in 30 (27.10%) cases. Left ventricle (LV) clot was present in 1 (1%) patient. Valvular abnormality was present in 21 (19%) cases. Anterior wall hypokinesia (HK) was present in 40 (36%) cases, global HK in 24 (21.70%) cases, inferior wall HK in 12 (10.80%) cases, and lateral wall HK in 5 (4.50%) cases (Table 2).

In the patients with SVD, DVD, and TVD, there was a similar mean CKMB (18.13 ± 13.19 vs 20 ± 9.59 vs 13.21 ± 10.17, $p = 0.079$), and an abnormal valve was present in 8, 5, and 8 patients, respectively ($p = 0.111$). LV clot was present in only one patient in the TVD group ($p = 0.423$). There was a significant difference in clinical features among the three groups ($p = 0.049$). Compared to patients with SVD and DVD, those with TVD had a significantly lower occurrence of fatigue (3 vs 11 vs 0)

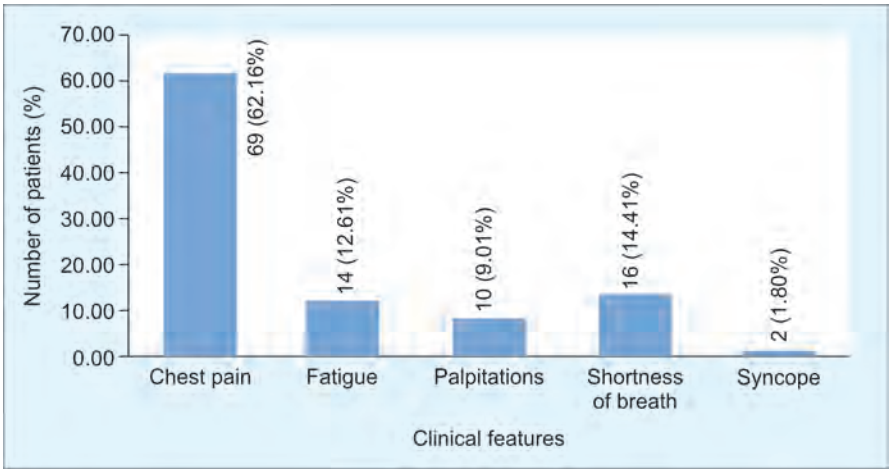

Fig. 1: Clinical features distribution

Table 1: Demographic characteristics distribution

Demographic characteristics	*n (%)*	*Mean ± SD*	*Median (25th–75th percentile)*	*Range*
Age (years)	–	55.7 ± 13.7	56 (45–66.5)	23–84
Gender				
Female	27 (24.32)	–	–	–
Male	84 (75.68)			
Current smoker	8 (7.20)	–	–	–
DM	28 (25.20)			
Dyslipidemia	24 (21.60)			
Family history	23 (20.70)			
Hypertension	28 (25.20)			

Table 2: Investigations findings

Risk factors	*Frequency*	*Percentage*
Inferior leads (II, III, aVF)		
Q waves	8	7.20%
ST depression	8	7.20%
ST elevation	12	10.80%
T wave inversion	17	15.30%
Anterior leads (leads V1–V4)		
ST elevation	30	27%
T wave inversion	25	22.50%
ST depression	5	4.50%
Qs waves	22	19.80%
Lateral leads (V5–V6, lead I, aVL)		
T wave inversion	18	16.20%
ST elevation	2	1.80%
ST depression	6	5.40%
CAD		
SVD	64	42.30%
DVD	17	23.40%
TVD	30	34.20%
CAD		
LAD	43	38.70%
RCA	19	17.10%
LAD + RCA	17	15.30%
LAD + RCA + LCX	30	27%
LCX	2	1.80%
CAD (percentage of blockage)		
Mean ± SD	83.95 ± 9.24	
Range	70–99	
2D echo findings		
LVEF >40%	27	24.32%
LVEF <40%	84	75.68%
Mean ± SD	35.42 ± 11.85	
Range	20–55	
RWMA		
RWMA absent	30	27.10%
RWMA present	81	72.90%
LV clot (2D echo)		
Absent	110	99%
Present	1	1%
Valves		
Normal	90	81%
Valvular abnormality	21	19%
Hypokinesia		
Anterior wall HK	40	36%
Inferior wall HK	12	10.80%
Lateral wall HK	5	4.50%
Global HK	24	21.70%
Normal	30	27%

HK, hypokinesia

and palpitations (1 vs 7 vs 2). Chest pain was present in 39 patients with SVD, 14 patients with DVD, and 16 patients with TVD. Shortness of breath was present in 7 patients with SVD, 1 patient with DVD, and 8 patients with TVD (Table 3).

On performing univariate regression, none of the parameters was found to be a significant risk factor for TVD (Table 4).

Table 3: Association of various parameters with SVD, DVD, and TVD

Parameters	*SVD (n = 64)*	*DVD (n = 17)*	*TVD (n = 30)*	*p-value*	*Test performed*
CKMB (mean ± SD)	18.13 ± 13.19	20 ± 9.59	13.21 ± 10.17	0.079	ANOVA; F-value = 2.603
LV clot					
Absent	64	17	29	0.423	Fisher's exact test
Present	0	0	1		
Valve					
Normal valves	56	12	22	0.111	Fisher's exact test
Abnormal valve	8	5	8		
Clinical features					
Chest pain	39	14	16	0.049	Fisher's exact test
Fatigue	11	0	3		
Palpitations	7	2	1		
Shortness of breath	7	1	8		
Syncope	0	0	2		

Table 4: Univariate logistic regression to find out significant risk factors of TVD

Variable	*Beta coefficient*	*Standard error*	*p-value*	*Odds ratio*	*Odds ratio lower bound (95%)*	*Odds ratio upper bound (95%)*
Age (years)	–0.006	0.016	0.721	0.994	0.965	1.025
Gender						
Female				1.000		
Male	–0.425	0.478	0.373	0.654	0.256	1.667
Hypertension	0.126	0.483	0.794	1.135	0.440	2.927
Diabetes mellitus	–0.107	0.496	0.829	0.898	0.340	2.375
Current smoker	0.537	0.761	0.480	1.712	0.385	7.608
Dyslipidemia	–0.675	0.580	0.245	0.509	0.163	1.589
Family history	0.485	0.500	0.332	1.624	0.609	4.329

Discussion

Acute coronary syndrome may present differently depending on the population type, comorbidities, age, gender, and the diagnosis and management also depend on the healthcare facilities. In this study, we thoroughly analyzed the patients with ACS in terms of the clinical profile, demographic characteristics, and investigation profile, and attempted to analyze the factors that may affect multivessel disease, that is, TVD.

In the present study, common clinical features were chest pain in 69 (62.16%) cases, followed by shortness of breath (14.41%), fatigue (12.61%), palpitations (9.01%), and syncope (1.80%). Among other studies, Revaiah et al.[11] reported that 98.9% of patients had angina, 4.9% had dyspnea, and 1 (0.5%) patient had atypical chest pain. Haider et al.[12] reported that chest pain was present in 96% of patients, followed by shortness of breath (45%), atypical pain (8%), cardiac arrest (4%), syncope (3%), and palpitation (2%).

The study results showed that SVD involvement was the most common in the study cohort, as seen in 64 (42.30%) cases, with DVD in 17 (23.40%) cases and TVD in 30 (34.20%). Likewise, Revaiah et al.[11] also showed that SVD was the commonest, as seen in 89 (53%) of the cases, followed by DVD in 20 (12%) and TVD in 8% of cases. In another study, Mohammad et al.[9] also found SVD involvement to have the highest proportion, as seen in 23.3% of cases, followed by DVD in 14.3% and TVD in 21.3% of cases.

Among various types of multivessel and SVD, we found that the LAD artery was the most commonly involved artery, as seen in 43 (38.7%) cases. The findings were in line with the study by Revaiah et al.,[11] where LAD affected 68 (40%) cases, followed by LCX and RCA. Even Mohammad et al.[9] found that the most frequently affected vessel was LAD, as seen in 60.7% of cases, followed by the RCA, left circumflex artery, and left main stem (46.3, 43.7, and 6%, respectively). Even Haider et al.[12] reported that, on angiography, LAD was the most commonly affected vessel in 57%, followed by RCA in 42%, and LCX in 32% of patients.

The significance of the LAD lies in the fact that it is one of the three largest coronary arteries, that is, LAD, RCA, and LCX. Occlusion of the LAD may cause ischemia in the anterior wall of the LV and manifest as precordial ST-segment elevation on ECG.[12] Based on the extent of myocardial involvement, STEMI caused by LAD is reported to be associated with worse clinical outcomes.[14]

With respect to the vessel involved, the concern always remains about the number of vessels involved—multivessel disease, that is, TVD—which needs immediate bypass surgery or stenting. As for risk factors for TVD, we found that none of the factors individually was significant enough to cause TVD; rather, a multitude of factors, starting from age, gender, family history, comorbidities, and smoking, was found to affect the progression of the blockage of coronary arteries in their own way.

The mean age of the study subjects in the present study was 55.7 ± 13.7 years. Although ACS primarily occurs in people over 50 years old, it can also affect younger adults.[15] However, older patients make up a significant number of ACS cases. Those aged 75 and above represent around 30–40% of all hospitalized ACS patients, and most ACS-related deaths occur in this age-group.[16] Among previous studies, Mohammad et al.[9] conducted a study on 300 patients in the age-group from 20 years to >60 years, where the

mean age of the patients was 55.5 ± 10.4 years. Tsega et al.[10] reported that the mean age of 216 patients (≥80 years) was 59 ± 13.8 years. Revaiah et al.[11] reported a lower mean age of 182 patients, that is, 35.5 ± 4.7 years. Similarly, in the study by Haider et al.,[12] the mean age of 109 ACS patients was 39.98 ± 7.52 years.

On this background, the age range in our population also varied from 23 to 84 years, but the odds ratio for increasing age and its association with TVD in ACS was found to be 0.994 (95% CI: 0.965–1.025, $p = 0.721$). In contrast, Agrawal et al.[17] showed a significant correlation of age with multivessel disease ($p = 0.023$). Adiarto et al.[18] also found that age >60 years showed a significant association with TVD (OR = 1.579, $p < 0.05$), showing a link between increasing age and multivessel involvement.

As for gender distribution, in the present study, 84 (75.68%) participants were males, while 27 (24.32%) were females. In comparison, Revaiah et al.[11] reported that 96.2% of the patients were males. Even in the study by Haider et al.,[12] 92.7% were males. Tsega et al.[10] reported that 67.5% of the patients were males. Overall, a male predominance has been shown—factors for which could stem from chromosomal, hormonal, or reproductive influences, as well as gender-specific societal roles influencing activity levels or career choices. Access to education and health information may also play a role. From adolescence onward, differences in blood lipid levels and blood pressure emerge between men and women, suggesting that men may experience greater cumulative effects of risk factors like smoking, high blood pressure, high cholesterol, lack of exercise, and poor diet, leading to a higher risk of arteriosclerosis compared to women due to longer exposure durations.[19]

Though the prevalence remained high, the risk association of male gender (in comparison to females) for progression to TVD was nonsignificant, with an odds ratio of 0.654 (95% CI: 0.256–1.667, $p = 0.373$). However, Agrawal et al.[17] found that female sex showed a significant association with more severe disease ($p = 0.04$). Huckaby et al.[20] reported that male patients were more likely to have TVD ($p = 0.002$). This may be due to confounding effects of additional comorbidities, hormonal differences, and addictions.

Elderly populations are prone to have a multitude of comorbidities. In the present study, 28 (25.20%) of the patients had diabetes mellitus, 28 (25.20%) had hypertension, and 24 (21.60%) had dyslipidemia.

Among other studies, Revaiah et al.[11] reported that hypertension was present in 29.7% of patients and diabetes mellitus in 15.9% of patients. In the study by Mohammad et al.,[9] the comorbidities in the patients were hypertension (55.3%), followed by dyslipidemia (42.7%) and type 2 diabetes mellitus (29%).

Takieddin et al.[21] reported that diabetes (62.60%), dyslipidemia (62.44%), and hypertension (61.46%) were the comorbidities in the patients. In the study by Haider et al.,[12] dyslipidemia, hypertension, CAD, myocardial infarction (MI), and percutaneous coronary intervention (PCI) were present in 33, 28, 14, 6, and 4% of patients, respectively. Tsega et al.[10] reported that hypertension was present in 47.3% of patients, diabetes in 25.1%, retroviral infection (RVI) in 7.4%, and dyslipidemia in 7.4%.

Overall, diabetes mellitus, hypertension, and dyslipidemia were the commonest comorbidities found in the studied populations. These are of importance since all three may be linked to the blockage of coronary vessels due to the deposition of LDL cholesterol, leading to atheroma formation in the background of dyslipidemia.[12,21]

Hyperglycemia works by producing advanced glycation end products and reactive oxygen species (ROS), which initiate and progress atherosclerosis. ROS may raise the risk of heart failure by causing cardiomyopathy and microvascular complications. The renin-angiotensin-aldosterone system (RAAS) can also be activated by hyperglycemia and insulin resistance, which raises the risk of CVD.[22]

Lastly, patients with hypertension can contribute to atherosclerosis development through mechanical stress and raise the risk of MI and heart failure by causing cardiac hypertrophy.[22]

However, specifically when we analyzed the risk association of these comorbidities to cause TVD, we found that none of them was a strong independent risk factor. On the contrary, Agrawal et al.[17] found that TVD was more associated with diabetes than nondiabetics ($p = 0.01$). Similarly, Arroyo-Rodríguez et al.[23] observed that diabetes and hypertension showed a significant association with three-vessel CAD. Adiarto et al.[18] also reported that diabetes mellitus showed a significant association with TVD (OR = 1.412, $p < 0.05$).

Besides comorbidities, smoking is a significant risk factor for CAD and is often linked to unstable plaque formation. While the exact mechanisms behind smoking-induced atherosclerosis are not fully understood, there may be disruptions in the balance between the production and breakdown of the extracellular matrix. Nicotine, an addictive substance in cigarette smoke, stimulates the expression of MMP-2 and MMP-9, which can contribute to the formation of unstable plaques.[24]

In the present study, 8 (7.20%) of the patients were current smokers, which was a small population. Likewise, in the study by Mohammad et al.,[9] 11% were smokers. The odds ratio for smoking to predispose to TVD was 1.712 (0.385–7.608) in our study; however, it failed to cross the boundaries of statistical significance ($p = 0.48$). Similarly, Agrawal et al.[17] found that smoking was not associated with TVD. Arroyo-Rodríguez et al.[23] also reported that smoking showed a significant association with three-vessel CAD.

Another significant factor not under our control is the family history, which may increase the chances of events in future generations. Genetic predisposition plays a crucial role, as shared genetic factors among relatives can influence cholesterol metabolism, inflammation, and other processes related to CAD. Additionally, families often share similar lifestyles and environmental exposures, such as unhealthy habits like smoking, poor diet, and sedentary living, which can elevate the risk of CAD and TVD.[25]

In the present study, a family history of CAD was present in 23 (20.70%) patients. Among other studies, Agrawal et al.[17] reported that a family history of CVD was present in 11% of patients with ACS. In the study by Revaiah et al.,[11] a family history of premature CAD was present in 18.2% of patients. The odds ratio for a family history link with TVD was 1.624 (0.609–4.329) in our study; however, it was not statistically significant ($p = 0.332$). On the contrary, Hindieh et al.[25] reported that a family history of CAD showed a significant association with TVD (OR: 1.42; $p = 0.005$). The difference in the statistical associations might be due to a heterogeneous population, different sample sizes, and the confounding effects of various risk factors.

Limitations

As the present study was a single-center study, its findings cannot be generalized. Excluding patients with UA and asymptomatic patients may have limited the study's scope in understanding the full spectrum of ACS presentations and outcomes.

Conclusion

To conclude, ACS patients are predominantly elderly males with comorbidities like diabetes, hypertension, family history of heart diseases, and dyslipidemia. Clinical symptoms such as chest pain, shortness of breath, and fatigue were common, with chest pain being the most prevalent. CAD patterns varied, with SVD, DVD,

and TVD observed in different proportions. The occurrence of SVD surpassed DVD and TVD among ACS patients. Echocardiography showed reduced LVEF and RWMA in some cases, alongside valvular abnormalities. LAD was the most commonly involved coronary. Univariate regression analysis did not identify any individual significant risk factor for TVD.

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REVIEW ARTICLE

Erdosteine: Reigniting a Thiol Mucolytic for Management of Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a major health burden globally and in India. Oxidative stress plays a pivotal role in the pathogenesis of COPD, causing mucus hypersecretion, bronchoconstriction, and accelerated lung function decline. An important class of pharmacological agents that are often less discussed are the thiol mucolytic agents, which have a two-pronged effect of serving as both a mucolytic and an antioxidant. One of these agents which has reignited interest lately is erdosteine, with recent evidence demonstrating advantages over traditionally used N-acetylcysteine. In this review, we have summarized the key available evidence for the role of erdosteine in COPD, with takeaways on its place in therapy.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition distinguished by chronic respiratory symptoms (cough, sputum production, dyspnea, and/or exacerbations) due to airway (bronchitis, bronchiolitis) and/or alveolar (emphysema) abnormalities, which lead to persistent, often progressive, airflow obstruction.[1] There are approximately 392 million COPD patients globally, with India and China alone accounting for >50% of the global burden.[2,3] Due to the disease impacting multiple facets of a patient's life, cornerstones of therapy include addressing the symptomatology, lung function, and quality of life (QoL), while also focusing on prevention and treatment of acute exacerbations of COPD (AECOPD).[1]

Oxidative Stress in Pathophysiology of Chronic Obstructive Pulmonary Disease

An important contributor to the pathogenesis of COPD is oxidative stress, which accelerates pulmonary aging and the decline in lung function.[4] Reactive oxygen species (ROS) also signal for pro-inflammatory cytokines and cause pulmonary tissue damage, which leads to bronchoconstriction and mucus hypersecretion.[5] Inspissated mucus in the larger airways causes increased sputum production and coughing, while in the peripheral airways, it causes airflow obstruction.[6] The net effect is a greater predisposition to disease exacerbation, accelerated decline in forced expiratory volume in 1 second (FEV_1), and decreased accessibility of inhaled medication in peripheral airways (Fig. 1).[4–6]

Drugs with a thiol moiety are frequently used in pulmonary medicine as mucolytics. However, their effects are also majorly due to their potent antioxidant effect.[7] Three thiol molecules have been extensively studied for COPD, namely, N-acetylcysteine (NAC), carbocysteine, and erdosteine, of which NAC and erdosteine are available in India.

Erdosteine—Pharmacological Perspectives

Erdosteine, a prodrug, is rapidly absorbed after oral administration and swiftly transformed through first-pass metabolism to its biologically active metabolite, N-thiodiglycolyl-homocysteine (M1).[8] The active metabolite, M1 (also known as MET1), acts *via* a two-pronged approach: as a mucolytic to enhance mucus clearance and as an antioxidant to reduce inflammation, thereby attenuating mucus production and protecting α1-antitrypsin activity (Fig. 2).[5,7–9] The net effect is an improvement in lung function and symptoms, with a reduction in the rate of COPD exacerbations (Fig. 2).[10] Other pleiotropic anti-inflammatory and antibacterial effects of erdosteine are mentioned in Table 1. The absorption of erdosteine is independent of food intake. Also, its pharmacokinetics are unaffected by age.[8]

Clinical Evidence with Erdosteine

Key Clinical Trials of Erdosteine

Fioretti and Bandera conducted a randomized, placebo-controlled, double-blinded trial in 132 patients with chronic bronchitis. Investigators studied the effect of erdosteine administration for 26 weeks (i.e., 6 months) in these patients. Findings revealed that erdosteine significantly reduced the rate and severity of exacerbations compared to placebo. Also, patients on erdosteine had fewer absent days at work compared to placebo.[5,12]

The ECOBES trial was a multicentric, double-blind, randomized trial involving 237 patients with an acute exacerbation of chronic bronchitis due to infective etiology. These patients were randomized to receive either erdosteine 300 mg twice daily or placebo for 10 days, in addition to amoxicillin 1500 mg/day. Patients who received erdosteine along with amoxicillin showed a more swift improvement in cough, sputum viscosity, and breathlessness compared to those receiving amoxicillin alone.[13]

Aubier and Berdah conducted a multicentric study in 170 patients with chronic bronchitis. Trial participants were randomized to receive either erdosteine 300 mg twice daily or placebo for a total duration of 3 weeks. Patients who received erdosteine had a significantly better global efficacy index (composite of cough frequency, cough severity, breathing difficulty, and dyspnea) compared to placebo. Furthermore, there was a significant reduction in the frequency and intensity of cough in patients who received erdosteine compared to placebo.[14]

The EQUALIFE study was a multicentric, randomized, double-blinded, parallel-group trial that studied the effect of long-term erdosteine treatment in moderate COPD patients. In this study, 155 patients with moderate COPD were randomized to

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receive either erdosteine 300 mg twice daily or placebo for a total duration of 8 months. Erdosteine-treated patients experienced a significantly reduced number of AECOPDs and days of hospitalization. Additionally, there was significant improvement in health-related quality of life (HRQoL) in patients who received 8-month erdosteine treatment.[15]

Crisafulli and colleagues conducted a single-center, prospective, open-labeled pilot study in elderly patients (age >55 years) with bronchiectasis to study the additive effect of oral erdosteine (given for 15 days) over physiotherapy. Compared to patients who received physiotherapy alone, those who received erdosteine in addition to physiotherapy had a significantly better improvement in FEV_1 (by 200 mL) and forced vital capacity (FVC) (by 300 mL). There was also a significant reduction in mucus volume produced and mucus purulence.[16]

Moretti and Fagani conducted a single-center, single-blinded, randomized controlled trial (RCT) in patients hospitalized with AECOPD to determine if erdosteine had any benefits in the post-discharge period. Along with standard treatment, 40 patients hospitalized for AECOPD were randomized to receive either erdosteine 900 mg/day or a matching control. Treatment was continued for 10 days up to discharge. Patients who received erdosteine had a significant reduction in CRP (from 3.7 mg/dL at baseline to 0.8 mg/dL) after 10 days. Notably, at day 10, there was a 33% greater reduction in CRP in patients who received erdosteine (0.8 mg/dL) compared to the control group (1.2 mg/dL). Erdosteine treatment was associated with a 39% lower risk of exacerbations, an 83% relative risk reduction in the 60-day exacerbation rate [hazard ratio (HR) = 0.169, 95% confidence interval (CI) = 0.033–0.875] ($p = 0.034$), and a significant delay in time to first exacerbation at 1 and 2 months postdischarge ($p = 0.009$ at day 30, $p = 0.075$ at day 60) compared to matched controls. Hence, this study showed that erdosteine, added to standard care in hospitalized AECOPD patients, significantly reduced airway inflammation, improved AECOPD symptoms, and prolonged the time to the first exacerbation.[17]

Recently, interest in erdosteine was rekindled with the landmark RESTORE study (2017). It showed that in GOLD stage II and III COPD patients, treatment with erdosteine for 1 year significantly reduced the rate of all exacerbations by 19.4% and the rate of mild exacerbations by 57% (Fig. 3). The duration of exacerbations also reduced by 24.6% [9.5 ± 7.2 days in patients treated with erdosteine vs 12.6 ± 9.7 days in the control group; ($p = 0.023$)]. Notably, the reduction in exacerbations was irrespective of whether patients received background inhaled corticosteroids (ICS) or not.[18] This finding was in stark contrast to the BRONCHUS study, where NAC showed benefits only in those patients who were not receiving ICS.[19] Furthermore, significantly fewer patients treated with erdosteine required reliever medications compared to the control (10.2 vs 33.7%) ($p < 0.001$).[18]

In a *post hoc* analysis of RESTORE participants with moderate COPD (GOLD 2 subgroup), similar benefits were noted in

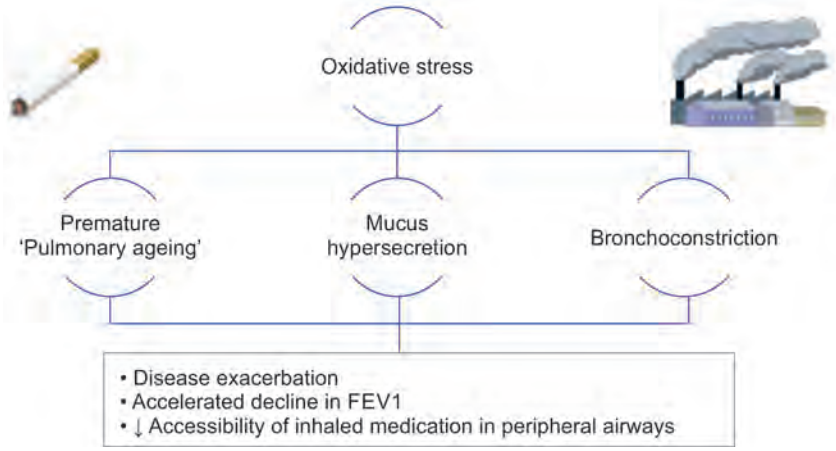


Fig. 1: Oxidative stress (which may arise due to risk factors like smoking or air pollution) can affect COPD pathogenesis at the cellular/genetic level. ROS cause telomere shortening, cellular senescence, DNA damage, mitochondrial dysfunction, decreased autophagy, stem cell exhaustion, decrease in anti-aging molecules, and auto-immune induction, resulting in premature pulmonary aging, mucus hypersecretion, and bronchoconstriction. The net effect is greater predisposition to disease exacerbation, accelerated decline in FEV_1, and decreased accessibility of inhaled medication in peripheral airways

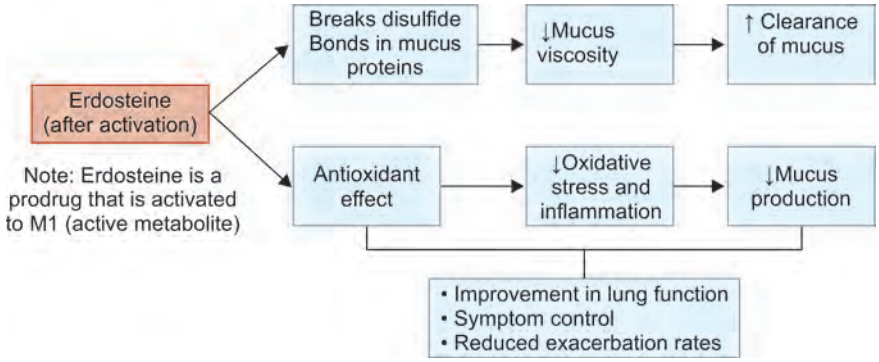


Fig. 2: Mechanism of action of erdosteine and resultant key clinical effects. Note that erdosteine is a prodrug that is converted to the active metabolite M1—which has a pharmacologically active—SH group. M1 exerts the pharmacological effects attributed to erdosteine, that is, mucolytic and antioxidant effects

Table 1: Other pleiotropic effects of erdosteine[5,11]

Anti-inflammatory activity	*Antibacterial activity*
↓ Cytokine release	↑ Antibiotic penetration
↓ Proteinase synthesis	↓ Biofilm formation
↓ Levels of pro-inflammatory proteins and activation of transcription factors	↓ Bacterial adhesion on epithelium

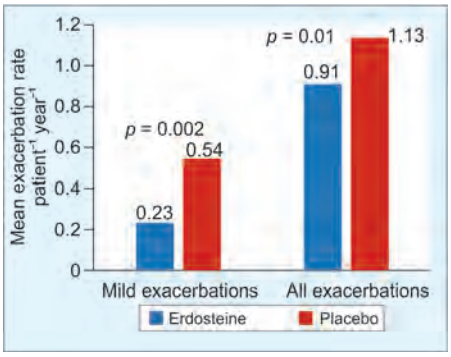


Fig. 3: In the RESTORE study, erdosteine reduced the rate of overall exacerbations by 19.4% and the rate of mild exacerbations by 57%[18]

the erdosteine arm, with a 47% reduction in the rate of exacerbations [0.27 vs 0.51 per-patient per-year (p = 0.003)] and a 26% shorter duration of exacerbations of COPD [9.1 vs 12.3 days, (p = 0.022)]. Patients who received erdosteine had a 58.3% reduction in the number (i.e., rate) of mild exacerbations [0.23 vs 0.53 per-patient per-year, (p = 0.001)] compared to the control group. Additionally, there was a significant prolongation of time to first exacerbation (p < 0.001) and an increase in mean exacerbation-free time by 51 days (p < 0.001) in the erdosteine group when compared to the control group. Of note, the beneficial effect of erdosteine on the rate of exacerbations was irrespective of baseline blood eosinophil counts.[20]

A second *post hoc* analysis on the entire RESTORE dataset revealed that in patients with moderate-to-severe AECOPD, erdosteine-treated patients (vs placebo) required a lesser mean duration of corticosteroid treatment (11.4 days in the erdosteine arm vs 13.3 days in the control arm). Also, 14.4% fewer patients required antibiotics + oral corticosteroids (p < 0.001) in the erdosteine arm as compared to the control. An improvement in QoL was also noted in the erdosteine arm, with greater improvement in SGRQ scores irrespective of the severity of exacerbation.[21]

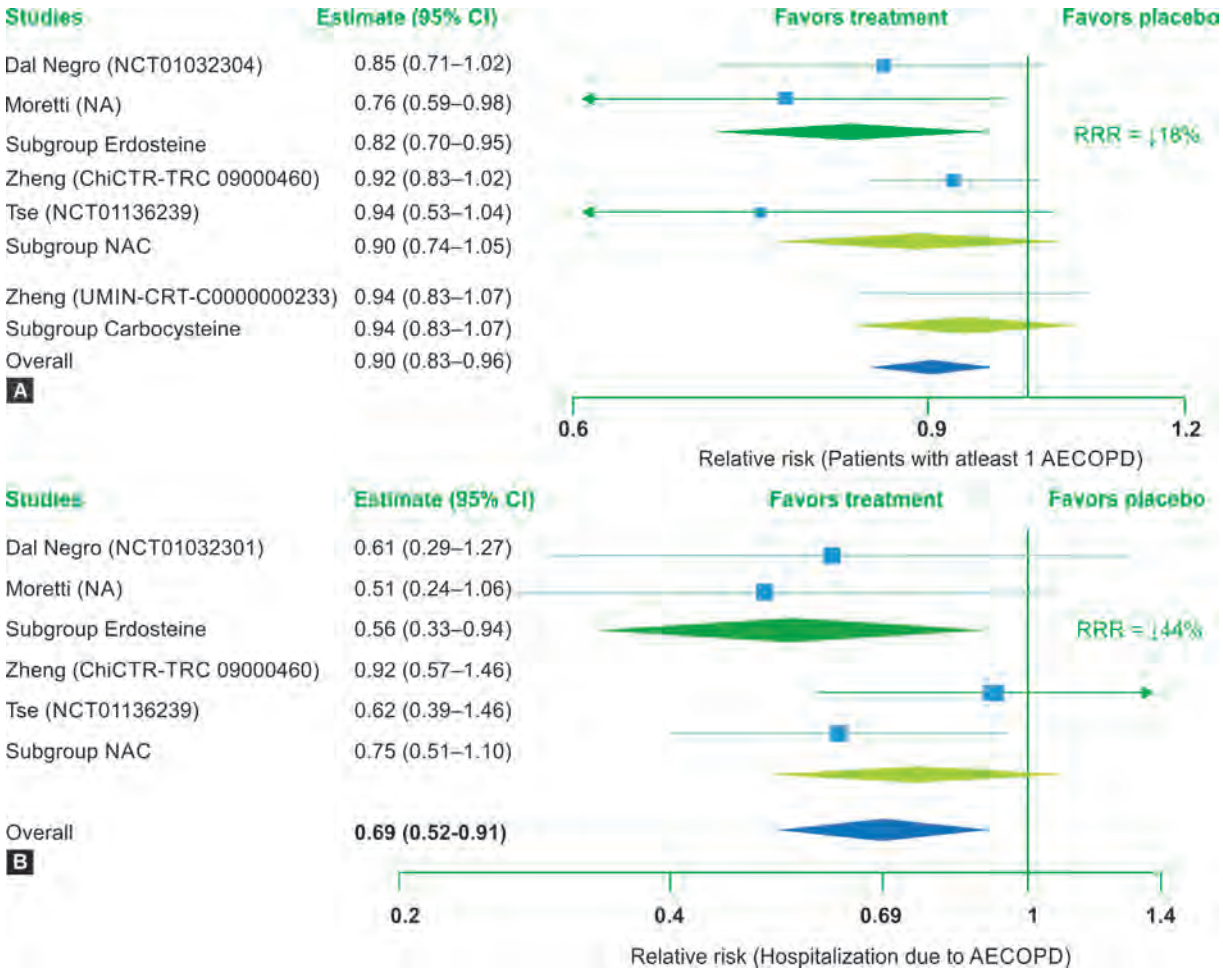
Summary and details of key clinical trials of erdosteine in COPD are summarized in Table 2.

Meta-analysis

A meta-analysis of 15 RCTs by Cazzola and Floriani showed that treatment with erdosteine resulted in significant symptom amelioration (sputum viscosity, cough intensity, catarrh ronchi, cough frequency) in patients with chronic bronchitis/COPD. Treatment with erdosteine was associated with double the chance of treatment success in comparison to placebo [odds ratio (OR) = 2.08, 95% CI = 1.09–3.96] or other mucolytics (OR = 2.19, 95% CI = 1.03–4.69).[22]

A 2018 meta-analysis of 10 studies, which included 1,278 patients with chronic bronchitis and COPD, established that erdosteine reduced the risk of exacerbations by 35% [relative risk (RR) = 0.65, 95% CI = 0.50–0.83] and even the risk of hospitalizations for COPD by 44% (RR = 0.56, 95% CI = 0.33–0.94). Erdosteine-treated patients also had a 29% lower risk of experiencing at least one exacerbation of COPD (RR = 0.71, 95% CI = 0.57–0.89). Patients treated with erdosteine had a lesser duration of AECOPD and a lengthened time period to first COPD exacerbation.[23]

A meta-analysis of seven RCTs was conducted by Rogliani and colleagues involving 2,753 COPD patients, comparing the efficacy of 3 thiol mucolytics—NAC, carbocysteine, and erdosteine. Only erdosteine, but not NAC, reduced the risk of experiencing at least one AECOPD by 18% (RR = 0.82, 95% CI = 0.70–0.95) and the risk of hospitalization for AECOPD by 44% (RR = 0.56, 95% CI = 0.33–0.94) (Fig. 4). The number needed to treat (NNT) for preventing one AECOPD was also the least for erdosteine (10.11) compared to NAC (15.69) and carbocysteine (30.92). The network meta-analysis revealed that among the three mucolytics studied, erdosteine



Figs 4A and B: Comparative meta-analysis of mucolytics in COPD showed that only erdosteine, but not NAC, reduced the risk of experiencing at least one acute exacerbation of COPD (p < 0.01) (RRR = 18%) (A). Also, only erdosteine, but not NAC, reduced the risk of hospitalization due to acute exacerbation of COPD (p < 0.05) (RRR = 44%) (B) (Adapted from Rogliani et al.)[24]

Table 2: Summary of key clinical trials[5,12–21]

Authors + trial name	*Trial design*	*Study duration*	*No. (n)*	*Disease condition*	*Results/takeaways*
Fioretti and Bandera (1991)[12]	Double blind, randomized	26 weeks	132	Chronic bronchitis	Erdosteine showed better reduction (vs placebo) • ↓ Rate of exacerbations • ↓ Severity of exacerbations • ↓ Number of days of work-absenteeism
Marchioni et al. ECOBES (1995)[13]	Multicenter, double-blind, randomized	10 days	237	Acute exacerbation of chronic obstructive bronchitis	Erdosteine with amoxicillin vs amoxicillin alone—faster improvement in: • Breathlessness • Cough • Sputum viscosity
Aubier and Berdah (1999)[14]	Multicenter, double-blind, randomized, parallel group	3 weeks	170	Stable chronic obstructive bronchitis with hypersecretion	Erdosteine better outcomes than placebo (statistically significant) for: • ↑ Global efficacy index (cough frequency + cough severity + breathing difficulty + dyspnea) • ↓ Cough intensity • ↓ Cough frequency
Moretti et al. EQUALIFE (2004)[15]	Multicenter, double-blind, randomized, parallel group	32 weeks	124	Stable moderate COPD	Erdosteine vs placebo showed significant • ↓ Number of AECOPDs • ↓ Hospitalization days due to AECOPD • ↑ In HRQoL • ↓ COPD-related disease cost per patient
Crisafulli et al. (2007)[16]	Single-center, prospective, parallel, open label, pilot study	15 days	30	Elderly patients (age >55 years) with bronchiectasis and chronic mucus hypersecretion	Erdosteine added to physiotherapy had significant ($p < 0.05$) improvement (vs only physiotherapy) on: • ↑ FEV_1 (200 mL) • ↑ FVC (300 mL) • ↓ Mucus volume produced • ↓ Mucus purulence At day 15, significant improvements were observed in 6MWT, VAS cough, and VAS dyspnea ($p < 0.01$) in both groups
Moretti and Fagnani (2015)[17]	Single center, prospective, randomized, controlled, single-blind study	Treatment for 10 days Duration of study—60 days	40	Patients hospitalized for AECOPD	At day 10, mean serum CRP significantly reduced by: • 78% compared to baseline in the erdosteine group (from 3.7 mg/dL to 0.8 mg/dL) • 33% greater reduction vs control group (0.8 vs 1.2 mg/dL) Improvements in symptom score and FEV1 were greater in erdosteine group vs control group Compared to control arm, erdosteine was associated with: • 39% lower risk of exacerbations • 83% risk reduction in 60-day exacerbation rate (HR = 0.169, 95% CI = 0.033–0.875) ($p = 0.034$) • Significant delay in time to first exacerbation (logrank test $p = 0.009$ and 0.075 at days 30 and 60 respectively)
Dal Negro et al. RESTORE (2017)[18]	Multicenter, double-blind, randomized, parallel group	52 weeks	445	Stable COPD (GOLD stage II and III)	Erdosteine vs placebo[18] • ↓ Rate of all AECOPD by 19.4% [0.91 vs 1.13 per-patient per-year ($p = 0.01$)] • ↓ Rate of mild AECOPD by 57.1% [0.23 vs 0.54 per-patient per-year ($p = 0.002$)] • ↓ Duration of AECOPDs by 24.6% [9.5 ± 7.2 days with erdosteine vs 12.6 ± 9.7 days with placebo; ($p = 0.023$)] • ↓Reliever medication use—erdosteine (10.2% patients) vs placebo (33.7% patients) ($p < 0.001$) • Improvement in subject and physician severity scores ($p = 0.022$ and $p = 0.048$, respectively) Of note: • Reduction in exacerbations was irrespective of background ICS use (contrast to NAC studies where similar benefits are only observed in patients not receiving ICS)[19]

Contd…

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Authors + trial name	*Trial design*	*Study duration*	*No. (n)*	*Disease condition*	*Results/takeaways*
Calverly et al. *Post hoc* analysis of RESTORE (2019)[20]	Multicenter, double-blind, randomized, parallel group	52 weeks	254	Stable COPD (*post hoc* analysis of GOLD 2 subgroup, that is, spirometrically moderate COPD	Erdosteine vs placebo • ↓ 47% lesser rate of exacerbations (mean) [0.27 vs 0.51 exacerbations per-patient per-year ($p = 0.003$)] • ↓ 58.3% lesser rate of mild exacerbations [0.23 vs 0.53 per-patient per-year ($p = 0.001$)] • ↓ 26% shorter mean duration of exacerbations [9.1 vs 12.3 days ($p = 0.022$)]. • ↑ Time to first exacerbation by 7.7% [182 days for erdosteine vs 169 days for placebo ($p < 0.001$)] • ↑ Mean exacerbation-free time was increased by 51 days ($p < 0.001$) Of note: • Beneficial effect of erdosteine was maintained irrespective of baseline blood eosiniphil count
Calverly et al. *Post hoc* analysis of RESTORE (2022)[21]	Multicenter, double-blind, randomized, parallel group	52 weeks	445	Stable COPD (GOLD stage II and III)	In patients with moderate-to-severe AECOPD, erdosteine-treated (vs placebo) had: • ↓ Mean duration of corticosteroid treatment (11.4 days vs 13.3 days) ($p = 0.043$) • ↓ 14.4% lesser patients required antibiotics + OCS ($p < 0.001$) GOLD 2 patients who exacerbated (erdosteine vs placebo) • ↑ SGRQ total scores regardless of exacerbation severity

Table 3: Summary of meta-analyses studies[22–24]

Authors (year)	*Disease*	*Number of studies (n = patients)*	*Key results*
Cazzola, Floriani and Page (2010)[22]	Chronic bronchitis or COPD	15 RCTs ($n = 1046$)	• ↓ Cough frequency • ↓ Cough intensity • ↓ Sputum viscosity • ↓ Difficulty to expectorate • ↓ Catarrh ronchi at auscultation • More than double odds of treatment success vs other mucolytics (OR = 2.19, 95% CI = 1.03–4.69) • More than double odds of treatment success vs placebo (OR = 2.08, 95% CI = 1.09–3.96)
Cazzola et al. (2018)[23]	Chronic bronchitis and COPD	10 studies ($n = 1278$)	• ↓ 35% reduced risk of exacerbations (RR=0.65, 95% CI = 0.50–0.83) • ↓ 29% reduced risk of experiencing at least one exacerbation (RR = 0.71, 95% CI = 0.57–0.89) • ↑ Time to first exacerbation • ↓ Duration of AECOPD • ↓ 44% reduced risk of hospitalization for COPD (RR = 0.56, 95% CI = 0.33– 0.94)

Rogliani et al. (2019)[24]	COPD	7 RCTs ($n = 2753$)	• Rank of Effectiveness (by SUCRA): Erdosteine > carbocysteine > NAC, that is, efficacy of erdosteine was rated the highest
			• Only erdosteine, but not NAC reduced
			  • ↓ 44% reduced risk of hospitalization due to AECOPD (RR = 0.56, 95% CI = 0.33–0.94) ($p < 0.05$)
			  • ↓ 18% reduced risk of experiencing at least 1 exacerbation of COPD (RR = 0.82, 95% CI = 0.70–0.95) ($p < 0.01$)
			• NNT to prevent 1 AECOPD was 10.11 for erdosteine, 15.69 for N-acetyl cysteine and 30.92 for carbocysteine.

had the highest efficacy (Fig. 5).[24] Summary and details of key meta-analysis studies with erdosteine in COPD are summarized in Table 3.

Consensus and Guideline Recommendations

A 2020 European Delphi Consensus on mucolytics in COPD consistently rated the use of erdosteine the highest. The panel also recommended that approved doses of mucolytic agents could be recommended for regular use in COPD patients with a bronchitic phenotype.[25] As per GOLD 2024 Guidelines, regular treatment with mucolytics such as erdosteine, carbocysteine, and NAC reduces the risk of exacerbations in select populations (level B). Based on RESTORE study evidence, GOLD 2024 Guidelines also mention that erdosteine may have a significant effect on exacerbations irrespective of concurrent treatment with ICS (in contrast to NAC, which showed no benefits in patients who received ICS).[1,19]

Place in Therapy

Erdosteine may find its place in the management of COPD, particularly in patients with chronic bronchitis and mucus hypersecretion. Its dual action as a mucolytic and antioxidant addresses two critical aspects of COPD pathophysiology—mucus

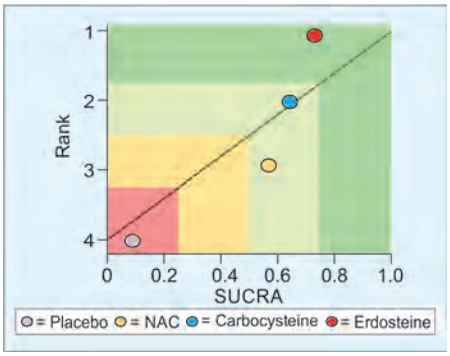

Fig. 5: Ranking plot resulting from the network meta-analysis in which treatments were plotted on the X-axis according to SUCRA (score of 1 being the most effective) and on the Y-axis according to the rank of being the best treatment (score of 1 being the most effective). Hence, erdosteine was the most effective drug, followed by carbocysteine and NAC (adapted from Rogliani et al.)[24]

clearance and oxidative stress reduction. Clinical studies have demonstrated its effectiveness in reducing the frequency and severity of AECOPD, improving lung function, and enhancing patients' quality of life.[12–24] Additionally, erdosteine has shown benefits irrespective of concurrent inhaled corticosteroid use, positioning it as a valuable therapeutic option as an add-on therapy in the long-term management of COPD, especially in the mucus-secreting phenotype.

Future Directions

The BETTER Trial (Trial Reg. No. ACTRN12621000315819) will investigate the effect of erdosteine in children and adults with bronchiectasis between the ages of 2 and 49 years. The study will inform us whether regular treatment with erdosteine is able to reduce the number of exacerbations and improve QoL in patients with bronchiectasis.[26]

Conclusion

There is a significant patient burden of COPD globally and within India. Though the mainstay pharmacotherapeutic agents in COPD are essential, thiol-mucolytics deserve special attention not only due to their mucolytic properties, but also their strong antioxidant effect. Erdosteine has a potent antioxidant effect which is beneficial in COPD management, both for short-term use as a mucolytic and in the long term for the prevention of AECOPD. Meta-analysis evidence has shown clear benefits over NAC and hence may be considered the thiol-mucolytic agent of choice for COPD patients in clinical practice.

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REVIEW ARTICLE

Tropical Infections and Acute Kidney Injury

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Abstract

Tropical febrile illnesses are important subsets of diseases leading to acute kidney injury (AKI) due to their geographical location, hot and dry climate, which predisposes individuals to dehydration, poor health infrastructure, and the prevalence of certain specific infectious diseases. Specific tropical infections need to be excluded while considering the differential diagnosis of febrile illness with AKI. Untreated infections may result in high mortality or may lead to long-term complications. Clinical symptoms related to other organ systems may help narrow down the diagnostic possibilities of these tropical infections. These infections require disease-specific treatment to prevent morbidity and mortality, in addition to supportive treatment. This review encompasses the epidemiology, pathophysiology, and specific renal pathological changes in common tropical infections resulting in AKI.

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Introduction

The tropical regions lie between the Tropic of Cancer in the Northern Hemisphere and the Tropic of Capricorn in the Southern Hemisphere. This region constitutes 40% of the world's population, which is projected to reach 50% by 2050. Because of global warming, tropical weather conditions are now expanding into the subtropical region.[1] Contrary to acute kidney injury (AKI) in the tropics, AKI in temperate zones primarily affects adolescents and younger individuals due to community-acquired infections and herbal medicines, which result in acute tubular necrosis (ATN).[2] What makes tropical AKI more unique is the scarcity of treatment facilities, prevalent malnutrition, dry climate leading to relative hypovolemia, and the triggering of hemolytic episodes when exposed to certain drugs and their toxins.[2] Additionally, specific tropical infections form an interesting subset due to their geographical importance, pathophysiology, and morbidity in young, apparently healthy, and economically productive populations. Infections are the most important reversible causes of AKI-related mortality. The important tropical infections causing AKI are malaria (*Plasmodium falciparum*, *Plasmodium vivax*, and mixed malaria), leptospirosis, dengue, scrub typhus, enteric fever, diarrheal illnesses, mixed infections, and undifferentiated causes (Tables 1 and 2).[3–5]

Malaria

Malaria continues to be a major public health concern in Africa, Latin America, the Eastern Mediterranean regions, and Southeast Asia, with an estimated 228 million cases of malaria worldwide in 2018.[6] India shares 3% of the world's total malaria burden and 47% of *P. vivax*'s malaria burden. Of all the notified malaria cases in India, the states of Odisha, West Bengal, Jharkhand, Chhattisgarh, Karnataka, and the North-eastern states contribute the most.[6]

Life-threatening complications of malaria, such as cerebral malaria, severe metabolic acidosis, severe anemia, AKI, deranged liver function, hypoglycemia, and acute respiratory distress syndrome (ARDS), are mostly associated with *P. falciparum* malaria. The combination of AKI with jaundice and cerebral malaria is a poor prognostic marker associated with high mortality.[7]

Complicated *P. falciparum* malaria with AKI is more common among nonimmune adults and older children in areas of low transmission.[7] Therefore, malarial AKI is seen more in nonmalarial areas and among travelers to endemic areas with high transmission. In sub-Saharan Africa, it is uncommon and is mostly seen in nonimmune young children and adults. Consequently, the increased prevalence of malarial AKI in the Indian subcontinent and Southeast Asia is associated with comparatively less intense malarial transmission. Factors predisposing to AKI include male sex, severe anemia, low platelet count, heavy parasitemia, underlying renal diseases, and proteinuria.[8] In the majority of cases, AKI is multifactorial and results from jaundice, intravascular hemolysis, heavy parasitemia, hypovolemia, respiratory failure, shock, pigment nephropathy, disseminated intravascular coagulation (DIC), and sepsis.[9] AKI and associated mortality vary across geographical locations, the time of presentation to healthcare facilities, delays in the institution of appropriate treatment, the duration of hospitalization, and the availability of renal replacement therapy (RRT). In 7% of cases, patients with severe AKI may progress to chronic kidney disease (CKD). The mortality rate of malarial AKI ranges from 10 to 50%.[3]

Table 1: Common tropical infections causing AKI

Parasitic infections	Malaria, filariasis, leishmaniasis
Bacterial infections	Leptospirosis, rickettsial disease, salmonellosis, shigellosis, melioidosis
Viral infections	Dengue virus, hantavirus, HIV, chikungunya virus

The pathophysiology of AKI in *P. falciparum* malaria has very unique characteristics (Table 3). The ability of *P. falciparum* to infect red blood cells (RBCs) of all ages leads to a heavy parasitic burden. The adherence of infected RBCs to the vascular endothelium (cytoadherence) due to their sticky nature occurs, especially in the capillaries of certain vital organs like the brain, liver, spleen, kidneys, lungs, and intestines. The RBCs infected with trophozoites and schizonts disappear from peripheral circulation and sequester in the microcirculation. In patients with cerebral malaria, sequestration of these infected RBCs in the microcirculation is significantly higher in the brain compared to other affected organs.[10] The infected RBCs also stick to each other, to uninfected RBCs, and to leukocytes, forming "rosettes," which contribute to the impediment of blood flow in vital organs.[10] "Cytoadherence" and "rosettes" obstructing blood flow to vital organs may be important to the pathophysiology of cerebral malaria and renal injury.[10,11]

Various other mechanisms that may precipitate renal injury include a "sepsis-like state" and "free oxygen radical"-mediated

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Table 2: Comparison of common tropical infections causing AKI

Diseases	*Incidence of AKI*	*Genus/species causing AKI*	*Reservoirs/vectors*	*Pathogenesis/characteristics of AKI*	*Treatment*
Malaria[6–13]	1–60%	*Parasite Plasmodium*: *P. falciparum*, *P. vivax*, *Plasmodium knowlesi*	*Anopheles* mosquitoes	Hemodynamic instability, cytokines release, cytoadherence of infected RBCs, ATN, TMA, GN, dyselectrolytemia	Artemisinin derivatives, quinine
Filariasis[46]	Few case reports	*Wuchereria bancrofti*, *Brugia malayi*	Reservoir—domestic cats/vector—*Aedes*, *mansonia*	Mechanical damage to glomeruli and tubules, immune complex deposition	DEC citrate
Leishmaniasis[49]	11–33.9%	*Leishmania donovani*, *Leishmania infantum*	Human/vector—*Phlebotomus*	AIN, GN, immune complex GN, ATIN	Amphotericin B, pentavalent antimonial compound, miltefosine
Leptospirosis[16–24]	10–87%	*Spirochetes Leptospira*: *Leptospira interrogans*, *Leptospira borgpetersenii*	Rodents, cattle, horses, pigs, dogs	ATIN, hemodynamic alteration, AIN, severe vasculitis, dyselectrolytemia	Penicillin G, ceftriaxone, cefotaxime
Rickettsial disease-scrub typhus[28–32]	10–60%	*Orientia tsutsugamushi*	Field rodents and vector mite/*Leptotrombidium delicense* (chigger) mite larva	ATN, hemodynamic alteration, AIN, GN, TMA	Doxycycline
Salmonellosis[25–27]	30–40%	*Salmonella*	Poultry, livestock/ fecal-oral route	ATN, rhabdomyolysis, hypovolemia	Supportive care—IV fluid, antibiotics—ceftriaxone, azithromycin.
Shigellosis[26,27]	<5%	*Shigella dysenteriae*, *Shigella flexneri*	Humans/ contaminated food, water	ATN, rhabdomyolysis, HUS, endothelial cell damage due to cytotoxic effects	Supportive care, antibiotics—fluoroquinolones, 3rd gen cephalosporin, ampicillin, trimethoprim-sulfamethoxazole
Melioidosis[2–4]	35–40%	Burkholderia pseudomallei	Humans/contaminated soil/water	ATIN, ATN, microabscesses	Ceftazidime/carbapenen/ cotrimoxazole
Dengue[41,35–40,42,43]	0.2–35.7%	Dengue virus type I–IV	*Aedes* mosquitoes: *Aedes aegypti*, *Aedes albopictus*	Hemodynamic alteration, cytokine release, ATN, GN, atypical HUS	Supportive care
Hantavirus[47]	70–80%	Hantavirus	Rodents/urine, droppings, and saliva	Hantavirus-induced HFRS, endothelial cell dysfunction	Supportive
Chikungunya[2–4]	20–45%	Chikungunya virus	Humans/*Aedes* mosquito	ATIN, ATN, GN, and nephrosclerosis	Supportive
HIV[2–4,48]	50%	HIV	Human/sexual, infected body fluids	Opportunistic infections may precipitate AKI. Hypovolemia from chronic diarrhea, nephrotoxic antiretroviral drugs, and contrast agents use will increase the risk of AKI. Renal biopsy—ATN, ATIN, TMA	Antiretroviral therapy

AIN, acute interstitial nephritis; ATIN, acute tubulointerstitial nephritis; ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy

Table 3: Pathogenesis of malaria-associated AKI

Mechanism	*Consequences*
1. Cytoadherence due to infected erythrocytes	Capillary clogging → tissue hypoperfusion → decreased RBF → ATN → AKI
2. Cytokines and inflammatory mediators release	Sympathetic activation, RAAS activation, arginine vasopressin release → decreased RBF → ATN
3. Immune response due to immune complex deposition and autoantibodies	GN → AKI
4. Indirect toxicity—hypovolemia, shock, hyperviscosity, rhabdomyolysis, hemolysis, hyperbilirubinemia, DIC	Decreased RBF → AKI

AKI, acute kidney injury; ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation; GN, glomerulonephritis; RAAS, renin angiotensin aldosterone system; RBF, renal blood flow

parenchymal injury (Table 4). Parasitized RBCs and mononuclear cells infiltrate the tubulointerstitial cells and glomerular and peritubular capillaries. The inflammatory milieu helps in the release of various cytokines (tumor necrosis factor-alpha, interferon-gamma, interleukins 1, 6, and 8) and reactive oxidants. Increased production of reactive oxygen species and depleted antioxidant defense mechanisms contribute to renal parenchymal damage.[11] Severe malaria leads to widespread vasodilation and a reduction in systemic vascular resistance, similar to septicemia. This results in hypotension and decreased intraglomerular pressure.

Table 4: Pathogenesis of leptospirosis associated AKI and factors associated with AKI

Pathogenesis	Direct toxicity—acute tubulointerstitial nephritis	Leptospira invades the renal tubulointerstitium → the outer membrane of leptospires contains antigenic components such as lipopolysaccharide, cytotoxic glycolipoprotein (GLP), peptidoglycans and lipoproteins (LipL), especially LipL32 → produce structural damage by using LipL32, bind to TLR-2, activate NF-κB and stimulate the production of pro-inflammatory cytokines and chemokines (I NOS, MCP-1, TNF-α) → tubular epithelial cell injury, loss of brush border, tubular cell apoptosis and necrosis
	Indirect toxicity—hemodynamic instability, hyperbilirubinemia, rhabdomyolysis	ATN
Factors	Disease factor	Species—*L. interrogans*, *L. borgpetersenii* Risk—hypovolemia, hyperbilirubinemia, rhabdomyolysis
	Patient factor	Older age Comorbidities—preexisting CKD, DM Immunocompromised status

CKD, chronic kidney disease; DM, diabetes mellitus; iNOS, inducible nitric oxide synthase; LipL32, lipoprotein L32; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor-κB; TLR-2, toll-like receptor-2; TNF-α, tumour necrosis factor-α

Various other factors, such as hyperviscosity, intravascular coagulation, hemolysis, rhabdomyolysis, jaundice, lactic acidosis, complement activation, and increased production of reactive oxygen species, further reduce renal blood flow (RBF). This may be further aggravated by poor fluid intake and fluid loss due to vomiting and dehydration. Vasodilation may also activate the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and vasopressin release. These hormones initially try to compensate and maintain normal intraglomerular pressure, but ultimately result in a decompensated state leading to renal ischemia and ATN.[7] The hemodynamic instability in these patients depends on the disease severity and its associated complications.

Glomerular histopathology is usually normal, with occasional mononuclear cell infiltration, mesangial hypercellularity, and mesangial expansion. The glomerular capillary lumen may show infected RBCs. There may be deposition of C3 and *P. falciparum* antigen in the mesangium and along glomerular capillaries.[11] Immune complex glomerulonephritis with demonstrable *P. falciparum* antigen in glomeruli may be present transiently.[12]

In approximately 70% of cases, oliguria occurs with a mean duration of 7–10 days.[3] The renal pathology is usually ATN, which may manifest from cloudy swelling to tubular degeneration. Electrolyte abnormalities, such as hypokalemia and hyponatremia, may be present. Asymptomatic hyponatremia, seen in 25–67% of patients, is caused by hemodilution and sodium wasting. This may be proportionate to the clinical severity of malarial infection and resolves within a few days posttreatment. Hyperkalemia is usually associated with intravascular hemolysis, rhabdomyolysis, and oliguria. Hypophosphatemia due to respiratory alkalosis is observed in 6–30% of these cases. Hypomagnesemia may be observed in 30% of patients. Hypoxia from poor tissue perfusion results in lactic acidosis, which is a poor prognostic marker.[3]

There have been case reports of AKI with *P. vivax* infection in recent times. Some of these may occur due to mixed *P. vivax* and *P. falciparum* infections. The pathogenesis is likely similar to that of isolated *P. falciparum* infection.[13] Malarial AKI requires prompt management with artemisinin combination therapy (ACT). The artemisinin derivative does not require any drug dose modification in the setting of renal dysfunction and is devoid of any major adverse effects. Fluid resuscitation is usually required. However, overzealous fluid therapy in oliguric AKI may lead to pulmonary edema, to which severe malaria patients are prone due to myocardial dysfunction and acidosis. Dialysis support may be needed if there is the presence of severe metabolic acidosis, reduced urine output, fluid overload, hyperkalemia, or any combination of these. The superiority of hemodialysis (HD) over peritoneal dialysis (PD) was demonstrated in a randomized controlled trial (RCT) consisting of patients with severe malaria and sepsis-related AKI.[14] In a retrospective observational study from eastern India, in patients with malarial AKI, PD was found to be superior to HD (mortality 36 vs 20%). In this study, PD was chosen for patients either with hemodynamic instability or on ventilatory support.[15]

Leptospirosis

Leptospirosis, a zoonotic disease with variable clinical manifestations, is caused by pathogenic spirochetes of the genus *Leptospira*. In approximately, 5–10% of symptomatic leptospirosis cases, icteric leptospirosis occurs. It is rapidly progressive with multiorgan involvement, associated with mortality rates of 5–15%.[16] Usually, icteric leptospirosis is accompanied by fever, jaundice, and renal dysfunction, a syndrome known as "Weil's disease." Diffuse alveolar hemorrhage, manifesting as ARDS, rhabdomyolysis, and myocarditis may be part of this clinical syndrome. In the majority of cases, renal involvement occurs as the spirochetes infiltrate renal parenchyma. Urinary electrolyte wasting may result in hypokalemia and hypomagnesemia.[17,18] The nonoliguric AKI is frequently accompanied by hypokalemia in 40–87% of cases. Renal involvement in the long term may be complicated by CKD and persistent proximal tubular dysfunction leading to dyselectrolytemia. Tubular disorders usually precede the progressive worsening of the glomerular filtration rate (GFR).[17] In an outbreak in the Philippines, the duration of illness before admission, elevated baseline renal function, and lower platelet count were independent risk factors for AKI.[19] A multicenter study revealed that urinary and plasma neutrophil gelatinase-associated lipocalin levels were elevated in only those patients with leptospirosis who developed AKI.[20] The etiopathogenesis of AKI is multifactorial and includes direct bacterial invasion of renal tissue, hypovolemia, rhabdomyolysis, hyperbilirubinemia, and spirochete membrane protein-induced glycocalyx and endothelial injury.[17] Tubular dysfunction may be accompanied by inner medullary collecting duct vasopressin resistance, decreased Na–K–ATPase expression, and enhanced Na–K–2Cl cotransporter expression on tubules.[18]

Specific clinical features such as hypotension, jaundice, muscle pain, renal dysfunction, low hemoglobin, dyselectrolytemia, and neutrophilic leukocytosis were predicted to distinguish leptospirosis from other diseases in intensive care settings. Endothelial injury markers prominent in AKI settings are noted to be syndecan-1 and intercellular adhesion molecule-1 (ICAM-1). The difference in microtranscriptome profiles was also predicted as a possible biomarker for patients

with severe leptospirosis. Renal histology may reveal acute interstitial nephritis, ATN, and vasculitis. The presence and severity of AKI and reduced urine output are predictors of increased mortality. Long-term outcomes data after leptospirosis AKI are scarce.[19–23]

Though the main treatment remains antibiotics of the penicillin group only, azithromycin, chloramphenicol, doxycycline, and cephalosporins have also been used in routine clinical practice. Most patients can recover spontaneously with adequate supportive care, including fluid management and ventilatory support. The actual benefit of antibiotics remains to be proven. Early protective ventilatory support, pulse corticosteroids, and extracorporeal membrane oxygenation have also been used in severe leptospirosis complicated by diffuse alveolar hemorrhage in various case reports.[17–19]

Enteric Fever

Renal involvement in typhoid can be due to immune complex-mediated glomerular damage. It may present as hematuria, proteinuria, renal dysfunction, pyelonephritis, or glomerulonephritis.[24] IgA nephropathy and postvaccination nephropathy have also been reported. Typhoid nephritis due to untreated typhoid in adults has a very high mortality of around 20–30%.[25,26] AKI is very uncommon and may be a part of septic shock or intravascular hemolysis.[27]

Scrub Typhus

Scrub typhus, a mite-borne infection, is caused by the intracellular Gram-negative bacteria *Orientia tsutsugamushi*. The clinical presentation may be an acute febrile illness with the characteristic findings of high-grade fever, rash, and vague symptoms such as myalgia and headache. The majority of scrub typhus patients have mild symptoms, but a few patients develop severe complications such as disseminated vasculitis in multiple organs. ARDS and meningoencephalitis are the most important causes of mortality in these critically ill patients.[28] In a recent study from India, while using a PCR-based diagnostic test, 24% of all unexplained febrile patients with multiorgan involvement had scrub typhus illness.[29] Renal involvement may present as hematuria or proteinuria to AKI, nephrotic syndrome, and CKD requiring dialysis support. AKI incidence may vary from 8 to 40% depending on the AKI classification criteria used in different studies. Worse prognosis and prolonged hospitalization were demonstrated in patients with comorbidities such as underlying CKD, diabetes, and hypertension.[30,31] Severe disease may present with multiorgan involvement such as respiratory failure, gastrointestinal bleeding, coagulopathy, meningoencephalitis, myocarditis, AKI, and septic shock. The overall mortality ranges from 7 to 9%, with increased risk in oliguric AKI patients. The pathological mechanism of renal tissue involvement in scrub typhus is still unknown. The rickettsial invasion may induce severe vasculitis, leading to direct renal injury. However, renal biopsies may reveal inflammation, proliferation of the tubulointerstitial tissues, and ATN without any evidence of vasculitis.[31,32] A decrease in RBF, accompanied by extravasation due to severe vasculitis, may lead to AKI. Hypoalbuminemia associated with AKI may occur due to the leakage of serum albumin secondary to vasculitis. AKI may also occur due to pan-coagulation and rhabdomyolysis. Underlying CKD, older age, hypoalbuminemia, and time to hospital presentation after symptom onset are important risk factors for developing scrub typhus AKI. The mortality rates in AKI associated with scrub typhus may vary between 13.3 and 0.8% in two different studies.[32] The renal prognosis after AKI is good once the patient survives.[28–32]

Dengue

Dengue, an arthropod-borne viral infection, is caused by the dengue virus (DENV) of the Flaviviridae family. It has four serotypes transmitted by the *Aedes* mosquito. Severe dengue is a leading cause of severe illness with fatal outcomes in some Asian and Latin American countries. Dengue is prevalent in urban and semi-urban areas, particularly in tropical and subtropical climates worldwide. Its incidence in India has steadily increased during the last decade. The incidence and mortality have declined since 2017–2018, with mortality <1%.[33,34] There may be a gross underestimation of disease burden due to underreporting of cases.

Data regarding AKI in dengue (DAKI) are being reported mostly by retrospective studies. Prevalence may vary by ~4–16%, depending on the definition criteria of AKI. There is an increased prevalence of DAKI due to a manifold increase in dengue incidence. Proteinuria and hematuria are common manifestations and may be present even without AKI, but nephrotic-range proteinuria is not so common.[35–40] Blood product transfusion due to severe thrombocytopenia is required in patients with DAKI.[41,35] Patients with DAKI have greater mortality and prolonged hospitalization (see Table 5).[35–40] Common electrolyte disturbances include hyponatremia (from plasma leakage, hypotonic fluid therapy, or renal salt wasting) and hypokalemia. Risk factors for DAKI include coinfection with another virus or bacteria, transaminitis, hypoalbuminemia, metabolic acidosis, septic shock, multiple organ dysfunction, use of vasopressors or nephrotoxic drugs, old age, obesity, rhabdomyolysis, diabetes mellitus, and delayed hospitalization.[35–40] Pathogenesis of DAKI is due to direct viral cytopathic effects and other associated conditions. The predominant mechanism appears to be the inflammatory milieu generated due to the virus itself (see Table 6). DENV enters and proliferates in cells of the reticuloendothelial system, particularly the dendritic cells and endothelial cells. Primary viremia affects mononuclear cells and spreads through lymphatics and the circulatory system. The variable and intense host inflammatory response due to the infection has been attributed to the condition's variable severity. Though virus particles have been detected in various organs, including kidneys, it has also been isolated from the liver parenchyma and peripheral blood mononuclear cells.[42] Hypotension, rhabdomyolysis, hemolysis, endothelial cell involvement, cytokine release, and inflammatory mediators appear to precipitate DAKI.[43] Various glomerulopathies resulting from human tissue antigens have also been demonstrated through animal models and case reports.[43] CKD as a long-term complication of DAKI has not been specifically studied. In the absence of specific antiviral treatment, management is centered on treating disease-related complications. Dengue with warning signs is promptly managed with fluid transfusion and supportive care. The development of DAKI is a poor prognostic factor with higher mortality. The requirement of RRT must be individualized based on clinical circumstances.

Leishmaniasis

Microalbuminuria/mild to moderate proteinuria may be present in >40% of patients with visceral leishmaniasis, even in those with normal GFR. Interstitial nephritis with subtle glomerular changes can be seen on histopathological examinations. Patients with AKI are comparatively younger or very old, male, and may have jaundice and secondary infections more often than non-AKI patients. Antibodies produced in response to leishmaniasis can be trapped in glomerular capillaries as immune complexes, or directly attached to glomerular antigens through different mechanisms.[44] Mesangial proliferative, membranoproliferative, and collapsing focal segmental glomerulosclerosis

Table 5: Studies related to DAKI

	Type/region	*Prevalence of DAKI (%)*	*Criteria used*	*Remarks*
Mehra et al.[41] 2012 *n* = 223	Retrospective/South India	10.8 AKIN-I 5.4 AKIN-II 3.1 AKIN-III 2.2	AKIN	AKI was associated with increased mortality around 9%
Eswarappa et al.[35] 2012–2015 *n* = 2416	Retrospective/South India	3.4 AKIN-I 70.73 AKIN-II 23.17 AKIN-III 6.09	AKIN	Proteinuria, hematuria and AKI = 9.59% DAKI is associated with increased morbidity, mortality, prolonged hospitalization Mortality 39.28% in the AKI group
Diptyanusa et al.[36] 2012–2017 *n* = 1484	Retrospective/ Bangkok (Thailand)	4.8 Stage 1 AKI 83.1 Stage 2 AKI 4.2 Stage 3 AKI 12.7	KDIGO	Hypoalbuminemia, thrombocytopenia, transaminitis, coagulopathy, rhabdomyolysis, prolonged hospitalization, and mortality associated with DAKI 14.1% with AKI received dialysis, and 12.7% of patients from the AKI group died
Sultana et al.[37] 2018 *n* = 316 (children)	Retrospective/Dhaka (Bangladesh)	4.1 Risk 46.15 Injury 23.07 Failure 30.7	RIFLE	Proteinuria, hematuria, and AKI in 9.8% of the patients. 30.7% needed PD with 10% mortality. Increased mortality was associated with DAKI and severe thrombocytopenia
Patel et al.[38] 2016–2017 *n* = 620	Retrospective/North India	16.36 AKIN-I 34.4 AKIN-II 36.6 AKIN-III 28.8	AKIN	Proteinuria and hematuria occurred in 14.5 and 2.4% of total patients respectively. Need for dialysis support in 22.23% of these patients with morality in 15.55%. DAKI was more common in patients with severe dengue and prolonged hospitalization. Complete recovery of renal function in 83% of patients
Khalil et al.[39] 2008–2010 *n* = 532	Retrospective/Karachi (Pakistan)	13.3 AKIN-I 64.8 AKIN-II 18.3 AKIN-III 16.9	AKIN	Complete recovery of renal function in 81% of patients with mortality around 11.3% DAKI was associated with prolonged hospitalization, morbidity, and mortality
Mallhi et al.[40] 2008–2013 *n* = 667	Retrospective/ Malaysia	14.2 AKIN-I 76.8 AKIN-II 16.8 AKIN-III 6.4	AKIN	Complete recovery of renal function in 51.6% with mortality around 1.2% 4.9% had pre-existing CKD

AKIN, acute kidney injury network; CKD, chronic kidney disease; KDIGO, kidney disease improving global outcomes

Table 6: Pathogenesis of dengue-associated AKI

Mechanism	*Consequences*
Direct effect	Primary viremia affects mononuclear cells and spreads through blood and lymphatics. The variable and intense host inflammatory response to the infection has been predicted to cause the condition's variable severity
Indirect effect	Rhabdomyolysis, hemolysis, hypovolemia, and immune response. Rhabdomyolysis may be due to viral muscle invasion and cytokine myotoxicity due to inflammation
Glomerulonephritis	Common glomerulonephritis such as antiglomerular basement membrane (GBM) disease, IgA nephropathy, and lupus nephritis are being demonstrated. Proteinuria may be occurring in up to 75% of cases. It may sometimes present as nephrotic range proteinuria. Renal biopsy may reveal the mesangial deposition of IgG, IgM, and C3. Electron microscopy may reveal focal GBM thickening, mesangial cell proliferation, and dense spheric particles, which may be a part of the dengue virus
Autoimmunity	Autoimmunity induced by molecular mimicry

(FSGS) are common glomerular patterns seen in association with leishmaniasis-related renal disease.[44] Amphotericin B is considered the drug of choice for leishmaniasis.

Filariasis

Few filariasis patients may present with acute nephritic syndrome and immune complex-mediated glomerulonephritis. Though tubulointerstitial involvement may be more common, there may be immune complex deposition in the glomerular basement membrane. Eosinophilic proliferative GN, mesangioproliferative GN, membranoproliferative GN, and collapsing FSGS have also been reported in the available literature.[45,46] There may be a direct toxic effect of microfilariae on glomerular capillaries and tubulointerstitial tissue. Steroid coadministration with diethylcarbamazine (DEC) may attenuate the side effects related to treatment.[46]

Hantavirus

Hemorrhagic fever with renal syndrome (HFRS) manifesting as AKI and proteinuria may be due to significant tubular and glomerular involvement. Renal injury is usually immunopathological and is characterized by endothelial cell dysfunction and altered barrier function due to cytokine release. The prevalence of certain Human leukocyte antigens (HLA) genes in the specific population may influence the AKI severity. Increased vascular permeability without endothelial apoptosis, reflected by interstitial edema and a few patchy mononuclear infiltrates, has also been reported.[47] The mainstay of treatment remains ribavirin and supportive therapy.

Human Immunodeficiency Virus

Acute kidney injury in human immunodeficiency virus (HIV) is due to hypovolemia, septicemia, nephrotoxic drugs, immune reconstitution inflammatory syndrome, rhabdomyolysis, hemolysis, and obstructive uropathy. It carries very high morbidity and mortality. Risk factors for developing AKI include advanced HIV disease, older age, diabetes, underlying CKD, and hepatitis coinfection or other liver diseases.[48]

Conclusion

Acute kidney injury due to various tropical infections is considered a medical emergency in an intensive care unit (ICU) setting. Community-acquired AKI is more prevalent in tropical areas, as socioeconomic and environmental factors play a major role in disease development. Usually, these patients are young, have a low prevalence of underlying CKD and comorbid illnesses, and experience more severe renal dysfunction requiring dialysis support. The treatment should be disease-specific, centered on the primary disease and its complications. Due to resource constraints, the majority of these patients might not receive dialysis support despite being clinically indicated.

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REVIEW ARTICLE

Integrated Phenotypic and Endotypic Assessment: A Need for Precision Medicine in Asthma Management

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Abstract

Asthma is a long-term, persistent disease characterized by inflammation in the lower airways. Patients with asthma can be of any age, from young children to elderly people, and present with various clinical manifestations such as chest tightness, wheezing, coughing, and difficulty in breathing. Distinguishing these variations is essential for the personalized and adequate management of the disease. Based on the factors that trigger asthma attacks, the duration of the illness, or the prognosis, clinicians have worked to categorize asthma into various phenotypes. Different pathobiological mechanisms can lead to similar symptoms but might be applicable to different phenotypes. These apparent pathways are referred to as endotypes, which are introduced to understand the complex pathophysiological mechanisms of asthma. Endotypes can be Th2 high or Th2 low, depending on the level of Th2 cells involved in the pathogenesis of the disease. There is a need to discuss various clinical presentations of asthma in the form of "phenotypes" and its complex pathomechanisms represented as "endotypes." Here, in this article, we have reviewed some research articles and literature based on various observable and intrinsic characteristics related to asthma. The present status of asthma classification has been outlined to better understand the disease and its precision treatment.

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Introduction

Asthma is a disease with chronic respiratory disturbance in the lower airways, characterized by variable clinical phenotypes due to its heterogeneity in symptoms, triggers, age of onset, and inflammatory patterns. The intensity and frequency of symptoms in asthma vary over time, along with a variable limitation of expiratory airflow. The name "asthma" originates from the Greek word "aazein," which means "panting," although asthma is also mentioned in ancient Egyptian, Hebrew, Indian, and other medical literature.[1,2] Asthma affects nearly 1–18% of the population in various nations, highlighting the ubiquitous pattern of this disease. Based on the most recent information, it is estimated that there will be 100 million more asthmatics worldwide by 2025. The prevalence of asthma varies significantly between nations, geographical areas, and even within nations, depending on regions and societal categories.[3] According to the Global Burden of Disease (GBD), India had a total asthma burden of 34.3 million, representing 13.09% of the global burden.[3–5] Based on existing demographic patterns, it is estimated that in the next 20 years, the number of people over the age of 65 affected by asthma will likely double. The precise number remains undetermined, but severe asthma is estimated to affect 5–10% of individuals.[6] Patient counseling and education are essential parts of treatment. Although asthma cannot be cured, proper management and inhaled drugs can control the condition and improve patients' quality of life. Asthma development is influenced by both genetic history (genetic polymorphisms) and environmental factors (air pollution, allergens, tobacco smoke).[7] There are many risk factors responsible for developing asthma, commonly referred to as asthma triggers. The common triggers include dust mites, cold and flu, pollen, smoke, or increased physical activity.[8,9] Due to multiple lifestyle factors, urban areas are predominantly affected. Asthma is challenging to divide into subgroups due to its heterogeneity in clinical symptoms and triggers. Asthma management can be effectively developed and monitored using the Asthma Control Questionnaire (ACQ), as recommended by international guidelines.[10,11] It is crucial to identify specific molecular biomarkers that correspond to the individual pathogenic mechanisms responsible for different phenotypes. To promote this objective, we summarize key advancements in our understanding of asthma over the last several years and encourage more research into the opportunities and challenges. The current understanding of asthma and tailored treatment for different phenotypes is included in this review.

Triggering Factors for Asthma Exacerbations

There are various factors that can lead to an increase in asthma symptoms and result in a poor quality of life, as depicted in Figure 1.[12] The most significant factors are as follows:

- Respiratory infections: Recurrent respiratory viral infections are associated with the early onset of asthma, and these viral infections in later life are responsible for asthma episodes. When a person with asthma contracts a respiratory infection, such as the common cold or influenza, it can exacerbate their asthma symptoms and increase the risk of asthma attacks.
- Incorrect inhaler technique: Inhaled therapy plays a significant role in asthma management. However, it is observed that 80% of patients do not use their inhaler devices correctly, which compromises the effectiveness of their treatment.
- Suboptimal adherence: Suboptimal adherence refers to patients failing to take their medication as prescribed by their clinician.[13] In 75% of cases, patients fail to adhere to their prescribed medication regimen, leading to poor management of asthma symptoms and control.
- Obesity: Obese individuals are at higher risk for developing asthma, regardless of whether they have an allergy. Obesity can cause mechanical changes in the respiratory system, including reduced lung volumes, decreased lung compliance, and increased airway resistance. These changes can contribute to asthma symptoms and impaired lung function.[14]

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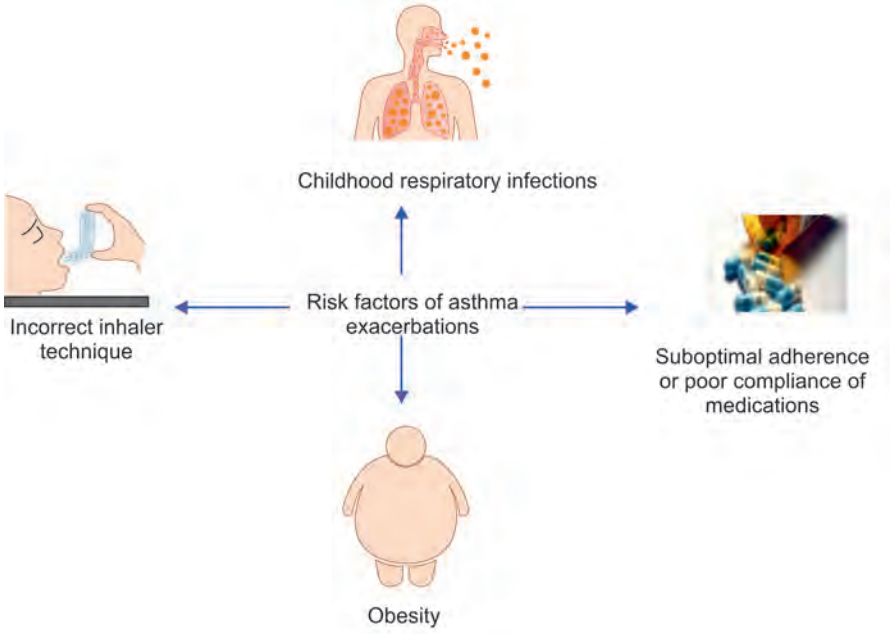

Fig. 1: Triggering factors for asthma exacerbations

Clinical Phenotypes in Asthma

Asthma phenotyping is a constantly evolving approach to achieve the goal of personalized medicine. Due to its complex pathomechanisms, there is a need for standard treatment and personalized medicine. Currently, strategies are being developed to link molecular pathways to phenotypes. To define and identify clinical phenotypes as well as the genetic processes of asthma, numerous cluster studies have employed methodologies that combine the effects of various relevant and significant factors in large cohort studies.[15,16]

The most common phenotypes observed in asthma patients, according to GINA guidelines, are:

- Allergic asthma: Allergic asthma often begins in childhood but may present at any age. These patients typically have a family history of allergic rhinitis, eczema, or food or drug allergies. It is defined based on sensitization to environmental allergens.[17] These patients exhibit eosinophilic airway inflammation and respond positively to inhaled corticosteroids (ICS).
- Nonallergic asthma: Patients with nonallergic asthma show a short-term response to inhaled corticosteroids (ICS). Their sputum cellular profile may be neutrophilic, paucigranulocytic, or eosinophilic. Nonallergic asthma is often diagnosed through negative results on skin prick tests or in vitro specific IgE testing for perennial allergens and local allergens such as *Dermatophagoides farinae*, *Aspergillus fumigatus*, *Candida albicans*, or *Staphylococcus aureus*.[18]
- Adult-onset (late-onset) asthma: This phenotype is mostly observed in women or adults who develop asthma for the first time in adulthood and are often non-allergic. Aging significantly affects methacholine response and airway hyperreactivity. Forced expiratory volume in one second (FEV_1) declines faster, especially among older adults or individuals with a smoking history exceeding 10 pack-years.[19] Despite treatment with inhaled and oral corticosteroids, high eosinophil counts may persist in late-onset eosinophilic asthma, often consistently over at least 5 years.
- Asthma with persistent airflow limitation: Some long-term asthma patients develop incompletely reversible or persistent airflow limitation due to airway remodeling.[20]
- Exercise-induced asthma (EIA): The immunological and inflammatory pathways of exercise-induced asthma are not well understood. These patients display low levels of eosinophilic inflammation. EIA occurs due to a sudden and significant increase in the volume of air entering the airways, necessitating heating and humidification.[21] This process triggers inflammatory, neurological, and vascular changes in sensitive individuals, leading to bronchial smooth muscle contraction and symptoms such as shortness of breath, wheezing, coughing up mucus, and chest tightness.
- Asthma with obesity: Obesity increases the risk of asthma and is associated with several other conditions such as atherosclerosis, high blood pressure, and type 2 diabetes. Obese females are more susceptible to asthma. Steroids, which are commonly used in asthma treatment, are less effective in obese individuals compared to lean patients.[14] Consequently, asthma control is often harder to achieve in obese patients.

There are various parameters based on which asthma can be classified into different phenotypes, as outlined in Figure 2 and Table 1.

Monitoring the Different Cellular Phenotypes

Asthma involves complex interactions between various cells in the airways, including inflammatory cells, structural cells, and immune cells. Monitoring the various cellular phenotypes in asthma is essential for understanding the disease's pathogenesis, predicting exacerbations, and customizing treatment strategies. These are some significant cellular phenotypes to monitor in asthma.[8,22]

Elevated levels of eosinophils in the airways are characteristic of eosinophilic asthma, a subtype of asthma associated with allergic inflammation. Monitoring eosinophil levels in sputum, blood, or bronchoalveolar lavage fluid (BALF) can help assess the degree of airway inflammation and guide treatment decisions, such as the use of corticosteroids or biologic therapies targeting eosinophils.

While eosinophils are often associated with allergic asthma, neutrophils play a prominent role in nonallergic or neutrophilic asthma. Monitoring neutrophilic inflammation in the airways can provide insights into disease severity and response to therapy, particularly in cases resistant to corticosteroid treatment. Dysfunction of airway epithelial cells contributes to asthma pathogenesis by promoting inflammation, mucus hypersecretion, and airway remodeling. Monitoring markers of epithelial cell damage or activation, such as cytokine release or gene expression profiles, can provide insights into disease progression and response to therapy.

Incorporating multiple modalities such as sputum cytology, bronchoscopy with BALF analysis, blood biomarkers, and advanced imaging techniques (e.g., positron emission tomography) can provide a comprehensive assessment of cellular phenotypes in asthma and facilitate personalized management strategies tailored to individual patient needs.

Identifying the specific inflammatory phenotype of asthma in an individual patient can help healthcare providers personalize treatment plans and optimize outcomes.

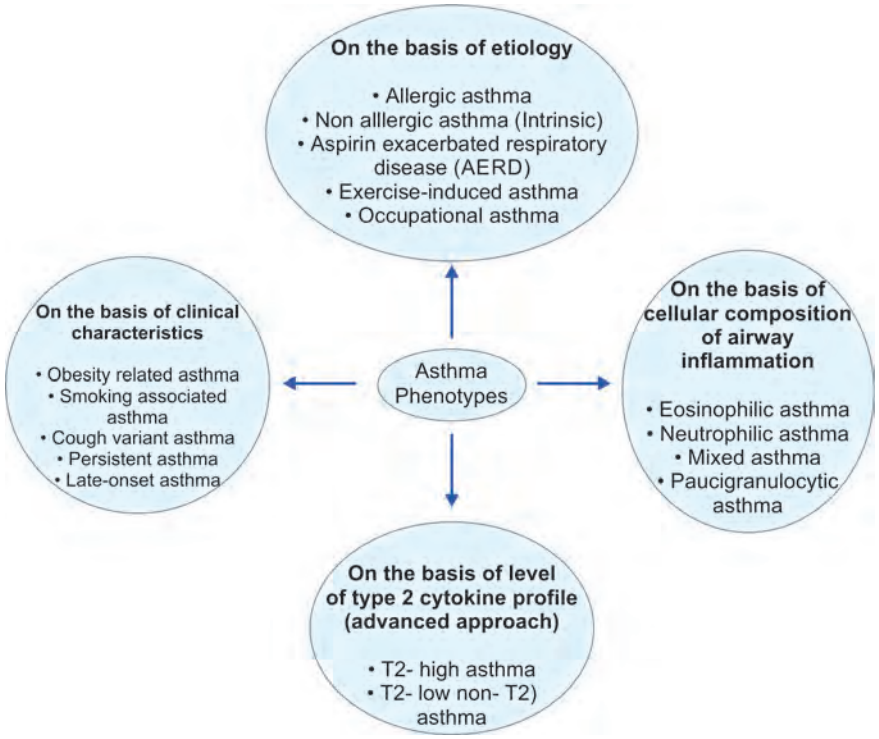

Fig. 2: Classification of asthma distinct phenotypes

Table 1: Classification of asthma phenotypes based on different parameters

S. no.	*Classification of asthma*	*Asthma phenotypes*
1.	Origin (cause)	Allergic asthma Nonallergic asthma Aspirin exacerbated respiratory disease (AERD) Asthma induced due to exercise Occupation related asthma
2.	Clinical symptoms	Obesity-associated asthma Cough variant asthma Smoking-related asthma Early-onset asthma Exacerbations—prone asthma Late-onset asthma
3.	T2 cytokine profile (modern approach)	T2-high asthma T2-low (or non-T2-high)
4.	Diseases associated with asthma	Eosinophilic granulomatosis with polyangiitis (EGPA) formerly—Churg–Strauss syndrome Allergic bronchopulmonary mycosis (ABPM) Asthma with bronchiectasis Immunocompromised asthma Asthma associated with alpha-1 antitrypsin deficiency (AATD)
5.	Cellular composition of airway inflammation	Eosinophilic asthma Neutrophilic asthma Paucigranulocytic asthma
6.	Treatment responsiveness and level of asthma management	Severe asthma Refractory asthma Difficult to treat asthma Uncontrolled asthma Steroid-resistant asthma Steroid-dependent asthma Mild asthma Benign asthma

Source: Popović-Grle et al.

A phenotype is significant for describing the clinical manifestation and triggers but still provides indiscriminate analysis for the diagnosis of asthma. Thus, there is a need to identify a personalized approach for its diagnosis, which can be fulfilled by understanding the mechanism of the disease, termed as "endotype." The endotyping approach, based on disease mechanisms, could eventually help in personalized asthma management.[8] Recently, the disease has been divided into two groups according to the Th2 inflammatory status: Th2-high and Th2-low asthma. Individuals with asthma can be classified into two groups: those exhibiting elevated levels of specific genes activated by IL-13—CLCA1, POSTN, and SERPINB2—referred to as "T2-high" asthma, and those with lower levels of this gene signature, termed "T2-low" asthma.[8,23] Type I hypersensitivity and eosinophilic inflammation are major characteristics of T2-high asthma, and these patients mainly respond to corticosteroids. Some distinct pathobiologic traits displayed by T2-high patients include a rise in subepithelial fibrosis and eosinophilic airways. Induced sputum eosinophilia accurately determines T2 gene expression. T2-low asthma comprises 30–40% of severe asthma patients and is more frequent among individuals with late-onset asthma, obese females, and highly symptomatic patients.[24,25] They exhibit poor response to inhaled steroid treatment.

Management of Asthma Exacerbations and its Treatment

Asthma exacerbations (AEs) can occur as the outcome of acute symptoms that involve the aggravation of shortness of breath, wheezing, dry cough, chest tightness, or any combination of these symptoms. An increase in respiratory rate, an elevated pulse rate, and reduced lung function as evaluated by FEV_1 (forced expiratory volume in one second) and peak expiratory flow (PEF) are some common predictors of acute exacerbations in asthma. Here are some essential elements of managing asthma:

- Better assessment: If someone has asthma or has been diagnosed with it, it's critical to speak with a doctor so they can provide an accurate diagnosis and help create a specialized asthma action plan.
- Recognition and prevention of triggers: It is important for an asthmatic patient to recognize and prevent asthma triggers. Allergens (dust mites, pollen, pet dander),

respiratory diseases, tobacco smoke, air pollution, exercise, and specific drugs are a few examples of common triggers.
- In medications:

Controller drugs are used every day to avoid asthma symptoms and lessen inflammation of the airways. They consist of long-acting beta-agonists (LABAs), leukotriene modifiers, and inhaled corticosteroids.

Short-acting beta-agonists (SABAs) are bronchodilators that work quickly to relieve asthma attacks or other acute symptoms.

Biologic medications: These drugs can help control symptoms of severe asthma. They are frequently taken in addition to other medicines.

- Create an asthma action plan. The NHLBAC Asthma Expert Working Group suggested some priority areas that need to be addressed for better asthma control.[26]
- Use of fractional exhaled nitric oxide (FENO) for the diagnosis of asthma, selecting treatments, and tracking their effectiveness.
- Removing indoor allergens (such as dust mites and pets) can improve asthma management.
- Regulating medicine dosage for asthma and recurrent wheeze.
- Long-acting antimuscarinic (LAMA) medications used in combination with inhaled corticosteroids (ICSs) to treat asthma.
- Asthma control with immunotherapy.
- In adults with severe asthma, bronchial thermoplasty (BT) can be preferred.

Discussion

Assessment of the future risk of asthma exacerbations is still unclear to date. Thus, in asthma assessment, clinical evaluations such as age of onset, presence or absence of atopy, and other exposures are important for better diagnosis and response to treatment. Poor adherence to medications in asthma leads to inadequate control of underlying inflammation. Accurate endotyping of asthma can reflect its natural history and help predict treatment response. Thus, prospective studies are needed to understand asthma endotypes that might be useful in clinical practice in the future. Comprehensive asthma control involves managing symptoms, improving lung function, and preventing acute episodes to promote overall well-being and quality of life for individuals with asthma.

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REVIEW ARTICLE

A Concise Review on Different Aspects of Influences of Coronavirus Disease 2019 on Liver and Metabolic Changes

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Abstract

Purpose: Coronavirus disease 2019 (COVID-19) is a viral disease, causing a deadly situation around the world. Significant cases need hospitalization and intensive care. Obese, diabetic, and immunosuppressed people have poor prognosis. Here, we are establishing the link between liver disease and COVID-19.

Methods: A thorough investigation was performed across several articles and databases from 2020 to 2022 to assess the impact of COVID-19 on the liver.

Results: As of June 2022, we identified 75 articles in electronic databases discussing the hepatic impact of COVID-19.

Conclusion: This review delves into the impact of COVID-19 on liver metabolism, specifically how it exacerbates morbidity and mortality in individuals with preexisting chronic liver disease (CLD).

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Introduction

A strong host immunological response is crucial, as the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic has shown. SARS-CoV-2, the virus responsible for Coronavirus disease 2019 (COVID-19), triggers significant immunological dysregulation, often leading to the development of a cytokine storm.[1] In COVID-19, elevated cytokine levels are prevalent and are linked to lung injury and multiorgan failure,[2] with a severe cytokine storm likely playing a key role in disease progression.[3] Key cytokines such as interferon (IFN)-γ–induced protein 10, interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), IFN-γ, macrophage inflammatory protein 1, and vascular endothelial growth factor are notably elevated in COVID-19 patients.[4] Among these, IL-6 levels, in particular, have been linked to disease severity and mortality.[5] COVID-19 manifests in a broad spectrum of immunological responses and clinical symptoms, but those who fail to control viral replication are more likely to experience immune dysregulation that contributes to disease progression (Fig. 1). Additionally, the global rise in obesity has led to metabolic conditions such as insulin resistance, diabetes, and chronic liver disease (CLD), posing a significant public health challenge. CLD arises from conditions such as nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), chronic hepatitis B and C, among others. Chronic liver inflammation, including nonalcoholic steatohepatitis (NASH), and fibrosis can advance to severe liver conditions such as cirrhosis and hepatocellular carcinoma (HCC), collectively responsible for almost 2 million fatalities each year.[3] Hepatocytes, comprising the predominant population of liver cells, are essential for sustaining both adaptive and innate immune processes. The liver plays a role in maintaining immunological homeostasis by dispersing gastrointestinal microbes and dietary antigens throughout the body and by creating soluble chemicals that are crucial for a proper immune response.[3] Nevertheless, liver impairment might hinder the immune system's ability to detect and eliminate pathogens by decreasing the synthesis of essential innate immunity proteins. Cirrhosis and chronic liver disease are characterized by immunological dysregulation, which impacts the liver's ability to maintain homeostasis.[6] In the multisystem immune response, CLD impairs the liver's homeostatic role. Liver cell damage triggers a systemic inflammatory response by activating specialized immune cells in the bloodstream and increasing the levels of pro-inflammatory molecules, including TNF-α and interleukin-6 (IL-6), in the blood serum.[3]

This immune dysfunction heightens susceptibility to infections, particularly in patients with CLD, who are at increased risk of severe COVID-19 outcomes. Individuals with cirrhosis face significantly higher mortality and morbidity rates in the context of COVID-19 due to immunological dysregulation[7] (Fig. 2). Patients with decompensated cirrhosis have a lower risk of dying from COVID-19 after receiving a liver transplant, which improves their liver function. Infection with SARS-CoV-2 can impact liver function in otherwise healthy people, and it can worsen chronic liver disease in people who already have it. Alanine transferase (ALT) and aspartate transferase (AST) levels that are abnormally high are common in COVID-19 patients.[3] Acute liver damage and cholestasis may be caused by cytokine storms; however, the exact ways by which SARS-CoV-2 impacts liver function are still unknown.[8] While it is still uncertain whether SARS-CoV-2 directly infects hepatocytes, immune dysregulation associated with the virus likely contributes to liver pathology in COVID-19. There is ongoing research on the impact of antiviral and anti-inflammatory medicines on the liver in COVID-19 patients, as the disease has been associated with a range of liver diseases, such as fatty liver disease, hepatitis, HCC, cirrhosis, and ALD.[3]

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Coronavirus-related Liver Injury Pathogenic Mechanisms

Hepatocytes are Damaged by Angiotensin-Converting Enzyme 2/ Dipeptidyl Peptidase 4

Renin-angiotensin system (RAS) proteins, produced by Ras sarcoma oncogenes, are a subset of small guanine triphosphatases (GTPases) that bind GDP and GTP, playing key roles in regulating cellular functions such as proliferation, migration, adhesion, and differentiation.[9] Numerous human disorders are associated with aberrant RAS signaling. ACE2 is an enzyme that increases the effects of angiotensin II, which in turn causes inflammation, endothelial cell migration, and atherosclerosis.[10] ACE2 is expressed in alveolar, intestinal, and arterial smooth muscle cells.[11] High levels of ACE2 receptors in the gastrointestinal epithelium allow viruses to enter bile duct cells, impairing liver function.[11] Herath et al. identified ACE2 in epithelial cells of the liver and bile ducts, with

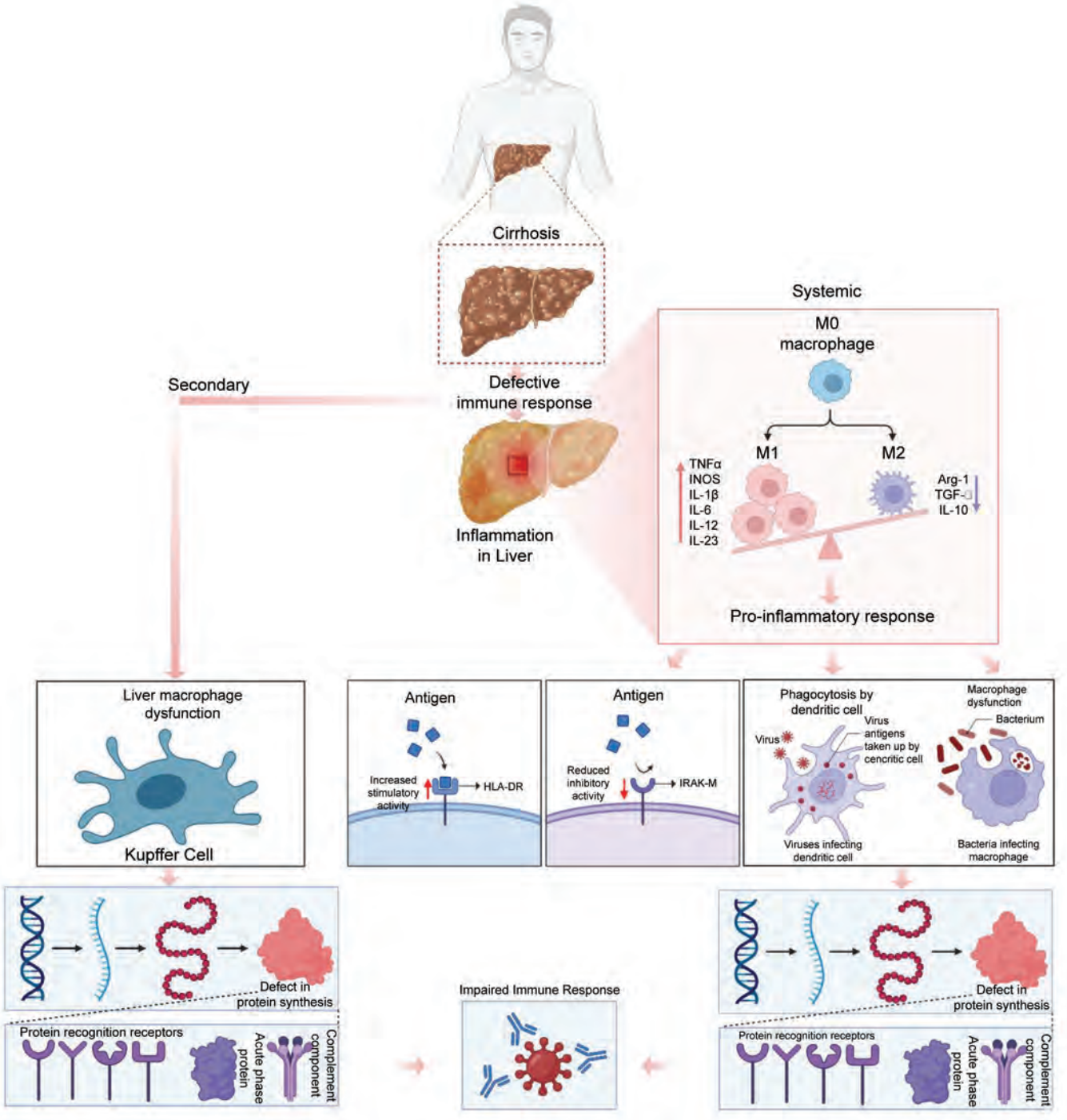

Fig. 1: SARS-CoV-2 pathophysiology. Cytokine storm may occur after SARS-CoV-2 infection due to inappropriate or inefficient pathogen recognition, immune evasion, exaggerated effector feedback, cytokine production, or failure to return to homeostasis. Fajgenbaum and June described the pathways. Showing drugs inhibit signaling pathways. Janus kinase–signal transducer and activator of transcription 3; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; Treg, regulatory T cell

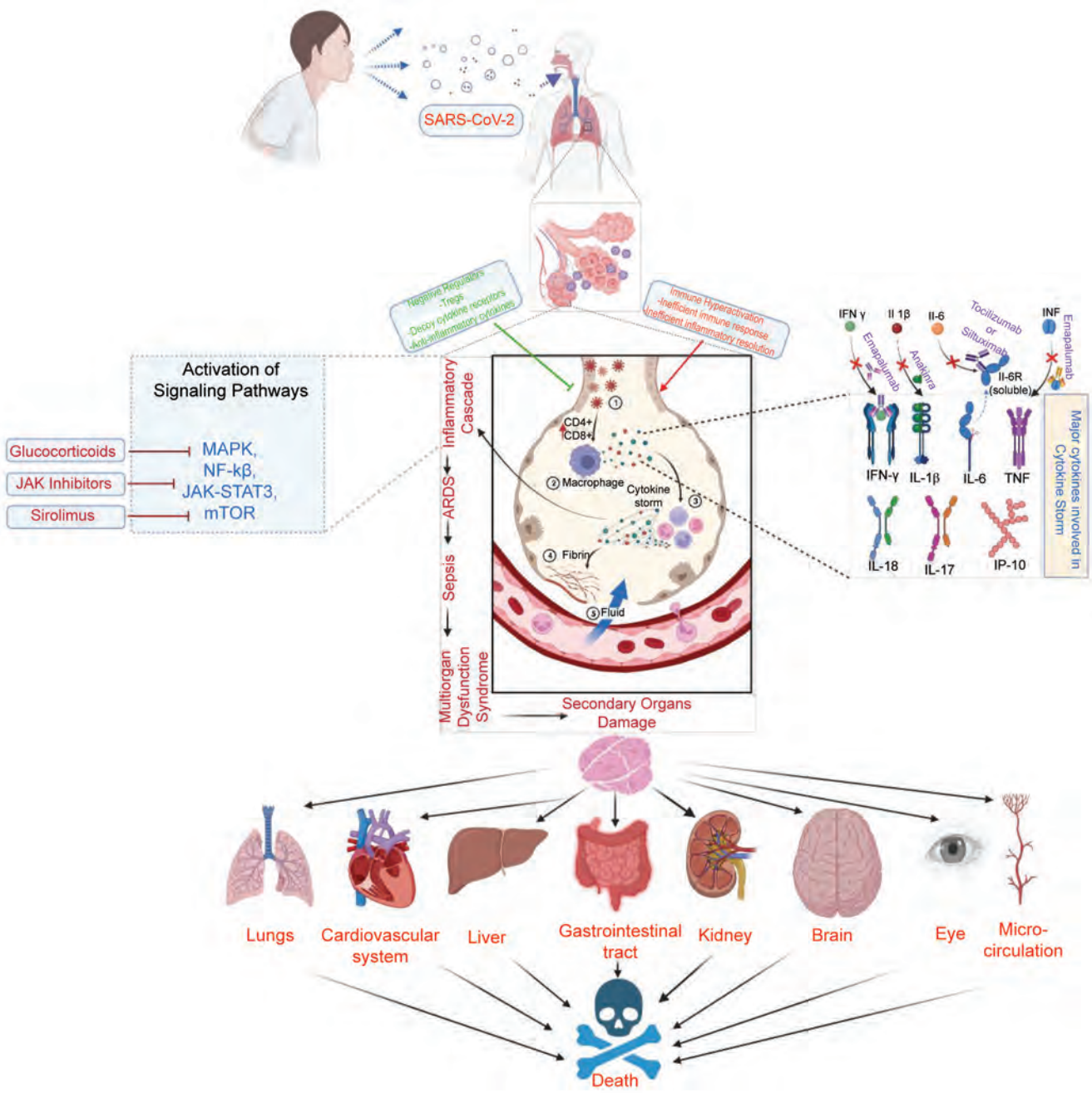

Fig. 2: Cirrhosis patients often have immunodeficiency. Cirrhosis disrupts liver architecture, cellular organization, and protein synthesis. Cirrhosis affects circulating and intestinal immune cells, causing abnormalities in cellular and soluble immune response components in the liver as well as systemically. CXCR1/2, chemokine receptor 1/2; HLA-DR, human leukocyte antigen-DR; IRAK-M, interleukin receptor-associated kinase 3; MERTK, c-mer proto-oncogene tyrosine kinase; PD-1, programmed cell death-1; TGF-β, transforming growth factor β; TIM-3, T-cell immunoglobulin and mucin-domain containing 3.

higher expression in the bile duct compared to liver tissue.[12] Elevated ACE2 expression in hepatocytes may induce compensatory bile duct proliferation, culminating in hepatic injury.[11]

In particular, SARS-CoV-2 has the ability to bind to ACE2 receptors on bile duct cells, which in turn impairs liver function. The lack of viral inclusions in COVID-19 liver biopsies raises the possibility that bile duct epithelial destruction, rather than direct hepatocyte infection, is the cause of liver damage in these patients. Liver cirrhosis has been linked to increased ACE2 expression in hepatocytes.[11] Normally, ACE2 is found in vascular endothelial cells, bile duct cells, and perivenular hepatocytes, but in cirrhotic livers, it is expressed in most hepatocytes, as well as bile ducts and vascular endothelium.[12,13] Elevated ACE2 levels enhance the susceptibility of hepatocytes to coronavirus infection, increasing the risk of liver damage in patients with cirrhosis who contract COVID-19.[11]

A target for MERS-CoV is dipeptidyl peptidase 4 (DPP-4),[11] which is abundantly expressed in the liver and cleaves various immune-regulating chemokines and peptide hormones.[14] Researchers developed a genetically modified mouse model with a human DPP-4 gene, optimized for codon

usage, demonstrating that MERS-CoV can infect hepatocytes through interaction with DPP-4, causing liver damage.[15] The hDPP4 transgenic mouse model displayed mild liver injury 5 days after MERS-CoV infection, including scattered hepatocyte necrosis in sinusoids, macrophage infiltration, and Kupffer cell activation.[11,16] By day 9, less hepatocyte necrosis was observed, but fatty changes were evident.[11]

Injuries Caused by the Immune System

Coronaviruses stimulate immune responses aimed at eliminating the virus, with the liver playing a key role in immune function.[11] The hepatic acute-phase response, which includes immune cell cytokines, is critical in protecting liver function from pathogens.[17,18] CD8+ and CD4+ T lymphocytes help balance immune responses to coronaviruses and immune tolerance. Although CD4+ T cells are present in the inflammatory organs, they make up the bulk of the immune cells in the liver when SARS-CoV-2 is present. When the number of CD4+ T cells in the liver decreases, the activation of B cells decreases as well. This leads to lower levels of SARS-CoV-2-specific antibodies and pro-inflammatory cytokines, like IL-1, IL-6, and TNF-α, which hinder the liver's capacity to expunge the virus.[11,19] CD4+ T cells are more susceptible to SARS-CoV and MERS-CoV compared to CD8+ cells, with severe coronavirus infections associated with hepatocyte inflammation, steatosis, sinusoidal proliferation, Kupffer cell hyperplasia, and immune cell infiltration.[11] Cytokines may lead to ischemia, hypoxia, and hepatocyte necrosis. Modifications in blood protein levels, such as cytokines and chemokines (such as TNF, IL-6, and IL-18), are associated with early coronavirus infection.[17,20] In a study conducted by Duan et al., liver failure was associated with elevated levels of IL-1, IL-6, and IL-10, suggesting a possible link between cytokine storms and hepatic injury in SARS patients.[11] Elevated levels of IL-2-receptor and IL-6 in SARS-CoV-2 patients are linked to disease severity. Th1 and Th2 cytokines, such as TNF-α, IFN-γ, IL-6, IL-8, IL-4, and IL-10, are elevated in SARS-CoV-2 patients, while IFN-γ, TNF-α, IL-15, and IL-17 increase during acute MERS-CoV infection. These findings raise the intriguing prospect that cytokine storms and SIRS contribute to the liver damage inflicted by coronavirus infections.[21–23] However, the mechanisms underlying pro-inflammatory cytokine activity and liver injury remain unclear.

Hypoxia and Ischemia

Over 40% of SARS-CoV-2 patients require oxygen therapy,[24] and elevated serum transaminases may indicate hypoxic liver injury due to oxygen dysregulation.[25] Acute respiratory distress syndrome, SIRS, and multiple organ failure can cause hypoxemia,[26,27] ischemia, and shock, with microthrombi potentially disrupting liver perfusion. Hepatic sinusoidal endothelial cells respond to inflammatory signals, contributing to liver damage. Ischemia-reperfusion injury (IRI) in the liver, characterized by reactive oxygen species (ROS), Kupffer cell activation, neutrophil infiltration, and calcium overload, can trigger inflammation and cellular injury. Under ischemic and hypoxic conditions, glycogen depletion and ATP exhaustion can inhibit hepatocyte survival signaling, leading to necrosis.[11] Hypoxia in ARDS patients can also increase oxidative stress responses, elevating ROS levels.[28] ROS and lipid peroxidation products regulate redox reactions and enhance the secretion of pro-inflammatory mediators, exacerbating liver injury.[11] These alterations in pathophysiology have the potential to worsen hypoxia and hepatic ischemia, which in turn hinders hepatotoxic chemical secretion and hepatocyte function.[29]

Thrombosis

MERS-CoV, SARS-CoV, and SARS-CoV-2 are known to induce hypercoagulable states, elevating the risk of thrombosis.[30] In the first phase of COVID-19 investigation, 36.2% of patients experienced thrombocytopenia and 46.4% had raised D-dimer levels; the cases with the most severe symptoms had the highest occurrences.[31] Microvascular thrombosis may contribute to end-stage organ damage and impaired liver function.[11] Historically, elevated serum alkaline phosphatase (ALP) levels have been considered a risk factor for ischemic stroke and hemorrhagic transformation.[32] Patients with thrombotic events in COVID-19 showed markedly high ALP levels, whereas those without thromboembolic events had normal or mildly increased ALP levels.[31] Furthermore, COVID-19 patients are at higher risk for disseminated intravascular coagulation (DIVC).[11] Patients infected with SARS-CoV-2 have a worse prognosis if they have elevated levels of fibrin degradation products, prothrombin time, and D-dimer. The autopsies conducted in Wuhan showed a variety of pathologies, including thrombosis, sinus congestion, hepatocyte degeneration, lobular necrosis, neutrophil infiltration, and lymphocyte and monocyte infiltration in the portal area.[11] These results provide more evidence that hypercoagulability in COVID-19 could exacerbate liver injury.

Drug-based Hepatic Injury

Subsequent to alcoholic and non-alcoholic fatty liver disease and viral hepatitis, drug-induced hepatotoxicity is the third most prevalent reason for liver damage.[33] Clinical studies and animal experiments have shown that antibiotics, anti-cancer drugs, antitubercular drugs, saikosaponins, and antimalarial drugs can all contribute to liver damage.[34–36] There were no effective treatments for SARS, but ribavirin and corticosteroids were frequently used.[37] The anti-inflammatory properties of corticosteroids and the broad-spectrum antiviral action of ribavirin made them attractive alternatives.[11] However, ribavirin withdrawal has been associated with hepatotoxicity, including hemolysis.[37] Most SARS-CoV-2 patients have a fever and take acetaminophen.[11] Acetaminophen, commonly used to treat fever in most SARS-CoV-2 patients, can cause liver damage or even failure when overdosed.[38] Lopinavir and ritonavir are additional medications that have been used to treat COVID-19. There is speculation that HIV protease inhibitors might prevent the replication of SARS-CoV-2. Wang et al. identified a link between hormone therapy, HIV protease inhibitors, and liver injury. Intravenous methylprednisolone has also been associated with acute liver injury, though the evidence for oral methylprednisolone is limited.[11]

Liver Disease in the Context of Coronavirus Disease 2019

Pandemic SARS-CoV-2 highlights the importance of a robust host immune response.[39] A cytokine storm is a hallmark of immunological dysregulation, which has been associated with SARS-CoV-2, the COVID-19 virus.[39,40] Severe cytokine storms are a critical component of the illness course in COVID-19 patients, and elevated cytokine levels have been linked to lung injury and multi-organ failure. Interleukin-1 and interleukin-6 levels, TNF, interferon-gamma (IFN-γ), macrophage inflammatory protein 1, and vascular endothelial growth factor are frequently elevated in COVID-19 patients.[3] In instance, poorer outcomes and higher death rates have been associated with raised IL-6 levels; specifically, worse outcomes and increased mortality have been associated with greater IL-6 levels.[41] People with impaired SARS-CoV-2 replication control are at increased risk for immunological dysregulation and serious disease.

Additionally, the global rise in obesity, insulin resistance, and endocrine disorders like

diabetes, alongside CLD, has amplified public health concerns.[39,40]

Nonalcoholic fatty liver disease and ALD are prevalent etiologies of chronic liver disease, while hepatitis B and C also play a substantial role. CLD may result in hepatic inflammation, NASH, liver fibrosis, and severe diseases including hepatocellular carcinoma and cirrhosis. Annually, cirrhosis, viral hepatitis (predominantly hepatitis B and C), and hepatocellular carcinoma (HCC) account for over 2 million fatalities worldwide.[39,40]

Hepatocytes, the primary cells of the liver, are vital for both innate and adaptive immune responses,[6,41] since they synthesize key proteins required for immune functions and contribute to liver immunological homeostasis by obstructing the ingress of microorganisms and food antigens from the gastrointestinal tract.[41] Preexisting hepatic damage hinders these processes, compromising protein synthesis essential for innate immunity and the recognition of pathogen-associated molecular patterns (PAMPs).

Dysregulation of the immune system is a characteristic of chronic liver disease and cirrhosis.[6] CLD compromises the liver's regulatory role in systemic immune responses, with damaged hepatocytes triggering systemic inflammation, activating circulating immune cells, and increasing pro-inflammatory cytokines like TNF-α and IL-6. This immunological impairment renders CLD patients susceptible to infections. Individuals with decompensated cirrhosis or those with inadequate responses to chronic liver disease treatment face a heightened mortality risk from COVID-19, as both cirrhosis and SARS-CoV-2 infection contribute to increased immunological dysregulation.[3] Liver transplantation is the sole option for these patients that can diminish COVID-19-related morbidity and mortality to levels akin to the general population (Fig. 3).[42]

SARS-CoV-2 may adversely affect liver health, even in previously healthy individuals, with particularly alarming implications for patients with CLD. COVID-19 patients frequently display abnormal liver function tests, with sudden increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The precise impact of SARS-CoV-2 on hepatic function, including the potential direct infection of hepatocytes by the virus, remains ambiguous. Nonetheless, liver damage may arise from severe cytokine storms, which can transpire independently of COVID-19; hence, immunological dysregulation generated by SARS-CoV-2 is likely a critical element in liver disease associated with COVID-19 (Fig. 1).

Infection with Severe Acute Respiratory Syndrome Coronavirus 2 and Preexisting Liver Disease

Nearly 1 million people die every year as a result of complications related to chronic liver disease.[11] Consequently, additional research into the effects of coronaviruses on various preexisting liver diseases is necessary. There is evidence of transcription and replication activities, as well as long-term liver damage after coronavirus infection, which calls for more study.[43] The inclusion of coronavirus-induced liver injury in persons with preexisting hepatic conditions may lead to exacerbated hepatic dysfunction, particularly in patients with severe liver diseases. The 2003 SARS epidemic demonstrated that comorbidity with hepatitis B could lead to exacerbated liver damage.[44] Nevertheless, if COVID-19 induces immune-mediated hepatic damage, the immunocompromised condition of individuals with cirrhosis and cancer may prove more beneficial than detrimental.[45] Moreover, individuals with liver cirrhosis or cancer frequently exhibit immunocompromised

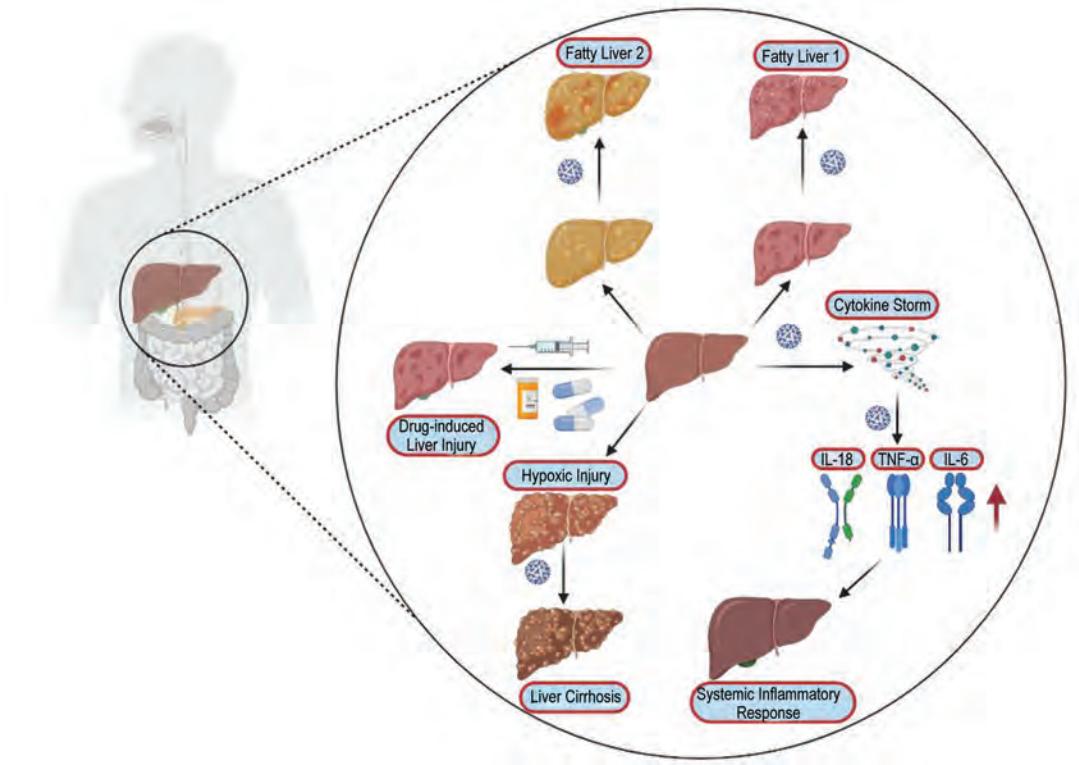

Fig. 3: Different effects on the liver of a COVID-19 patient

states, rendering them more susceptible to SARS-CoV-2 infection. The American Society of Clinical Oncology (ASCO), The American Association for the Study of Liver Diseases (AASLD), The European Society for Medical Oncology (ESMO), The European Association for the Study of the Liver (EASL), and The International Liver Cancer Association (ILCA) have all issued clinical practice guidelines for liver disease to healthcare professionals worldwide.[11] Here is a summary of the ways in which coronavirus outbreaks have affected the beginning, development, and treatment of four different liver diseases: issues related to the liver, including viral hepatitis, scarring, cancer, and transplantation.

Coronaviruses and Hepatitis B and C

Worldwide, >2 billion individuals are impacted by hepatitis B and C, with 350 million living with chronic infections.[11] Research shows that 3.6% of COVID-19 patients have a history of hepatitis B, while 0.6% have a history of hepatitis C.[46] A study conducted in Shanghai among 324 COVID-19 patients found that 6.5% were positive for HBsAg.[47]

Since then, researchers have paid special attention to how coronavirus infections affect the development of HBV and HCV.[11]

Patients with SARS infected by HBV and/or HCV had a higher propensity for liver damage and severe hepatitis due to enhanced hepatitis virus proliferation during SARS-CoV coinfection.[11]

Nonetheless, in cases where long-term hepatitis B patients and HBsAg-negative persons were infected with SARS-CoV, no significant differences in adverse clinical outcomes were seen. Individuals with acute hepatitis and/or noncompensated liver cirrhosis who develop SARS face an elevated mortality risk.[11]

In Wuhan, 23/1099 SARS-CoV-2 patients were infected with HBV, accounting for 2.4% of mild cases and 0.6% of severe cases, according to a study.[48] COVID-19 patients also showed a higher death rate (32.9% vs 15.3%) than HBV-negative individuals.[49] Liu et al. reported that the median duration for viral clearance in COVID-19 patients with HBV infection was 21 days (95% CI: 19–29), which exceeded the 14 days (95% CI: 13–21) observed in those without HBV infection.[50] Research into the underlying mechanism is necessary to improve COVID-19 treatment recommendations in light of these results, which indicate an interaction between coronavirus infections and viral hepatitis.

When clinicians construct personalized treatment strategies for individuals with hepatitis B and/or hepatitis C, the existence of coronavirus infectious disease and its consequences should be taken into account. Anti-HBV/HCV therapy should be started in three states, according to the AASLD guidelines: (1) newly diagnosed HBV/HCV cases; (2) individuals without SARS-CoV-2 infections; (3) if SARS-CoV-2 infection resources (drug treatments, staff for therapeutic approval, blood tests, and follow-up facilities through teleconference) have not been deployed.[11]

HBV reactivations have been recorded in individuals with HBV infection after taking tocilizumab or prednisone; consequently, these two medicines should not be utilized to prevent HBV reactivation. According to AASLD standards, long-term HBV therapy may be administered to patients with early hepatitis B and should be maintained as long as the individuals adhere to the treatment regimen, regardless of SARS-CoV-2 infection status. Consequently, therapeutic strategies for COVID-19 patients with advancing liver disease must be formulated to mitigate the risk of hepatic injury and potential organ failure, as both the advantages and disadvantages of an intervention must be evaluated throughout COVID-19 management.[11]

Antiviral medication and high-dose hormonal treatment for hepatitis B patients may trigger HBV replication and reactivation during SARS-CoV-2 infection if antiviral therapy is stopped. Indeed, studies have shown that using lopinavir and ritonavir to treat HBV/HCV patients can raise the risk of liver damage.[11] Prolonged administration of ribavirin may induce significant hepatotoxicity in people with hepatitis C, as evidenced by a clinical trial, potentially leading to metabolic alterations in the body.[51] Moreover, patients who are HBsAg positive and have positive hepatitis B core antibodies and who received corticosteroids exhibited an elevated risk of hepatitis B reactivation, which is associated with the dosage of corticosteroids administered.[11,52] Consequently, in the context of corticosteroid administration, the clinical status of chronic HBV infection must be meticulously evaluated, and nucleotide analog therapy should be contemplated to mitigate the risk of hepatitis B reactivation or hepatitis exacerbation.

Coronaviruses' Impact on Liver Cancer

Individuals with hepatocellular carcinoma face an elevated risk of catching the coronavirus, particularly if undergoing chemotherapy or immunotherapy within the facility.[53] COVID-19 was found in 0.79% (12/1,524) of cancer sufferers at a Wuhan hospital, which was greater than the community's rate during the same time.[54] Because of the COVID-19 pandemic's rapid spread, half of them were receiving cancer treatment continually.[11] Furthermore, cancer patients had a worse prognosis than COVID-19-only individuals, with death rates ranging from 5 to 20%.[55] To mitigate severe COVID-19 outcomes, persons with liver cancer should undergo certain treatments and implement measures. The absence of evidence-based clinical resources in overwhelmed institutions has impeded standard radiological assessments, pathological evaluations, and cancer treatments for patients with liver cancer.[11] The European Association for the Study of Liver Cancer (EASL), the European Society for Medical Oncology (ESMO), and the International Liver Cancer Association (ILCA) have issued specific recommendations for the surveillance, examination, and treatment of hepatic cancer patients infected with SARS-CoV-2.[11] The Society of Surgical Oncology recommends surgical removal of the gall bladder, pancreas, or liver from any patient with a metastatic tumor.[56] Patients who require surgical and also systemic chemotherapy might seek neoadjuvant chemotherapy to postpone surgery. Cancer screening for the liver and esophageal varices has been delayed, with the exception of those at high risk.[11] The American Association for the Study of Liver Diseases recommends delaying hepatocellular carcinoma surveillance for two months after weighing the benefits and drawbacks of doing so in COVID-19 patients. Retrospective studies have shown that half-yearly surveillance is more effective than annual surveillance in increasing the likelihood of early identification and improving patient survival.[57] Postponing screening for over a year can lead to liver cancer progressing, missing the window of opportunity for surgery, and potentially organ failure or death. Because the yearly HCC incidence is 2–3%, delaying HCC screening for a short time is likely appropriate, as 98% of persons will not acquire HCC during the surveillance interval.[58] These therapy adjustments may have elevated the incidence of variceal bleeding and liver cancer distant metastasis. Furthermore, several institutions have postponed live donor liver transplants and locoregional treatment for liver malignancies, thereby worsening the development and death of hepatic cancer. Many institutions are recommending specific measures such as employing serum biomarkers, expanding outpatient therapies (such as albumin transfusions), and integrating telemedicine.[11]

Coronaviruses and Liver Transplantation

Because of their immunosuppressed status, individuals with liver transplants are more likely to become infected and/or develop a serious course of COVID-19. Patients on immunosuppressant medications are at increased risk of contracting SARS-CoV-2, an illness that can cause devastating complications (1.4% mortality, 5.0% ICU admission, and 15.7% severe illness).[11] In a study involving 151 liver transplant recipients, Ji et al.[59] found that COVID-19 development was linked to NAFLD, being male, being older than 60, having a higher body mass index (BMI), and being male.[59] Their NAFLD is not correlated with their history of liver transplantation on its own. Research has also shown that NAFLD can independently predict the development of COVID-19 [odds ratio (OR) 6.4; 95% confidence interval (CI) 1.5–31.2]. Hepatic impairment and a prolonged viral clearance time are additional risks associated with NAFLD. Research has shown that there is a strong correlation between moderate and elevated fibrosis 4 (FIB-4) scores and an increased risk of developing severe COVID-19. As a result of their metabolic inefficiency and underlying hepatic condition, people with NAFLD are at a higher risk.[11]

Fatty Liver Interrelated with Coronavirus Disease 2019

The fact that NAFLD and NASH affect about 25% of the world's population makes it certain that they will occur at the same time as COVID-19. Obesity, together with other metabolic problems related to lifestyle, is paired with NAFLD (e.g., type 2 diabetes). Even before the COVID-19 pandemic started, there has been a correlation between obesity and hyperglycemia, two conditions that are associated with a poor prognosis.[3] Augmented levels of liver enzymes SGPT/SGOT [the higher limit than usual (i.e., 80 U/L)] are prevalent in COVID-19-affected individuals and are autonomously linked to poor clinical outcomes.[3] In one investigation, AST/ALT levels were shown to be elevated in 235 individuals with serious COVID-19.[60] A separate study included 31,461 individuals with COVID-19 and found that moderate to severe liver disease was associated with an increased mortality risk [OR, 2.62; 95% CI, 1.53–4.47].[61] In a related study of 2,780 COVID-19 patients, liver disorder was found to be linked to an elevated risk of death (OR, 2.8; 95% CI, 1.9–4.0).[62] Patients with NAFLD exhibit a significantly elevated risk of disease progression (6.6 vs 44.7%), an increased likelihood of abnormal liver function from admission to discharge (70 vs 11.1%), and a prolonged duration of viral shedding (17.5 ± 5.2 days vs 12.1 ± 4.4 days) compared to patients without NAFLD.[63] The substantial global prevalence of NAFLD places a considerable proportion of individuals at risk for severe COVID-19.

The prognosis of NAFLD is contingent upon the severity of liver fibrosis, leading to the assumption that persons with NAFLD and higher noninvasive liver fibrosis scores face an increased chance of severe COVID-19. Patients with NAFLD who have been detected with hepatic steatosis based on CT scan (OR, 4.32; 95% CI, 1.94–9.59) or have a moderate or increased fibrosis-4 (FIB-4) index (OR, 5.73; 95% CI, 1.84–17.9) have a significantly greater risk of serious COVID-19, regardless of metabolic comorbidities.[64,65] In comparison to younger individuals or those without NAFLD, patients with medium or high FIB-4 scores tend to be older, obese, diabetic, have elevated liver enzymes, elevated C-reactive protein, and lower concentrations of lymphocytes, platelets, triglycerides, cholesterol, and high-density lipoprotein.[39,40] In addition, complications such as obesity (OR 4.5), diabetes mellitus (OR 2.55), and FIB-4 >2.67 (OR 3.09) are associated with the need for mechanical ventilation in COVID-19 patients. Additionally, FIB-4 ≥2.67 is associated with an increased risk of 30-day death (OR 8.4; 95% CI, 2.23–31.7).[66]

The link between the severity of COVID-19 and NAFLD/NASH implies that a genetic risk score for NAFLD could be developed based on the weighted effect of risk variants in PNPLA3 (patatin-like phospholipase domain containing 3)–TM6SF2 (transmembrane six superfamily member 2)–MBOAT7 (membrane-bound O-acyltransferase domain-containing protein 7)–GCK3. In a research study including 1,460 individuals, 526 of whom tested positive for SARS-CoV-2 and 934 of whom tested negative, the genetic risk score for NAFLD was not associated with an increased risk of COVID-19. This study did find that the p.I148M PNPLA3 variant, encoded by the single-nucleotide polymorphism rs738409, provided protection against COVID-19. One possible explanation for the poor clinical outcomes seen in obese and NAFLD/NASH individuals is that they have an increased hepatic expression of SARS-CoV-2 receptors, namely ACE2 and TMPRSS2. As stated by one study, NAFLD/NASH did not influence the ACE2 and TMPRSS2 gene expression in the liver.[67,68] Nevertheless, a different study indicated that obese NASH patients exhibited substantially higher levels of gene expression, suggesting that the advanced stages of NAFLD would put them at risk for contracting COVID-19.[3] Additionally, gut bacteria and insufficient fatty acid oxidation products were associated with NAFLD/NASH and severe COVID-19; this association may have regulated the host immune response.

In the context of COVID-19, NAFLD/NASH considerably raises the risk of mortality and morbidity. There are many research trials ongoing for NAFLD/NASH because there are no therapies for it. However, due to the widespread spread of COVID-19, several of these studies have been put on hold. Research into NAFLD and NASH should proceed, as CLD is very common around the world.[3]

Alcohol-associated Liver Disease

ALD increases COVID-19 patients' mortality risk by 1.8-fold. Patients with ALD, as well as COVID-19, appear to have more severe liver injury, as only 6% of ALD patients lack cirrhosis compared to 62% of NAFLD patients. Two individuals admitted to the hospital with acute liver disease (ALD) ended up with nosocomial COVID-19 infections and severe pneumonia, according to a case report. Both patients died quickly from multiorgan failure. An additional study linked severe COVID-19 to ALD [OR, 7.05; 95% CI, 6.30–7.88] and cirrhosis (OR, 7.00; 95% CI, 6.15–7.97).[69] The effects of alcohol on the COVID-19 epidemic and the potential pathophysiology of alcohol and ALD have been the subject of very few investigations. Overconsumption of alcohol may suppress the immune system and cause bacterial and viral infections. About 3.3 million people die every year as a result of alcohol poisoning. Alcohol causes cirrhosis and chronic liver damage. Globally, alcohol consumption is rising. Social distancing, as well as lockdown measures, increase alcohol abuse, leading to increased cases of CLD and liver damage.[70]

Drugs Used in Coronavirus Disease 2019 Management Causing Hepatotoxicity

Drug-induced liver damage combined with COVID-19 treatment may also damage the liver of COVID-19 patients. Over half of COVID-19 patients with normal liver damage indicators on arrival had abnormal liver marker readings 1 week later, according to one study. Lopinavir-ritonavir raises AST, ALT, and bilirubin[71]; remdesivir raises AST and ALT, and acetaminophen and hydroxychloroquine cause abnormal liver markers. Remdesivir's liver toxicity is controversial. Randomized clinical trials compared remdesivir-treated

and control groups' liver enzyme increases.[3] Furthermore, the safety report database of World Health Organization (WHO) clearly indicates that the use of remdesivir is associated with a statistically significant risk of hepatic injury.[72] Therapeutic options for COVID-19 encompass angiotensin 2 receptor blockers in conjunction with ACE inhibitors. These medicines are also causing enhanced liver enzymes.[3] The repurposed medications showed negligible efficacy against COVID-19. Immunomodulators appear to be more effective in addressing COVID-19 mortality and morbidity, with corticosteroids like dexamethasone enhancing survival rates and reducing morbidity among hospitalized COVID-19 patients and those with moderate to severe cases. Corticosteroids, derived from cholesterol metabolism, might impair glucose homeostasis; thus, their impact on hepatic steatosis and liver metabolism warrants consideration. Corticosteroid therapy has been associated with considerable hepatic damage in COVID-19 individuals.[3] An elevation in ALT has been noted with the administration of tocilizumab, a monoclonal antibody targeting the IL-6 receptor, utilized in the treatment of rheumatoid arthritis and the prevention of cytokine-mediated injury in COVID-19. Tocilizumab was linked to a markedly increased rise of ALT in this retrospective observational cohort investigation.[3] Furthermore, antibiotics used in COVID-19, which are among the most likely reasons for drug-induced liver damage, may cause liver damage in COVID-19 patients[73] and could be available shortly. Future research should determine how new SARS-CoV-2 medicines affect COVID-19 patients' liver function. These studies could include CLD patients. Favipiravir, an oral broad-spectrum ribonucleic acid (RNA) polymerase inhibitor, is licensed in Japan for the treatment of influenza and has a minor effect on COVID-19. Favipiravir appeared safe. A person with ALD-related liver damage reported favipiravir-caused cholestatic liver damage. This case report on favipiravir indicates baseline chronic liver disease prior to the initiation of antiviral medication.[3,74]

Conclusion

Liver steatosis, liver fibrosis, and elevated liver enzymes may serve as prognostic markers for the severity of COVID-19, as they are associated with liver injury and CLD. The immune-inflammatory response induced by liver dysfunction is especially pertinent in viral illnesses. This becomes especially critical with the increasing incidence of NAFLD, NASH, and the COVID-19 virus. It is essential to carefully monitor and manage patients with CLD, such as those with hepatocellular carcinoma, viral hepatitis, NAFLD/NASH, and ALD. Priority should be given to patients with cirrhosis and acute liver damage due to CLD, particularly in the context of SARS-CoV-2 vaccination.

Tracking immunized patients with CLD over time could provide insight into the underlying causes of their suboptimal immune response. The COVID-19 pandemic had a detrimental effect on the care that people with CLD received because of the lengthier wait times or decreased access to healthcare services. These disruptions likely contributed to higher morbidity and mortality related to CLD, as delays in diagnosing and treating various liver conditions worsened patient outcomes. Additionally, the pandemic led to a significant decline in liver transplants and organ donations, while global efforts to eliminate viral hepatitis were also adversely affected. Patient habits detrimental to liver health, combined with the pandemic's effect on liver-related healthcare services, may exacerbate the global liability of liver disorders. In people who are otherwise healthy, SARS-CoV-2 infection appears to result in very minor liver damage. Nonetheless, additional investigation is required to comprehend the long-term implications of COVID-19 on hepatic function.

Consent to Participate

All the authors mutually agree to participate in this work.

Consent for Publication

All the authors mutually agree to submit the manuscript for publication.

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UPDATE ARTICLE

Role of Desmopressin in Bleeding Disorders: What Indian Physicians Need to Know?

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Abstract

Desmopressin (1-deamino-8-D-arginine vasopressin), formerly introduced for the treatment of diabetes insipidus, is a well-known analog of vasopressin, that is, antidiuretic hormone (ADH). Subsequently, after the late 1970s, it has emerged as the medication of choice for type 1 von Willebrand's disease (vWD) and minor hemophilia A. Prothrombotic factors FVIII and von Willebrand factor (vWF) are released from storage sites when vasopressin receptors are targeted by desmopressin. It also facilitates platelet-vessel wall adhesion, resulting in a substantial hemostatic effect. Research studies have shown that desmopressin administration can lead to up to a fourfold increase in vWF levels, highlighting its hemostatic actions. Desmopressin is commonly used in conditions like nocturnal polyuria leading to nocturia or nocturnal enuresis, diabetes insipidus, von Willebrand disease, uremic bleeding, and hemophilia A. Desmopressin is also used to avoid rapid sodium correction along with hypertonic saline, management of intracranial bleed due to the use of antiplatelet agents, and trauma resuscitation with active hemorrhage. It is also used in bleeding disorders, dental extractions, epistaxis, and menstrual bleeding. Hence, it is imperative that clinicians become acquainted with the use of desmopressin, which has become a common medication for many patients with congenital bleeding disorders. Desmopressin is included in the treatment guidelines for vWD.

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Introduction

Desmopressin acetate (DDAVP) is an antidiuretic peptide drug synthesized by removing the amino group from 1-cysteine and substituting the *levo* form of arginine with *dextro*. It has been shown to be therapeutically used for nearly 50 years in a variety of formulations, including an oral lyophilisate, a melt formulation for the last 20 years, tablets for about 35 years, injectables for about 35 years, and an intranasal solution for 50 years. In India, it is available in all three formats, that is, tablet, melt, and intranasal spray (brands like Minirin, Minirin Melt, and Minirin RTS-Room Temperature Stable). However, there is a need for an injectable format, particularly for the management of bleeding. It has been used for about 50 years to treat conditions like bedwetting and nocturia. By increasing the distal convoluted tubule's and kidney's collecting tubules' capacity to reabsorb water, it lowers the amount of urine produced. Desmopressin therapy has a response rate of 60–70% and is well tolerated, thus it is even utilized in diabetes insipidus.[1,2] Since desmopressin has higher resistance to vasopressinase, it shows an enhanced and long-term antidiuretic effect and causes lesser stimulation of uterine muscles and vasoconstrictive effects, resulting in decreased side effects like convulsions and hyponatremia. In India, it is available in the form of an oral tablet, intranasal spray, and oral disintegrating tablet (ODT), making it suitable for easy administration.[3]

Desmopressin is well-studied in indications like central diabetes insipidus, nocturnal enuresis, and nocturia, and abundant clinical studies are available on the same. However, there is hardly any data from Indian patients.[2–4]

Desmopressin: Mechanism of Action

The V2 receptors are present at the collecting ducts and distal convoluted tubules (DCT) of the kidneys. The Gs-protein coupled V2 receptor initiates a signaling cascade of adenylate cyclase, resulting in an increase in cyclic adenosine monophosphate (cAMP) in the renal tubule cells, leading to increased water penetrability. This movement leads to a reduced volume of urine and raised urine osmolality. The signaling cascade resulting in the production of cAMP also stimulates the exocytosis of von Willebrand factor (vWF) and factor VIII from its storage sites. It also stimulates the Weibel-Palade (WP) bodies and the alpha granules of platelets. Thrombogenesis is triggered by vWF, acting as the bridging factor of the Gp1b factor on platelets to the subendothelial collagen following tissue injury. By utilizing synthetic antidiuretic hormone (ADH) analogs, such as desmopressin, the clotting cascade is facilitated poststimulation of V2 receptors and can result in hemostasis.[5]

Following desmopressin administration, cAMP signals the secretion of vWF and tissue plasminogen activator (t-PA) from WP bodies in endothelial cells into plasma.[6,7] Highly multimerized vWF is released and augments binding to the subendothelial matrix and platelets, increasing hemostatic efficacy.[7] Desmopressin administration leads to the liberation of FVIII from storage sites. Desmopressin administration also increases plasma vWF and protects FVIII from proteolytic degradation, contributing to a prolonged increase in FVIII activity.[5] DDAVP-induced release of t-PA leads to a transient rise in fibrinolysis but with limited impact on the overall hemostatic efficacy of desmopressin. The expression of glycoprotein Ib/IX and CD62 (P-selectin) on platelet surfaces is increased by desmopressin, which leads to increased platelet activation, rolling, and adhesion.[8,9] Together, these actions can curtail the bleeding time and regularize shear-induced platelet aggregation.[8–11]

Current Treatment of Bleeding Disorders

Blood Transfusion

Initially, hemophilia treatment was restricted to just transfusions of whole blood products. Later, fresh frozen plasma (FFP) infusions were introduced. Once newer technologies were introduced for the production of plasma-derived coagulation factor concentrates and recombinant proteins, they ensured safety and efficacy with the possible replacement

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of clotting factors. This turned out to be a boon for hemophilia patients in developed countries. However, there is still not much hope for patients suffering from rare bleeding disorders due to deficiencies of FV and FII.[12] Though promising, it still has limitations in terms of disease and treatment. Despite receiving prophylaxis, there are bleeding cases in patients. Current licensed products have shorter half-lives, which are not promising, and even cases of subclinical bleeding occur, which can lead to long-term joint disease. The frequency of intravenous doses multiple times per week is painful and not suitable, so it might lead to poor adherence.[13]

Antifibrinolytic Agents

Antifibrinolytic agents like epsilon, tranexamic acid, and aminocaproic acid are commonly used in hemophilia patients, particularly with oral bleeding or elective dental surgeries.[14] There is limited data on the safety and efficacy of epsilon or aminocaproic acid, irrespective of their rampant use.[15]

Oral Contraceptive Pills

Studies with oral contraceptives have shown a reduction in menstrual blood loss in type 1 von Willebrand's disease (vWD) patients. It is hypothesized that oral contraceptives lead to an increase in factor VIII and vWF levels.[16] Studies have shown that oral contraceptives induce venous thromboembolism episodes.[17]

Immunosuppressive Agents

Immunosuppressive agents like steroids and cyclophosphamide can show a decrease in signs and symptoms in patients with hemophilia, but there is a significant risk of mortality due to serious infections.[18,19]

Role of Desmopressin in Bleeding Disorders

Desmopressin increases clumping of platelets and raises the concentration of factor VIII, which helps to stop bleeding. Additionally, since desmopressin is a synthetic moiety, there are no chances of any kind of infection.[20] The strong antidiuretic actions of desmopressin could lead to retention of water and may cause severe hyponatremia, but the reported incidence of such volume overload or cerebral edema has been sporadic. Nevertheless, the pediatric and geriatric populations should avoid unnecessary fluid intake when on treatment with desmopressin. One of the rare but notable phenomena associated with desmopressin therapy is tachyphylaxis, leading to progressively poor response in some patients.[21] Desmopressin has advantages beyond just cost factors. The substance might be required to fulfill religious demands, such as the replacement of blood components among Jehovah's Witnesses. More significantly, it probably protects many people from contracting HIV type 1 infection.[22] Since its debut in clinical practice in 1977, desmopressin has been one of many nontransfusion pharmacological medicines that clinicians can use to control bleeding episodes. It has significantly reduced the need for blood products in the management or prevention of bleeding episodes, revolutionizing the treatment of bleeding diseases.[23]

Clinical Studies of Desmopressin

Desmopressin 0.3 gm/kg was intravenously given to 20 adults with CF5F8D over the course of 20 minutes in a study. Estimation of blood samples after 1 hour for factors V and VIII studies showed raised factor VIII levels, but no change in the level of factor V was found. Desmopressin is a good option for patients suffering from both combined factors VIII (FVIII) and V (FV) insufficiency based on these findings.[24]

Hemophilia A is the most prevalent bleeding problem among Indian patients who are admitted to hospitals, in contrast to the white population. In India, platelet function issues come in a close second and are quite uncommon in white people.[25]

Advantages and Disadvantages of Desmopressin

Because desmopressin is less expensive and does not carry the danger of producing inhibitory antibodies, it is seen as a suitable substitute for factor concentrates. Desmopressin may be a reliable treatment for the indicated population in countries with limited resources, as it is recorded that 60–70% of hemophilia victims globally still do not have access to factor concentrates. As a result, it is also listed among the essential medications by the World Health Organization (WHO). Desmopressin is a significant therapy option for those with mild hemophilia A, as evidenced by the fact that 60% of patients had acceptable factor levels.[26]

Desmopressin rarely has negative side effects; however, excessive dosing might cause fluid retention and a drop in plasma osmolality. For individuals who drink too much water, it is even linked to severe hyponatremia and convulsions. Due to reports of myocardial infarction and stroke, older adults with vascular disease might be at risk.[27]

Conclusion

In India, desmopressin is commonly used for the management of nocturnal enuresis, nocturia, and diabetes insipidus for a long time. Desmopressin exhibits action on the vasopressin receptors of the body and shows a substantial hemostatic effect by releasing prothrombotic factors vWF and FVIII from storage sites, promoting platelet-vessel wall union. It is one of the treatments of choice for patients with vWD and mild hemophilia A. The signaling cascade of cAMP induces exocytosis of vWF and factor VIII from its storage sites, as well as the WP bodies and the alpha granules of platelets responsible for blood clotting. Current treatment of bleeding disorders includes blood transfusion, antifibrinolytic agents, oral contraceptives, and immunosuppressive agents, which have safety and efficacy concerns. Desmopressin is cost-effective and prevents blood-related infections, so it can be a boon for hemophilia A disorder, commonly found in India. There are some limitations, such as fluid retention and hyponatremia leading to seizures and stroke. Desmopressin may be used judiciously for bleeding disorders, and further study is required on the same.

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CASE REPORT

Spontaneous Cervical Epidural Hematoma: A Case Report

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Abstract

An acute spinal cord compression can very rarely cause a spinal epidural hematoma. The functional recovery will be the highest if early detection and prompt surgical management are undertaken. The conservative management was successful in the present case of the cervical epidural hematoma with lesser neurodeficits and smaller hematoma size with minimal cord compression. The patient had no neurodeficit at the end of 7 days.

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Introduction

Spinal epidural hematoma is an infrequent cause of acute spinal cord compression. The maximum functional recovery can be achieved if early detection and prompt surgical treatment are undertaken.[1] Generally, blood dyscrasias, coagulopathies, anticoagulant treatment, infection, tumors, pregnancy, and vascular malformations are linked with spinal epidural hematoma. However, in about 50.0% of patients, no ostensible cause is reported.[2] The spinal epidural hematoma in the cervical region is usually spontaneous and of acute onset.[3]

It is estimated that spontaneous spinal epidural hematoma occurs in 0.1/1,00,000/year.[4] If left untreated, it can have disastrous results. The pathophysiology and etiological agents of this disorder remain obscure and are a matter of active research. A high index of suspicion with magnetic resonance imaging (MRI) of the spinal cord is essential for the diagnosis. Emergency evacuation of the hematoma has been the norm to prevent devastating neurological injury. The present rare case report shows the role of conservative management and spontaneous resolution of the cervical epidural hematoma.

Case Description

A woman aged 71 years, with no history of prior trauma to the neck or head, came to the casualty of our hospital with excruciating continuous pain originating from the right side of the neck and radiating to the right upper extremity up to the fingers for 45 minutes. The pain and neurological deficit were sudden in onset and constant. The pain was associated with weakness of the right arm, forearm, and fingers. The pain exacerbated with movement of the neck. The patient complained of tingling and numbness in the fingers of the right hand and the ulnar aspect of the right forearm. There was no associated history of exertion or extreme neck movement around the time of onset.

The patient has a history of type 2 diabetes mellitus for the last 9 years, on regular oral hypoglycemic agents: teneligliptin 20 mg once a day (OD), gliclazide 60 mg OD, and metformin 500 mg twice a day (BD). She was also a known hypertensive for 24 years, on nebivolol 5 mg OD, S-amlodipine 2.5 mg OD, and telmisartan 80 mg OD. She was also a known case of dyslipidemia, on fenofibrate 160 mg OD and rosuvastatin 10 mg OD. She was not on any antiplatelet or anticoagulant medication in the past.

The examination revealed that the patient was conscious, oriented, and obeying commands. Her body mass index was 20 kg/m^2. Her body temperature was 36.7°C, with a pulse rate of 90/minute and blood pressure of 152/84 mm Hg in the supine position. Her higher functions and cranial nerves were normal on examination. Her motor system examination revealed a reduced tone and decreased power in the right arm and forearm, with movements at the shoulder joint and elbow graded 3/5 on the Medical Research Council (MRC) muscle power scale.[5] She had a weak right-hand grip of 50% compared with the left hand. Reflexes in the right biceps, triceps, and brachioradialis were diminished. Motor examination of the rest of the limbs was normal. The plantar reflexes were flexor. The sensory examination showed reduced pinprick and touch sensations over the tips of the fingers of the right hand.

The patient was advised bed rest with a cervical collar. Intravenous (IV) diclofenac 75 mg was given for pain relief. Suspecting a space-occupying lesion of the cervical cord and to rule out acute ischemic stroke in the window period, an MRI of the brain and entire spine was done. There was no evidence of acute ischemic stroke. The MRI of the spine revealed the presence of a nonenhancing posterior extra-axial epidural spindle-shaped shadow, which was isointense to the spinal cord on T1 imaging and heterogeneously hyperintense to the spinal cord on T2 imaging. It extended from the C3–C7 level for a length of 52 mm, causing compression of the thecal sac, more marked at the C4–C5 level on the right side, findings consistent with an organized extradural hematoma on the right paramedian plane (Figs 1 and 2).

Once the MRI findings were ascertained, a computed tomography (CT) angiography of the spine was advised to rule out the presence of an arteriovenous (AV) malformation. However, the CT angiography did not reveal the presence of any AV malformation. Her entire coagulation profile, including international normalized ratio (INR), partial thromboplastin time (PTT) test, and fibrinogen levels, was normal.

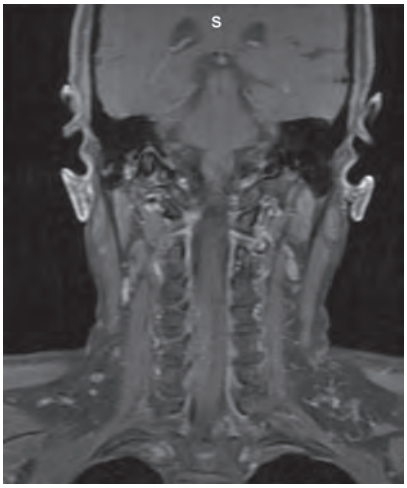

Fig. 1: Coronal T1 weighted image showing an isointense spindle shaped lesion in the right-side cervical region on day of admission

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The patient was started on IV methylprednisolone 125 mg, along with IV fluids. Her pain subsided substantially, and power improved to 4+/5 MRC in the first few hours. The neurosurgeon advised conservative management in view of the improving neurodeficit and small size of the hematoma, with continuous neuromonitoring. IV methylprednisolone 125 mg BD was continued in an attempt to reduce the perilesional edema. Close neurological monitoring was done, and IV diclofenac was given if required for pain relief. Blood glucose levels were monitored and corrected with subcutaneous boluses of human insulin. A blood pressure of 140/90 mm Hg was targeted. Complete bed rest was advised.

After 12 hours of onset of the symptoms, the patient had grade 5/5 motor power in the right upper limb and minimal neck pain on the right side. Neuromonitoring and IV methylprednisolone were continued for the next 5 days. A repeat MRI of the cervical spine done on the 6th day after onset of symptoms showed a near complete resolution of the posterior right-sided extradural hematoma. A tiny residual T2 hypointense posterior extradural hematoma along the right laminae of the C4 vertebra, mildly indenting the thecal sac, measuring 4.9 × 10.7 mm in the axial plane, was observed (Figs 3 and 4). No cord edema was seen.

The patient was discharged with a cervical collar. She was also advised to avoid straining, lifting weights, and to avoid pillow use during sleep. At the 7th day follow-up, the patient reported very mild neck pain only on neck movements, with no worsening of power. The patient was also advised to have a repeat CT angiography of the spine at the end of 3 months to look for AV malformations that may have been collapsed at the time of presentation. The patient remained symptom-free at the end of 3 months, as revealed *via* a telephonic follow-up.

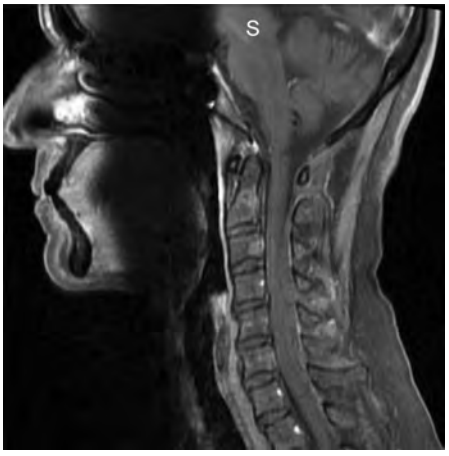

Fig. 2: Saggital T1 weighted image showing an isointense spindle shaped lesion in the posterior extradural cervical region on day of admission

Discussion

Jackson first described the spinal epidural hematoma.[6] In about half of the patients, the cause of the spinal epidural hematoma could not be found; hence, it was labeled as spontaneous.[6,7] Spinal epidural hematomas show a bimodal distribution of age, with most of the cases occurring in the second and seventh decades of life.[8] Most of them are located dorsal to the spinal cord, with peaks at C6 and T12 levels and 3.6 vertebral lengths on average.[9,10]

Both the venous and arterial sources as the cause of spontaneous epidural hematomas are supported by current evidence. Due to the lack of valves in the spinal epidural veins and their vulnerability to changes in abdominal or thoracic pressure, the most broadly acknowledged theory for the cause of bleeding is venous.[1,4]

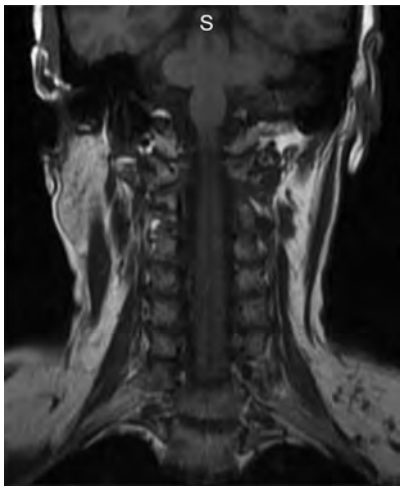

Fig. 3: Coronal T1 weighted image showing near complete resolution of the hematoma on day 6

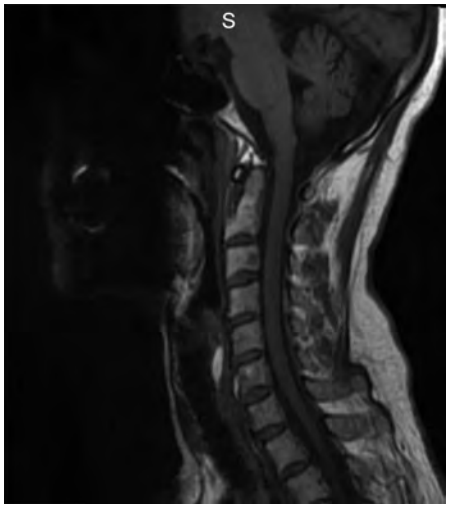

Fig. 4: Sagittal T1 weighted image showing complete resolution of the hematoma on day 6

According to the Bruyn and Bosma hypothesis, increasing intrathoracic and intraabdominal pressure causes a momentary rise in IV pressure in valveless and thin-walled epidural veins, which ultimately results in their rupture. This explains the cases that have been linked to motions like straining, bending, neck manipulation by a barber, coitus, coughing, sneezing, etc.[2] The venous etiology argument is further supported by a study by Liao et al., in which most of the cases stated a straining-linked incident through the early occurrence. This venous concept, however, does not appear to hold true in the cervical section due to low venous epidural pressure (even lower than intrathecal pressure).[11] A cervical epidural hematoma's rapid development also suggests that it has an arterial origin. Beatty and Winston hypothesize that free anastomotic arteries running in the epidural space, which also connect with the radicular arteries, are the source of arterial bleeding in cervical epidural hematomas.[3]

Clinical presentation includes acute severe neck pain or back pain followed by neurodeficits ranging from acute radiculopathy to quadriplegia, depending on the size and speed of evolution of the hematoma. Most patients also complain of sensory symptoms in the affected areas, with neck or back pain and radicular pain. This condition presents like a disk prolapse and, in some cases, acute stroke. Patients with a smaller hematoma size (and thus, lesser spinal cord indentation) and lesser neurodeficits generally show rapid recovery and tend to do well with conservative therapy. In some cases, the hematoma spreads throughout the epidural space, thereby leading to decreased compression over the spinal cord and the nerve roots.[9,12]

The definitive diagnosis of spontaneous epidural hematoma of the spinal cord is done by MRI, which is isointense to the spinal cord on T1W images in the first 24 hours. Detection of AV malformations may require the use of contrast magnetic resonance (MR) angiography or CT angiography.[10]

Treatment includes conservative as well as surgical evacuation of the hematoma. Surgical decompression has been shown to have better clinical outcomes when performed early (36–48 hours) and in cases with partial neurodeficits at the onset. The results are better with incomplete deficits than complete deficits.[11,13] Patients managed conservatively had less severe signs, smaller lesions, and lesser mass effect on the spinal cord.[14,15] However, it is reported that clinical

recovery was followed by deterioration, and the patients had to undergo evacuation.[15] Hence, close monitoring for neurological deterioration is mandated at a center with neurosurgical services.

Awada et al. reported a 14-year-old boy with C6 level acute spontaneous cervical epidural hematoma who progressed to tetraplegia at the time of surgery, almost 9 hours after onset of symptoms. Despite undergoing laminectomy of C4–C7 levels, the patient did not improve significantly in neurodeficit and was wheelchair bound at the end of 3 months. They opined that a better functional recovery could have been possible if the preoperative neurodeficit had been lesser.[1]

A case series published by Duffil et al. showed that all four patients of acute spontaneous cervical epidural hematoma who were managed conservatively had a smaller size of hematoma, lesser cord compression, and improving neurodeficits at the time of hospitalization. They opined that conservative management could be possible in patients where there is improvement in neurodeficits with steroids and observation, at a center where emergency neurosurgical services are available.[14]

In the present case, an old female patient with no predisposing factors came to the hospital in severe, excruciating, continuous pain starting from the right side of the neck and radiating to the right fingers. She was diagnosed with a spontaneous epidural hematoma in the cervical region on an MRI study and responded to conservative management and IV steroids. The patient began showing recovery from the first day itself. The hematoma had reduced in size by the 6th day of onset, as shown by the follow-up MRI. No AV malformation was found on CT angiography done later. The patient was later discharged and had no neurodeficit at the end of 7 days. A CT angiography of the spine was planned to look for AV malformations at the end of 3 months.

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CASE REPORT

Hyperglycemia as a Rare Cause of Quadriplegia: A Case Report

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Abstract

Osmotic demyelination syndrome (ODS) [mostly central pontine myelinosis (CPM)] is mainly reported with rapid correction of hyponatremia and very rarely with hyperglycemia. We report a very rare case of a young male presenting with altered mentation and quadriplegia due to hyperglycemia-induced pontine and extrapontine myelinosis. To our knowledge, it is the first case where both structures were involved in a single patient. The presentation of ODS depends upon the areas (pontine or extrapontine) of the brain involved, ranging from mild tremor to seizure, encephalopathy, and quadriplegia.

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Introduction

The most common cause of osmotic demyelination syndrome (ODS) is a rapid change in serum sodium levels during the treatment of hyponatremia. In other cases, it mostly occurs as a complication of treatment for underlying conditions, such as in chronic alcoholics, individuals with undernutrition, and, rarely, with hyperglycemia. Oligodendrocyte cell death and the penetration of macrophages, which destroy myelin, cause unprovoked demyelination in the pontine and extrapontine areas, based on which it is classified as central pontine myelinosis (CPM) and extrapontine myelinosis.[1] Quadriplegia is rarely attributed to hyperglycemia.

Case Description

A young male presented with acute-onset altered mentation, quadriplegia, and urinary retention.

General examination showed Glasgow Coma Scale (GCS) = 6/15; the patient was stuporous with signs of dehydration, including tachycardia. His respiratory, cardiovascular, and abdominal examinations were not contributory. Neurological examination revealed hypotonic quadriplegia with absent deep and superficial reflexes and normal-sized pupils reacting to light.

Abnormal investigations included increased blood sugar (550 mg/dL), cerebrospinal fluid (CSF) sugar (149 mg/dL), and urine sugar (3+). CSF protein was 113 mg/dL, but the cell count was normal. Serum osmolality was 330 mOsm/kg H_2O. Electroencephalogram (EEG) showed a mild to moderate degree of electrophysiological dysfunction. Hemoglobin A1c (HbA1c) was 11%. Complete blood count (CBC) showed increased total leukocyte count (TLC), mostly secondary to dehydration, as the infective panel, including procalcitonin, C-reactive protein (CRP), blood and urine cultures, and the tropical panel, were normal.

Routine investigations on admission, including Na/K, blood gases, urine ketones, and renal and liver function tests, are summarized in Table 1. Nerve conduction studies and radiological investigations, including magnetic resonance imaging (MRI) of the brain and spine, were normal, as shown in Figure 1.

The patient progressively deteriorated in mentation, developing respiratory distress that required mechanical ventilation support. The patient was managed symptomatically with insulin, IV fluids, and ventilator support.

After 1 week of hospital stay, the patient showed eye opening and a locked-in state appearance, raising clinical suspicion of pontine involvement. MRI of the brain was repeated, which showed hyperintensity lesions in the pontine area (Fig. 2) and extrapontine areas (Figs 3 to 5) on fluid-attenuated inversion recovery (FLAIR)/diffusion weighted imaging (DWI) images, suggestive of ODS [CPM and extrapontine myelinosis (EPM)].

In the next 3 weeks, the patient showed improvement in the level of consciousness and limb power (UL = 4/5 > LL = 1/5) and was weaned off the ventilator. He was discharged with antidiabetic medication after 35 days of hospital stay, with a urinary catheter *in situ*. His CE-MRI brain with spine on the 22nd day showed the same findings as the previous MRI.

The patient came for follow-up after 15 days, fully recovered except for lower limb power (2/5) and the urinary catheter *in situ*.

Discussion

In our case, the patient presented with symptoms of ODS (altered sensorium, coma, quadriplegia) and newly detected hyperglycemia. The diagnosis was confirmed by MRI brain FLAIR and DWI images showing areas of demyelination suggestive of ODS. Other conditions, such as hyponatremia, infectious causes, cerebrovascular accident, metabolic causes, malignancy, and alcohol consumption, were ruled out before reaching the diagnosis.

Few cases of ODS occurrence in DM have been reported in the literature.[2–9] In these cases, hyperosmolar hyperglycemic state (HHS) was the main etiology, and demyelination was caused by the fast correction of hyperglycemia,[2–5] hyperglycemia/hypoglycemia episodes,[8] and persistent hypernatremia.[9] All these causes lead to variations in serum osmolality, resulting in ODS.

Some case reports also reported ODS in DM without HHS[10–13] due to either discontinuation of insulin, leading to an increase in glucose,[12] or rapid correction of glucose,[11,13] causing variation in serum osmolality and leading to demyelination. ODS cases have also been reported during the treatment of liver disease, Sjogren's syndrome, and non-Hodgkin's lymphoma.[1] In our case, we report *de novo* hyperglycemia presenting as ODS without hyponatremia,

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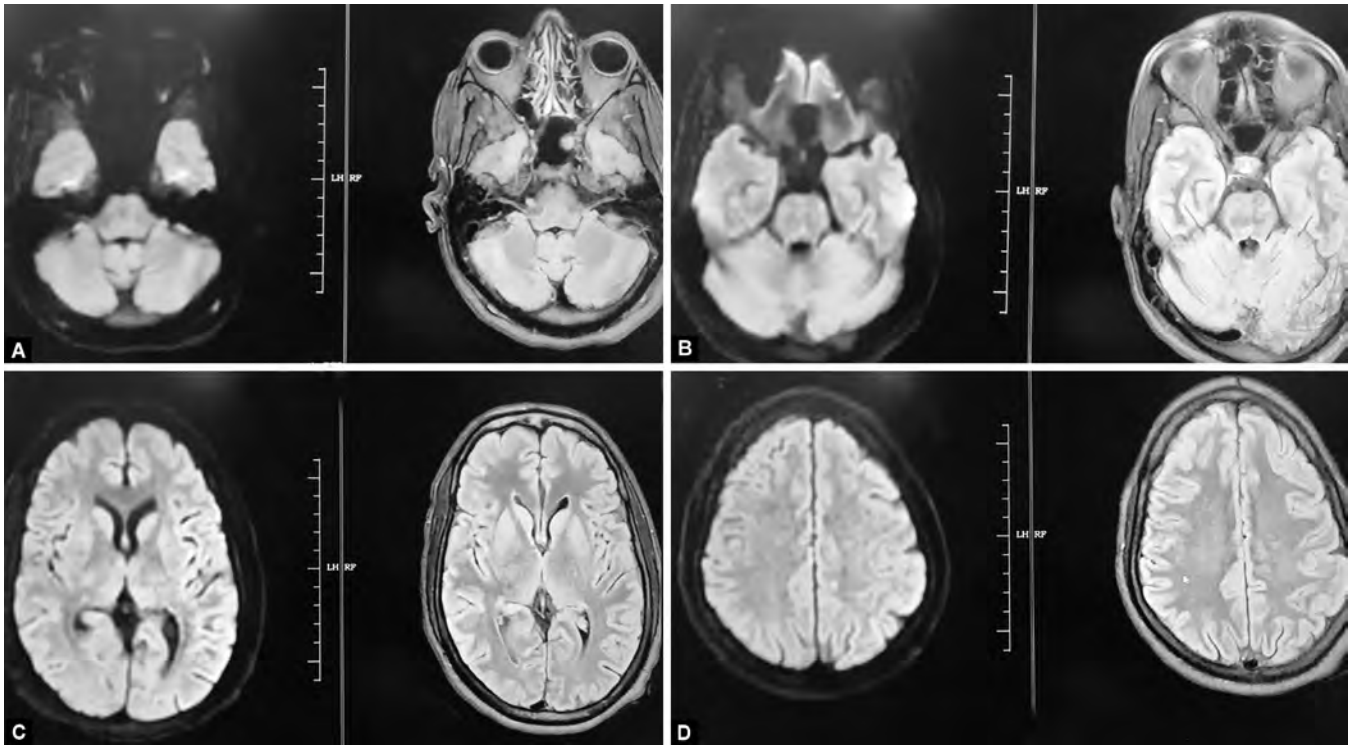
Table 1: Investigation

Test	*Result*	*Reference range*	*Unit*
Random blood sugar	550	60–140	mg/dL
Urea	42	12–42	mg/dL
Creatinine	0.96	0.1–1.4	mg/dL
Total bilirubin	1.1	0.2–1.2	mg/dL
Direct bilirubin	0.49	0.00–0.25	mg/dL
SGPT	42	00–49	mg/dL
SGOT	45	00–46	mg/dL
Alkaline phosphatase	276	80–306	mg/dL
Sodium	140	135–145	mg/dL
Potassium	4.4	3.5–5.1	mg/dL
HBA1C	11	<5.6	
HB	10.9	13–17	gm/dL
TLC	19200	4000–11000	cumm
Platelet count	501000	150000–400000	cumm
ESR	40	0–20	mm/hour
CRP	18.20	0–6	mg/L
Procalcitonin	0.40	<0.5	
PH	7.43	7.35–7.45	
PCO_2	35.10	35–45	mm Hg
Po_2	101.60	83–108	mm Hg
Chloride	105	98–107	mmol/L
Ca++	1.1	1.1–1.33	mmol/L
HCO^-_3	22.90	21–28	mmol/L
TSH	0.4	0.4–5.3	uIU/mL
Mg	1.61	1.5–2.0	mEq/L
Ammonia	100	27–90	µg/dL
Urine sugar	3+		
Urine ketone	Neg		
Serum osmolality	330	275–295	mosm/kg H_2O
CSF—sugar	149	40–80	mg/dL
CSF—protein	113	20–40	mg/dL



Figs 1A to D: (A) (pons) Pontine area and extrapontine area on (B) cerebellar peduncle, (C) internal capsule, (D) cerebral white matter showing no significant changes on MRI brain FLAIR and DWI images during admission

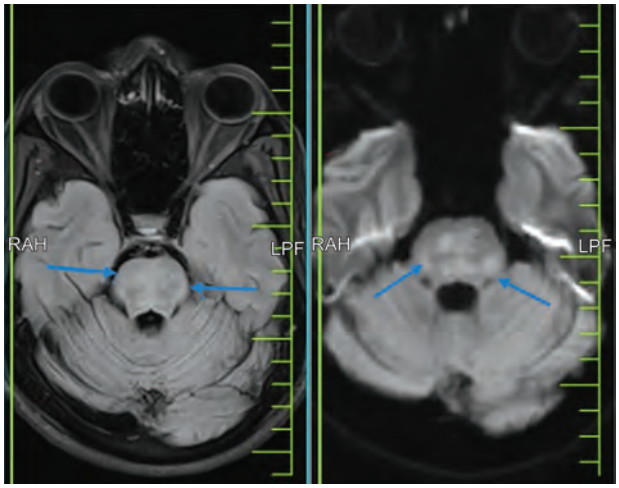


Fig. 2: Showing hyperintensities in the pons on FLAIR and DWI images

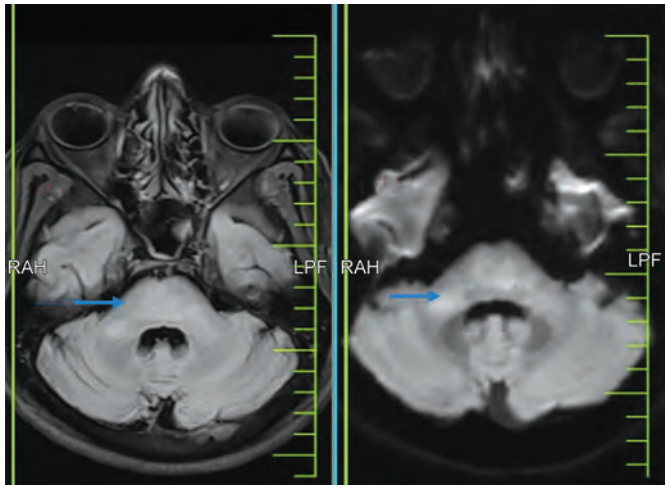


Fig. 3: Showing hyperintensities in the cerebellar peduncle (extrapontine) on FLAIR and DWI images

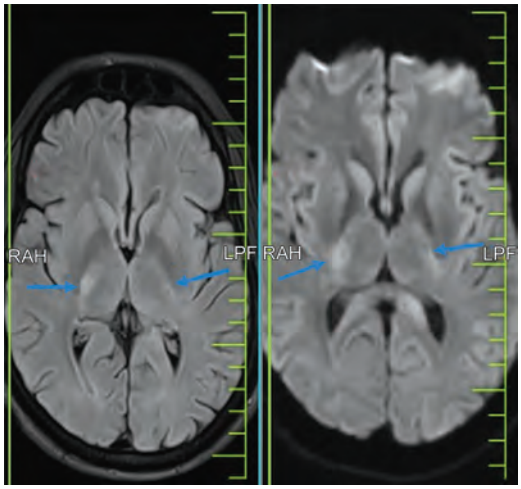


Fig. 4: Showing hyperintensities in the internal capsule

HHS, or DKA during admission, and later during hospitalization, indicating untreated hyperglycemia as the cause of ODS, which is rarely reported.

Central pontine myelinosis involves the pons and presents as dysphasia, dysarthria, flaccid or spastic paralysis, coma, or delirium. EPM involves the basal ganglion, hippocampus, internal capsule, cerebral white matter, cerebral peduncle, and corpus callosum, and presents as tremor, ataxia, mutism, catatonia, or dystonia.[14]

In general, the pathophysiology of ODS is not well understood. It may be due to variation in serum osmolality, causing osmole disproportion, which leads to damage to oligodendroglial cells located in the pontine and extrapontine areas.[4]

In patients with hyperglycemia, the old assumption was that blood-brain barrier damage occurs due to osmolar shift caused by hyperosmolality variation from raised blood glucose, leading to plasma leakage and brain edema, which causes demyelination. In the last few years, a new theory has emerged, suggesting that serum osmolality variation induces osmotic stress, which causes the release of nitric oxide, inflammatory mediators, and harmful substances, leading to damage to oligodendroglial cells and causing demyelination.[10,15]

The suggested assumptions behind osmotic demyelination in the presence of hyperglycemia are: in these cases, demyelination is mainly caused by hyperglycemia leading to changes in brain cells,[16] variation in osmolality due to rapid changes in serum glucose,[7] and hypertonic damage due to hyperglycemia.[5]

There is no specific therapy for ODS, and only some patients with ODS can fully recover and remyelinate within months. In our case, hyperglycemia presented as quadriplegia due to ODS (CPM and EPM).

Conclusion

We have reported a rare etiology and presentation of ODS with the characteristic clinical and radiological findings (both CPM and EPM) as the initial manifestation of hyperglycemia, which is seldom reported. Acute osmolality changes and subacute changes contribute to this condition. Therefore, hyperglycemia should be considered in the etiology of quadriplegia due to ODS. Definitive treatment for ODS is not available to this day, but symptomatic management and comfort care have improved results.

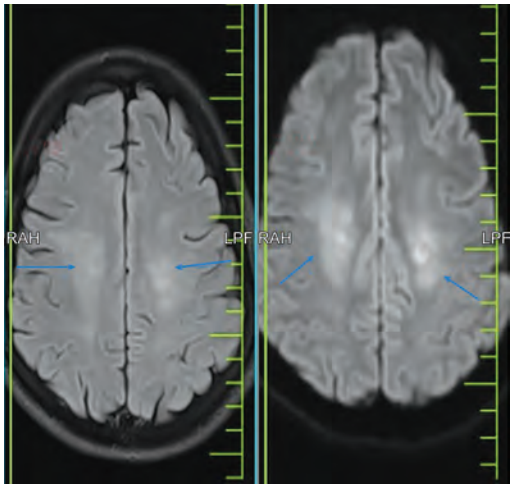


Fig. 5: Showing hyperintensities in the cerebral white matter (extrapontine) on FLAIR and DWI images

Patients with uncontrolled hyperglycemia can develop ODS (CPM/EPM) without hyponatremia, DKA, or HHS.

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CASE REPORT

Unraveling the Mysteries: Paroxysmal Nocturnal Hemoglobinuria and Its Unexpected Link to Stroke in Young Adult

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Abstract

The increasing incidence of stroke among young adults challenges the conventional belief that strokes predominantly affect the elderly. This case report explores the complicated intersection of paroxysmal nocturnal hemoglobinuria (PNH) and strokes in young individuals, examining diagnostic challenges, underlying mechanisms, and the need to recognize this less-explored association for timely intervention. Here, we describe a case of a young male who presented to intensive care with a stroke against a background of recurrent thrombosis and was diagnosed with PNH. While conventional risk factors like hypertension and atherosclerosis are commonly associated with strokes, this case report sheds light on the less-explored connection between PNH and strokes in young adults, emphasizing the need to unravel these seemingly unrelated conditions for enhanced diagnostic precision and improved management.

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Background

Stroke, once considered a condition primarily affecting older individuals, is now becoming a noteworthy issue among younger adults. This case report challenges conventional knowledge about strokes and reveals an unexpected connection with paroxysmal nocturnal hemoglobinuria (PNH). By exploring the growing incidence of strokes in young people and the increasing prevalence of PNH, this case report aims to provide a comprehensive analysis of these interactions. Other factors affecting the prevalence of ischemic strokes include a significant influence from an increased occurrence of modifiable risk factors, such as hypertension, hyperlipidemia, obesity, smoking, and undiagnosed cardiac disease. Stroke in young Indian adults is higher than in Western populations, with major risk factors being hypertension and diabetes.[1] Arterial thrombosis is less prevalent than venous thrombosis in PNH, especially in cerebral and coronary arteries. The patient's history of recurrent blood transfusions and recent abdominal surgery adds complexity to the diagnostic puzzle.[2]

Case Description

A male student in his early 20s with a history of recurrent blood transfusions for anemia and recent abdominal surgery for mesenteric ischemia presented to the emergency department with sudden right-sided weakness, speech impairment, and a history of seizure-like activity lasting 2 days. It was not associated with loss of consciousness. On examination, the patient was unconscious and nonresponsive to verbal commands, with a Glasgow Coma Scale (GCS) of E2V1M4. On general physical examination, pallor was noted, blood pressure was 140/90 mm Hg, and a regular pulse of 67/minute was observed. Central nervous system (CNS) examination revealed reduced tone on the right side, brisk tendon reflexes, loss of superficial reflexes, and an extensor plantar response. The left side of the body was essentially normal. Due to severe neurological involvement and its potential link to his medical history, urgent diagnostic measures were taken, including a computed tomography (CT) brain scan. The patient was then transferred to the critical care medicine intensive care unit (ICU) for comprehensive evaluation and therapeutic management. Immediate neurosurgical consultation was sought based on the findings of the CT head.

Hospital Course

In the emergency department on day 1, a noncontrast CT scan of the head (Fig. 1) was performed, which showed a large infarct in the left middle cerebral artery territory involving the left frontal-parietal lobe, with multifocal hemorrhage, a midline shift of 8 mm, and edema. Medical management, including anti-edema and cerebroprotective measures, was initiated. On day 2, a CT angiography revealed multiple thrombotic ischemic infarcts in the left middle cerebral artery territory. By day 3, a slight improvement in the GCS was observed, with a score of E3V2M4. However, by day 6, the patient's condition deteriorated, leading to a fall in GCS to E1V1M2 and seizures. An urgent neurosurgical consultation was done, and urgent decompressive craniotomy was planned. On day 8, the patient's GCS improved to E3VtM4, seizures were controlled, and PRBC transfusion addressed persistent anemia. On day 15, the GCS improved further to E4VtM5, with varying degrees of recovery in motor function. A repeat CT scan (Fig. 2) showed evidence of a left frontal-temporal postoperative bleed with brain edema.

Investigations

An exhaustive examination of the patient's laboratory results over the course of hospitalization provides valuable insights into the dynamic nature of his condition. Fluctuations in hemoglobin levels, leukocytosis, thrombocytopenia, and abnormal liver function tests, international normalized ratio (INR), and other coagulation profiles were scrutinized, with an emphasis on the trends that guided the medical team's decision-making process, such as performing a bone marrow examination and sending a blood sample for PNH flow cytometry (Table 1).

Differential and Final Diagnosis

Various close differentials were ruled out, as shown in Table 1. The revelation of the diagnosis through a bone marrow examination exposed hyper-cellular bone marrow with erythroid hyperplasia. PNH flow cytometry detected a PNH clone in RBCs (15.72%), granulocytes (78.05%), and monocytes (82.79%). PNH flow cytometry confirmed the diagnosis and also analyzed the distribution of PNH clones in different blood cell populations.

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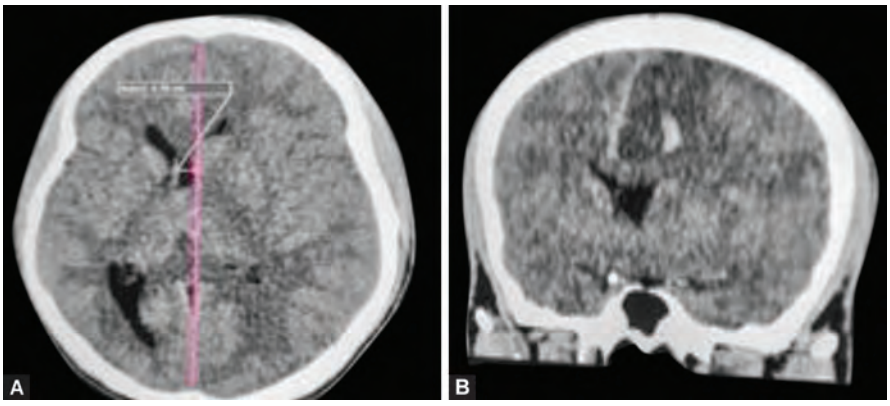
Outcome and Follow-up

The patient was discharged with a response to verbal stimulus and was trained for supportive home care. Anticoagulant therapy was initiated. Regular follow-up of the patient was done for 2 weeks, after which the patient was advised to visit a hematology center.

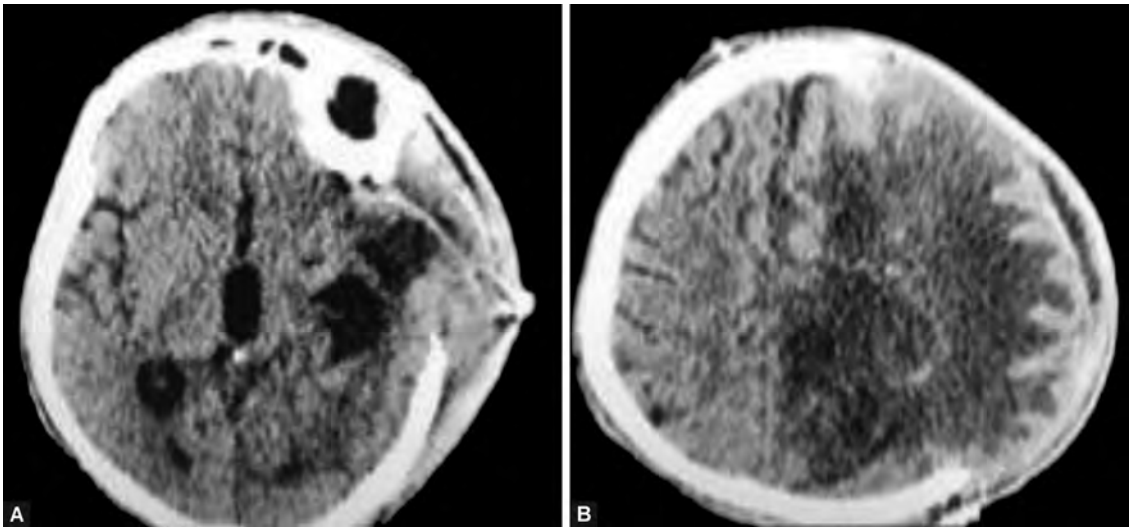
Discussion

Luzzatto et al. stated that "PNH is the most vicious acquired thrombophilic state known in medicine," underscoring the profound concern surrounding thrombotic complications in individuals with PNH and their hematologists.[3] PNH is a disease characterized by the fine interplay of thrombosis and hemolysis, as stated by Crosby and Dameshek.[4]

PNH is characterized by uncontrolled complement activity, leading to systemic complications primarily through two mechanisms: the first is intravascular hemolysis, and the second is platelet activation.[3,4] It results from a somatic mutation in the phosphatidylinositol glycan A (PIG-A) gene within bone marrow stem cells, leading to a deficiency of GPI (glycosylphosphatidylinositol)-anchored proteins and complement regulatory proteins CD55 and CD59 on the cell membrane.[5] This deficiency enhances complement sensitivity in PNH cells, triggering intravascular hemolysis, inflammatory mediator release, and systemic hemoglobin release.[6] Results from previous data suggest that 29–44% of patients experience at least one thrombotic episode in their lifetime. The maximum incidence is of visceral thrombosis, around 19%. This includes thrombosis in the inferior vena cava (IVC), splenic vein, portal vein, mesenteric vein, and hepatic vein.



Figs 1A and B: (A) NCCT head revealing the ischemic stroke with a midline shift of 8 mm; (B) Sagittal section of the brain showing features of stroke



Figs 2A and B: Postdecompressive craniotomy image showing the postoperative changes with bleed and absent skull bone

Table 1: Review of laboratory parameters of the patient

Days	*Day 1*	*Day 7*	*Day 15*	*Day 20*	*Day 30*
Hemoglobin (gm/dL), MCV (fL)	5.6, 92	6.7, 97	6.5, 93	5.5, 93	6.2, 91
TLC ($\times 10^3$/dL)	6.23	4.2	4.6	2.1	7.24
PLT ($\times 10^3$/µL)	150	57	87	40	41
BUN/creatinine (gm/dL)	25/0.6	12/0.50	11.9/0.57	16/0.50	12.5/0.5
Na/K (mM/L)	142/4.3	140/5.1	159/5.3	138/4.3	140/3.0
SGOT/SGPT (U/L)	104/71	67/31	53/18	28/16	32/16
INR	1.66	1.37	1.48	1.92	2.27

1. Lupus anticoagulant by DRVVT—negative
2. Serum beta-2-glycoprotein-1 (IgG, IgM)—negative
3. Serum cardiolipin antibody (IgM, IgG)—negative
4. ANA, dsDNA—negative
5. Vasculitis profile—C3, C4, CH50, ANCA—normal limits
6. Activity of protein C, S & AT-III—89, 95, and 93%, respectively
7. Factor V Leiden mutation—not detected

Classification of PNH is based on the degree of hemolysis, presenting symptoms, and nature of bone marrow cellularity.[7] Various types of PNH include hemolytic PNH—prominence of hemolysis as evidenced by LDH above 1.5 times the upper normal limits, PNH granulocyte clone >50%, normal white blood cells (WBC), platelets, and cellular bone marrow with erythroid hyperplasia; thrombotic PNH—current thrombosis or history of thrombotic events plus PNH clone >30% of granulocytes and LDH >1.5 UNL; subclinical PNH—PNH granulocyte clone is <20% with no substantial evidence of hemolysis or thrombotic signs, LDH <1.5 UNL; and PNH with bone marrow failure—associated with severe symptomatic leukopenia and/or thrombocytopenia that falls under severe aplastic anemia or high-risk myelodysplastic syndrome with variable granulocyte PNH clone. PNH as an etiology for thrombosis can be suspected when a young person has thrombosis at an unusual site with evidence of hemolysis and any cytopenia. Mechanisms of thrombosis in PNH include platelet activation—major, complement-mediated hemolysis, reduced nitric oxide (NO) availability, endothelial dysfunction, fibrinolytic system dysfunction, and release of inflammatory mediators.[8–11]

For thrombotic events, urgent intervention is required due to the high associated mortality. Treatment must be balanced to avoid treatment-related excessive bleeding or bleeding due to underlying bone marrow failure. Undertreatment can lead to the progression of thrombotic events. Immediate treatments include full anticoagulation with IV heparin or low molecular weight heparin to maintain the target level of 0.5–1.0 for anti-Xa levels.[12,13] This is used concurrently with monoclonal antibodies, such as eculizumab, or other newer monoclonal antibodies like ravulizumab.[14,15] Pegcetacoplan is the latest pegylated peptide that targets the complement protein C3, which inhibits both intra- and extravascular hemolysis.[16] This patient had thrombotic PNH, and as none of the newer modalities were available at my center, we were able to manage the patient with low molecular weight heparin and bridge to warfarin, along with multiple transfusions of PRBC and platelets due to persistent anemia and thrombocytopenia (platelet count <50000/µL). During the hospital stay, he developed multiple episodes of sepsis and seizures, which were controlled with appropriate medications. Finally, the patient was discharged with a referral to a higher hematology center. An in-depth exploration of the management strategies employed in this case, from neurosurgical intervention to long-term care, provides insights into the multidisciplinary approach required for optimal outcomes. Prognostic considerations, including the potential for residual deficits and the importance of ongoing monitoring, are discussed in the context of strokes associated with PNH.

Take Home Messages

- Importance of early detection and appropriate management for individuals with PNH.
- Consideration of both common and uncommon causes of stroke differentials is emphasized in young adults.
- The significance of recognizing key signs and symptoms leading to the diagnosis of rare hematological conditions is underscored, with a call to action for healthcare providers to remain vigilant in diverse clinical scenarios.

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CASE REPORT

Cladophialophora bantiana Brain Abscess in an Immunocompetent Host: A Diagnostic Challenge

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Abstract

Cladophialophora bantiana has been identified as one of the most common causes of cerebral pheohyphomycosis. While intrafungal cerebral abscesses are historically known to be associated with immunocompromised patients, *C. bantiana* has a specific predilection for immunocompetent hosts. Successful treatment is based on accurate microbiological and histopathological diagnosis as well as the initiation of targeted antifungal treatment. We hereby report a case of a 64-year-old male who presented with atypical chest pain for 1 day, pain in both lower limbs, and blackish discoloration of the left foot. He also had left foot drop for 1 month. During his hospital stay, he developed a lower respiratory tract infection, was diagnosed with polycythemia vera, and later developed severe headache and dizziness. He was found to have a space-occupying lesion in the cerebellum and a pulmonary nodule. He was started on antitubercular therapy based on a lung biopsy suggestive of necrotizing granulomatous inflammation. However, the patient's sensorium kept worsening, and he was intubated. The fever persisted, and he had episodes of upper and lower gastrointestinal (GI) bleed. His sensorium continued to worsen. Autoimmune and immunodeficiency workups were inconclusive. Repeat imaging suggested an increase in the size of the lesions. Suboccipital craniectomy was performed and showed the growth of *C. bantiana*.

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Introduction

Primary cerebral phaeohyphomycosis is a rare infection caused by dematiaceous fungi, which are brown-black pigmented fungi.[1] Phaeohyphomycosis causes infrequent but life-threatening central nervous system (CNS) infections due to their recognized neurotropism.[2] *Cladophialophora bantiana*, *Exophiala dermatitidis*, *Rhinocladiella mackenziei*, and *Ochroconis gallopava* are some of the recognized dematiaceous fungi causing CNS infections.[3] Despite the use of both systemic and intrathecal antifungal therapy and advances in surgical excision, these infections have significantly high mortality (~ 70%).[4]

Case Description

A 64-year-old male, smoker, known case of hypertension, a businessman from Delhi, presented to us with complaints of sudden onset chest pain with sweating for 1 day. He also had pain in both lower limbs for 1 month with blackish discoloration of the left foot. He also had left foot drop for the last 2 months, which had been diagnosed as left common peroneal nerve palsy and was being managed conservatively for the same. A clinical diagnosis of acute coronary syndrome was made, and he was admitted to the cardiac unit. On examination, the patient was conscious, oriented, and hemodynamically stable with a random blood sugar of 94 mg/dL. The left foot was cool to touch, and no peripheral pulses were palpable in the left foot, suggestive of peripheral vascular disease. There was weakness of dorsiflexion and eversion with reduced sensation in the dorsum of the left foot, suggestive of left common peroneal palsy. The rest of the systemic examination was normal. His electrocardiogram (ECG) showed poor R wave progression in V1–V6, qs in II, III, and aVF. His cardiac enzymes were normal. The two-dimensional (2D) echo did not reveal any signs of acute ischemia. It showed nonobstructive hypertrophic cardiomyopathy, an ejection fraction of 65%, and concentric left ventricular hypertrophy. In view of peripheral vascular disease, ultrasonography (USG) Doppler of the left lower limb was done, which revealed thrombotic occlusion of the superficial femoral and popliteal artery, and he was planned for transfemoral embolectomy. However, on the 2nd day of admission, the patient developed fever with cough. Respiratory BioFire revealed human metapneumovirus. Transfemoral embolectomy was postponed. Lab investigations showed elevated hemoglobin (21.1 gm/dL) and hematocrit (65.7%). Liver function tests (LFT) and kidney function tests (KFT) were grossly normal. In view of raised Hb/PCV, erythropoietin levels were done, which were low (2.1 mu/mL), and JAK-2 came positive. A diagnosis of polycythemia was made, and hydroxyurea was started, and phlebotomy was done. Cough and fever persisted. Sputum culture and sensitivity (C/S) revealed *Escherichia coli* and *Klebsiella pneumoniae*. Antibiotics were added as per sensitivity. On the 7th day of admission, the patient complained of persistent headache and had one episode of dizziness followed by transient loss of consciousness while sitting in a chair. Contrast-enhanced magnetic resonance imaging (MRI) of the brain revealed a well-defined space-occupying lesion in the left cerebellar white matter/middle cerebellar peduncle region with evidence of hemorrhage within (Figs 1A and B).

In view of the space-occupying lesion in the brain on MRI, a whole-body positron emission tomography (PET) scan was done, which showed a fluorodeoxyglucose (FDG)-avid pleural-based nodular lesion in the left lung (Figs 2A and B) and an FDG-avid heterogeneously enhancing mass lesion in the left cerebellum (Figs 3A and B).

An ultrasonography-guided biopsy of the left lung nodule was done, which showed necrotizing granulomatous inflammation (Fig. 4). Microbiology [Gram stain, TBXpert, Ziehl–Neelsen (ZN) stain for acid-fast bacilli (AFB), potassium hydroxide (KOH) for fungus, routine cultures, tuberculosis (TB) cultures] of the tissue biopsy was all negative. The patient's family was unwilling to proceed with a brain biopsy, and hence, based on the lung biopsy findings (necrotizing granulomatous inflammation), the patient was started on first-line antitubercular therapy as per the National Tuberculosis guidelines. On day 17 of admission, the patient had an episode of involuntary movements of the right arm followed by altered sensorium. Noncontrast computed tomography (NCCT) head was done, which showed evidence of an ill-

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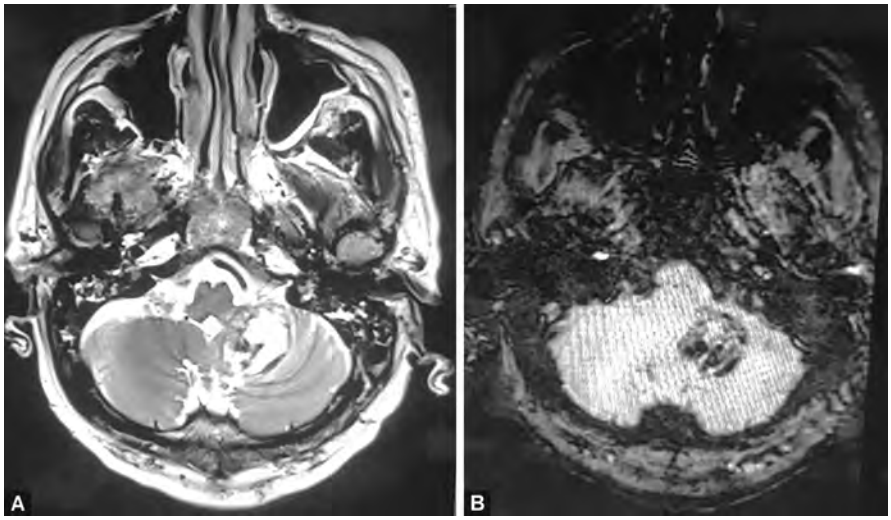
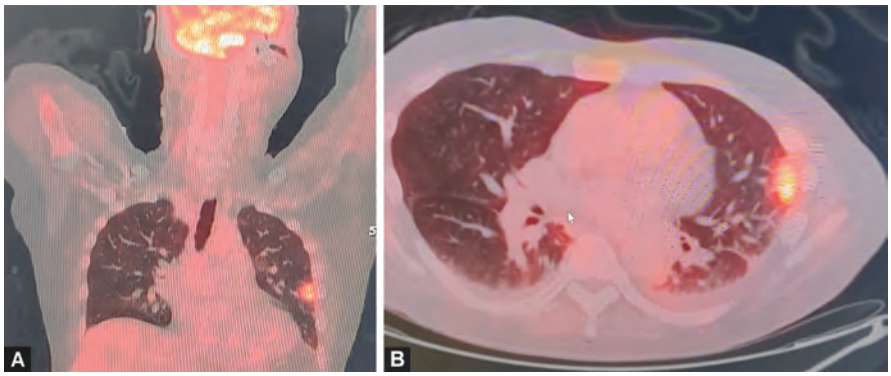
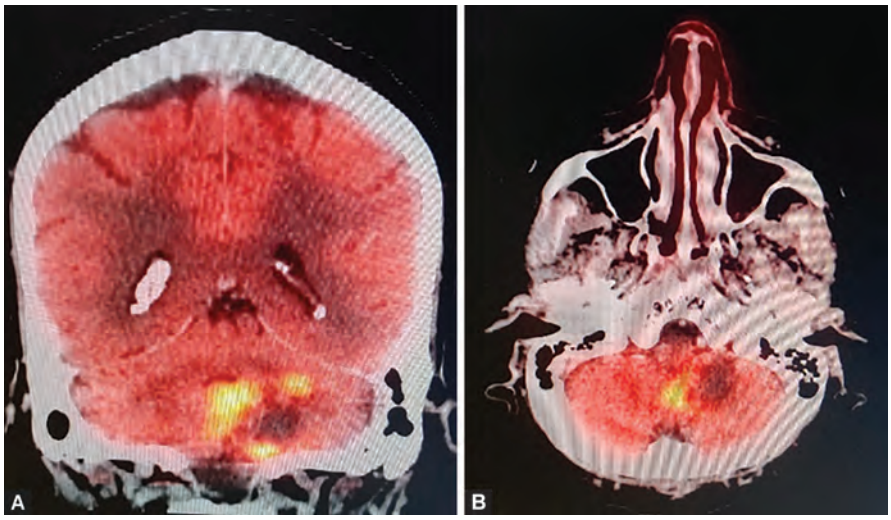


Figs 1A and B: Contrast-enhanced magnetic resonance imaging (CEMRI) of brain: well defined space occupying lesion in the left cerebellar white matter with evidence of hemorrhage within



Figs 2A and B: Whole body PET scan: FDG avid pleural-based nodular lesion in the left lung



Figs 3A and B: Whole body PET scan: FDG avid heterogeneously enhancing mass lesion in the left cerebellum

defined hypodense lesion causing mass effect in the left cerebellar hemisphere (Fig. 5).

In view of the mass effect, steroids were started. Relatives were again counseled for a brain biopsy, but they did not agree to proceed. On day 20 of admission, the patient had an episode of desaturation with a fall in sensorium. He was intubated in view of worsening sensorium. The patient had one episode of lower gastrointestinal (GI) bleed on the 24th day of admission. An emergency sigmoidoscopy was done, which revealed

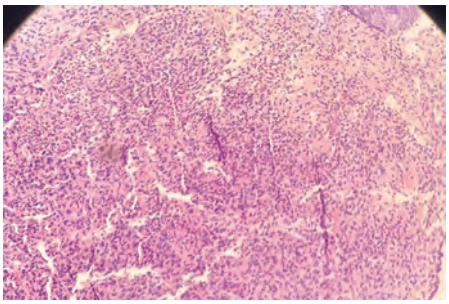


Fig. 4: Necrotizing granulomatous inflammation in tissue biopsy of left lung nodule

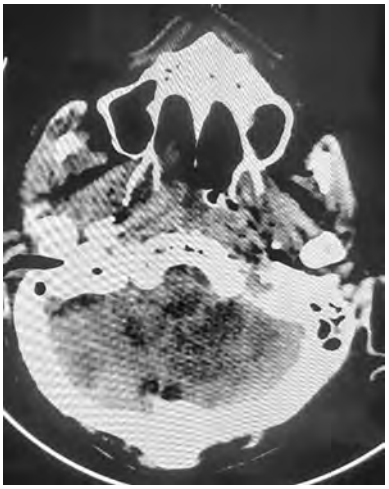


Fig. 5: NCCT head revealed ill-defined hypodense lesion causing mass effect in left cerebellar hemisphere

a rectal ulcer with Dieulafoy's lesion, and clipping was done. The patient also developed upper GI bleed from the Ryles tube on the same day. Emergency upper GI endoscopy was done, which revealed lesser curvature erosion, and argon plasma coagulation was performed. Our patient had neuropathy, peripheral vascular disease, hypertension, and GI bleed, and hence, a clinical suspicion of polyarteritis nodosa/DADA was made. However, autoimmune workup (ANA IF, ANA profile, c-ANCA, p-ANCA) came back negative, and sural nerve biopsy did not reveal any signs of vasculitis. The patient was worked up for an immunodeficiency state, but HIV, HBsAg, HCV, and primary immunodeficiency panel came back negative. The patient continued to worsen, fever persisted, his sensorium deteriorated, and he was on continuous mandatory ventilation (CMV) mode of ventilation with FiO_2 requirements of 80%. Repeat blood and urine cultures were negative. In view of the patient's worsening sensorium, repeat MRI brain was done, which revealed areas of hemorrhage and ischemia that had expanded to both cerebellar hemispheres, cerebellar peduncles, the left side of the midbrain, and pons, with

involvement of the splenium of the corpus callosum. Postcontrast MRI of the brain revealed multiple cerebellar abscesses in the posterior fossa region, with a possibility of pyogenic or fungal etiology (Fig. 6).

Patient was started on amphotericin B based on the MRI findings. Dexamethasone was stopped. The patient's family finally gave consent for surgery, and he underwent a midline suboccipital craniectomy with placement of a right frontal external ventricular drain and Ommaya reservoir on the 40th day of admission. CSF and tissue biopsies were sent for microbiology and histopathology examination. CSF examination was inconclusive (glucose: 77 mg/dL, protein: 3 mg/dL, cell count: 2:100% lymphocytes, meningitis/encephalitis panel negative, gram stain, KOH, routine cultures, cryptococcal antigen, India ink for cryptococcus, ZN stain for AFB, MTB GeneXpert, cytology for malignant cells, autoimmune encephalitis panel were all negative). Tissue biopsy revealed balls of fungal hyphae (broad, septate, pigmented, and branching) mixed with acute inflammatory cells and necrosis, suggestive of a fungal abscess with dematiaceous fungi (Figs 7A and B). Tissue KOH revealed septate, branching fungal hyphae (Fig. 8). Tissue culture revealed filamentous fungus—*C. bantiana* (Figs 9A and B). Antifungals were upgraded (voriconazole and amphotericin B). Transesophageal ECHO was done, which did not show any vegetation. Fundus examination did not show any evidence of fungal infection. The patient progressively worsened and succumbed to sepsis on the 50th day of his admission.

Discussion

Cerebral phaeohyphomycosis is a rare infection caused by darkly pigmented fungi, namely dematiaceous fungi. Dematiaceous fungi share a common phenotypic trait of being dark-colored due to the presence of dihydronaphthalene melanin in cell walls.[5] This melanin pigment has been postulated to contribute to its neurotropism by binding with specific receptors in the blood-brain barrier, allowing access to brain parenchyma.[6]

Brain abscess due to cerebral phaeohyphomycosis can occur in both immunocompetent and immunocompromised groups, though its prevalence is slightly higher in the former due to unknown reasons.[7] *C. bantiana* is a ubiquitous soil saprophyte that inhabits living or dead plant material. Exposure to soil and plant matter can cause paranasal sinus or pulmonary infection, whereas traumatic inoculation may cause subcutaneous infection. The fungus can invade the brain by direct extension from the sinuses or *via* blood/lymphatics through the primary site of infection, such as the lungs or subcutaneous tissue.[3]

Presenting symptoms of cerebral phaeohyphomycosis vary, but most patients present with features of raised intracranial pressure: headache, seizures, vomiting, and altered sensorium.[6] Fungal cerebral abscesses are considered great mimickers and can be difficult to distinguish from high-grade gliomas, lymphomas, and/or metastatic cancers.[8] Cerebral biopsy and microbiological culture with histological analysis are the gold standard for diagnosis.[9]

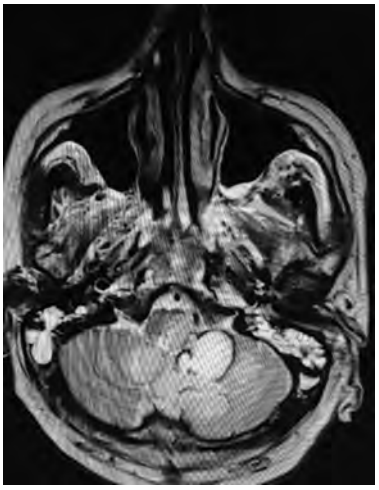


Fig. 6: CEMR brain revealed multiple cerebellar abscesses in the posterior fossa region of brain

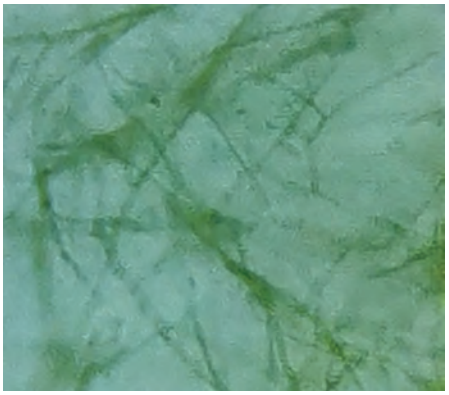
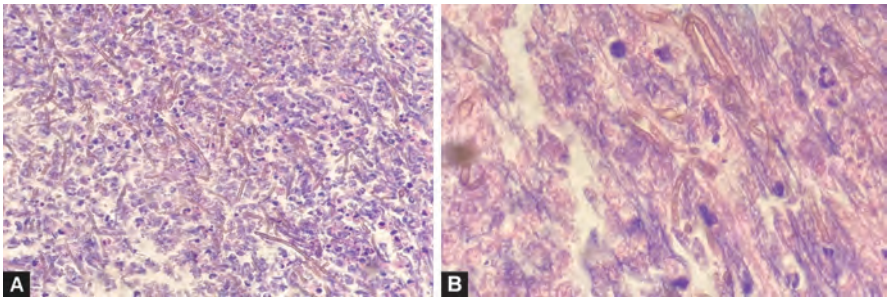
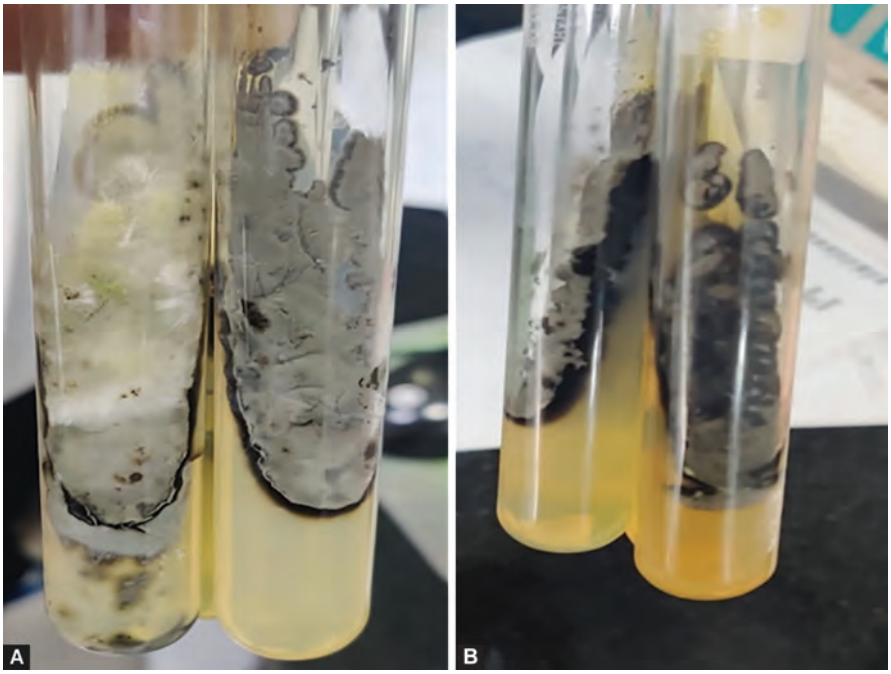


Fig. 8: KOH stain for fungus revealed septate branching hyphae



Figs 7A and B: Fungal hyphae (broad, septate, pigmented and branching) in the tissue: dematiaceous fungi



Figs 9A and B: Growth of black brown filamentous fungus in culture: *C. bantiana*

Tissue biopsy and histopathology examination are the gold standard for the diagnosis of fungal cerebral abscess, and a sample from the lesion should be obtained as early as possible. The primary intraoperative aim should be to obtain an adequate specimen for microbiological examination, with the second being source control in the form of maximum resection of the tumor.[2]

C. bantiana forms olivaceous black colonies and has a velvety texture. It can also survive at higher temperatures (42°C). Microscopically, short-chaining septate hyphae and smooth conidia resemble *Cladosporium* spp., however, they lack conidiophores.[10]

Antifungal therapy with surgical intervention is the preferred treatment for CNS phaeohyphomycosis.[7,11] Optimal duration of treatment for CNS phaeohyphomycosis has not been clearly defined, but antifungal therapy is usually given for several weeks to months, or even longer.[12] Despite the use of both systemic and intrathecal antifungal therapy and advances in surgical excision, these infections carry a high mortality of up to 70%.[3]

Among available antifungals, 5-flucytosine and voriconazole are known to achieve higher cerebrospinal fluid concentrations as they have low molecular weight, low to intermediate lipophilicity, and low protein binding.[13] It is usually treated with a combination therapy of amphotericin B, azoles, and 5-flucytosine.[14,15]

We also treated our patient with a combination of systemic antifungal therapy and excision of the affected brain tissue; still, our patient could not be saved. The possible factors that contributed to mortality in our patient were: first, the delay in the tissue biopsy from the brain, which, if done earlier in the course of illness, might have altered the prognosis. Second, our patient also developed lower respiratory tract infection, upper and lower GI bleed, sepsis, and shock on a background of hypertension, polycythemia vera, peripheral vascular disease, and left common peroneal nerve palsy. Third, and probably the most important, is the deadly nature of the disease itself, which, despite the best possible treatment, carries a high mortality.

Our case also highlights the importance of tissue biopsy in making a diagnosis. As practicing clinicians, every now and then, we stand at crossroads where we need microbiological/histopathological evidence to guide us further. Therefore, tissue biopsy should be obtained as early as possible for prompt diagnosis and management.

Conclusion

C. bantiana brain abscess has been recognized as an emerging infection in Asian countries, especially India, with a higher frequency observed in young, immunocompetent individuals and those from rural backgrounds. Early and aggressive tissue excision for diagnosis and treatment, together with systemic antifungal therapy, should be targeted in cerebral phaeohyphomycosis to improve overall management and survival of the patients.

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CASE REPORT

The Use of Recombinant Activated Factor VII for Controlling Life-threatening Bleeding in Severe Dengue Fever

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Abstract

We report a case of severe dengue fever (DF) in a patient who presented with severe bleeding and discuss the role of recombinant activated factor VII (rFVIIa) in managing life-threatening bleeding in these patients. He presented with spontaneous retroperitoneal, gastrointestinal, and bilateral pleural hemorrhage. In all, 39 units of blood and blood products were transfused within 48 hours of admission, but he continued to experience a drop in hemoglobin. At this stage, the role of rFVIIa was discussed with the family, and he was administered 6 mg of rFVIIa intravenously. Following a single dose of rFVIIa, his ongoing bleeding stopped, and his hemoglobin stabilized. No thromboembolic complications were observed. rFVIIa appears to be a promising intervention in maintaining hemostasis in a subset of severe DF patients who continue to bleed despite all possible efforts. Further studies are warranted.

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Introduction

Dengue fever (DF) is a tropical febrile illness caused by infection with one of the four dengue viruses (DENV) and is transmitted by *Aedes aegypti* or *Aedes albopictus* mosquitoes during mosquito bites. It may remain asymptomatic or present with a wide range of clinical manifestations, including mild febrile illness to a severe life-threatening shock syndrome. Various factors, including viral, host, vector, and epidemiological factors, can affect the risk of acquiring infection, disease, and disease severity. In 1997, a classification scheme was developed and published by the World Health Organization (WHO) describing three categories of symptomatic DENV infection: DF, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).[1] However, in 2009, the WHO introduced a revised classification of dengue illness into the following three categories: dengue without warning signs, dengue with warning signs, and severe dengue.[2] Bleeding in DF can manifest in various forms, ranging from a positive tourniquet test, petechiae, ecchymosis or purpura, bleeding from the mucosa, injection, or venepuncture sites to life-threatening gastrointestinal, pulmonary, cerebral, genitourinary, intramuscular, intraperitoneal, and/or retroperitoneal hemorrhages. However, it is rare to have severe persistent ongoing hemorrhage despite taking adequate and timely interventions. The exact pathophysiology behind bleeding in DF is not clearly elucidated. There are several hemostatic abnormalities described in the literature which resolve spontaneously without causing severe bleeding.

We report a case of severe DF with severe and unusual spontaneous retroperitoneal, gastrointestinal, and bilateral pleural hemorrhages, who continued to bleed despite resuscitation with adequate blood and blood component transfusion and supportive measures. The role of recombinant activated factor VII (rFVIIa) as a therapeutic measure to manage bleeding in such cases is discussed.

Case Description

A 19-year-old male patient had a high-grade fever on 19th September 2023 for 1 day, followed by pain in the abdomen, body aches, and occasional vomiting. He took treatment locally and tested positive for dengue virus NS1 antigen and IgM antibodies on 25th September 23. He remained admitted in a local hospital from 25th to 28th September 2023. His outside prothrombin time (PT) was deranged, and a partial thromboplastin time (PTT) was within normal limits. He was transfused with 2 units of packed red blood cells (PRBC), 5 units of fresh frozen plasma (FFP) along with other supportive treatment. He was then referred for further management. He attended Fortis Escorts Hospital, Jaipur, triage, on 28th September 2023. In triage, his blood pressure was 109/44 mm Hg, heart rate 136/minute, SpO_2 95% on room air, and he was afebrile. He looked pale and had altered sensorium, a diffusely tender and firm abdomen (left > right), and bilateral decreased air entry. He had multiorgan dysfunction and was admitted for further management in the medical intensive care unit. His magnetic resonance imaging (MRI) of the brain was unremarkable. Noncontrast computerized tomography (NCCT) chest showed mild right and moderate left pleural effusion (Fig. 1). The visualized part of the abdomen showed ascites and a multiloculated collection in the left renal-suprarenal fossa. Ultrasonography (USG) of the abdomen showed hepatomegaly with increased peri-portal echogenicity, gall bladder (GB) wall edema, ascites, and a large heteroechoic fluid collection measuring 184 × 105 × 121 mm with dense internal echoes in the retroperitoneal region on the left side of the abdomen and pelvis. The left kidney was not visualized (Fig. 2). In view of poor GCS, he was intubated and taken on mechanical ventilation. He also developed left-sided focal seizures. His hematology and biochemistry parameters showed severe anemia, normal platelet counts, markedly raised transaminases, severe hypoproteinemia, raised PT, azotemia, raised procalcitonin, creatinine kinase, and troponin—consistent with organ failure/dysfunction involving the liver, kidney, heart, coagulopathy, and rhabdomyolysis. He was transfused with 4 units of PRBC and 9 units of FFP on 28th September 23. His two-dimensional (2D) echo showed mild tricuspid regurgitation with right ventricular systolic pressure of 32 mm Hg + right atrial pressure (RAP) and minimal circumferential pericardial effusion. However, he continued to have a fall in hemoglobin and hematocrit despite resuscitation with blood and blood components. He was given a total of 9 units of PRBC, 13 units of FFP, and 8 units of cryoprecipitate along with vitamin K, levetiracetam, antibiotics, tranexamic acid, and supportive care. His hematology and biochemistry are shown in Table 1. On 29th September 2023, the off-label role of rFVIIa was discussed with the family, and a 6 mg

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dose (100 µg/kg rFVIIa) was given on 30th September 23 around 8 pm. His hemoglobin and hematocrit stabilized following rFVIIa.

On 30th September 2023, his blood culture grew Gram-negative bacilli (GNB) and he had continuous fever. Antibiotics were escalated, and intravenous access lines were changed. 700 mL of hemorrhagic fluid was tapped from the left pleural cavity on 1st October 2023. On 2nd October 2023, the blood culture grew *Burkholderia cepacia*, endotracheal secretion culture grew *Acinetobacter baumannii* and *Klebsiella pneumoniae*, and arterial line blood showed budding yeast cells. Antibiotics were adjusted accordingly, and antifungal treatment was added. Cerebrospinal fluid examination was done on 3rd October 2023 and was unremarkable. Electroencephalogram showed a slowing of the background. NCCT chest done on 2nd October 2023 showed moderate right and mild left pleural effusion with CT density Hounsfield unit (HU) 45–50, possibly indicating hemothorax/thick fluid and features of an infective etiology. 200 mL of hemorrhagic fluid was tapped from the right pleural cavity (Fig. 3). He later developed adult respiratory distress syndrome (ARDS), sepsis, and ICU-associated weakness. He had melena on 7th October 2023 with a drop in hemoglobin, and 2 units of PRBC were transfused. Upper gastrointestinal endoscopy showed a blood clot in the body of the stomach—likely erosive gastritis. The colonoscopy was unremarkable. A repeat USG abdomen done on 9th October 2023 showed edematous GB wall thickening and sludge, bilateral grade II renal parenchymal changes, and a large thick loculated septate collection in the left perinephric region indenting the left kidney. His initial 6 days of hematology and biochemistry are mentioned in Table 1. He was shifted to a government facility on 11th October 2023 due to financial constraints. Further follow-up could not be done.

Discussion

Severe bleeding is generally considered unusual in DF and is responsible for fatal outcomes in some patients. As discussed earlier, hemorrhagic manifestations of varying range and severity are observed in the febrile phase and/or critical phase of DF and may range from a positive tourniquet test to life-threatening hemorrhage. Fatal DHF may be associated with diffuse petechial hemorrhages involving the stomach, skin, heart, intestine, and lungs.[3] Besides major skin and/or mucosal bleeding (gastrointestinal, urinary, or vaginal), other less frequent manifestations include heavy menstrual bleeding (40%), hematemesis (15–30%), epistaxis (10%), melena (5–10%), and hematuria.[4] Besides these, spontaneous hematomas have often been described in the brain (subdural hematoma or intracranial hemorrhage), thorax, abdominal cavity, retroperitoneum, muscle parenchyma, and joints.[5] Various factors and mechanisms acting synergistically may contribute to bleeding manifestations in DF. These include thrombocytopenia, vasculopathy with activation, injury of endothelial cells and increased vascular fragility, activation of coagulation and increased fibrinolysis, immunological disturbance, and imbalance between procoagulation and anticoagulation.[6,7]

A 2017 systematic review on prophylactic and therapeutic interventions for bleeding in dengue showed that almost all of these hemostatic abnormalities spontaneously resolve in due course without any clinically significant bleeding. Further, it also recognized that major bleeding manifestations in DF do not necessarily correlate with coagulation abnormalities and the severity of thrombocytopenia. Also, coagulation parameters may not necessarily be a useful guide for determining the risk of bleeding in dengue.[8–11] There are also no guidelines as to whether or when a clinician should attempt to correct thrombocytopenia or deranged coagulation parameters. Over the past many years, the practice of transfusing platelets prophylactically has decreased greatly unless the counts drop significantly to below 10 × 10^3/mm^3. Some of the other therapeutic agents, including rFVIIa, intravenous anti-D globulin, intravenous immunoglobulin (IVIg), tranexamic acid, and recombinant human IL-11, have been studied with the aim of preventing or reducing bleeding in DF. However, at present, the guidelines for the management of dengue do not recommend the use of any of these therapeutic agents for prevention or treatment of bleeding.[12,13]

The control of bleeding in children with DHF using rFVIIa was studied in a randomized, double-blind, placebo-controlled study. It concluded that rFVIIa appears to be a useful adjunctive treatment to blood component transfusion for controlling active bleeding in children with DHF.[13] The authors have also earlier reported the successful use of rFVIIa in a case of DHF presenting as massive postpartum hemorrhage and highlighted the role of rFVIIa not only in obstetric emergencies but also in DHF.[14]

In the case presented, platelets remained stable throughout his illness, and no platelets were transfused. However, blood components other than platelets were transfused before and during admission as required, depending on the clinical status. PRBC were indicated for falling hemoglobin with ongoing bleeding,

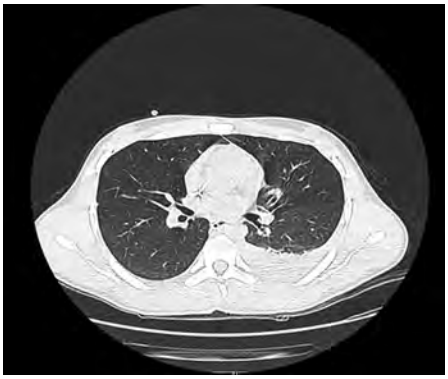

Fig. 1: HRCT chest 28th September 2023

Fig. 3: Right side pleural fluid

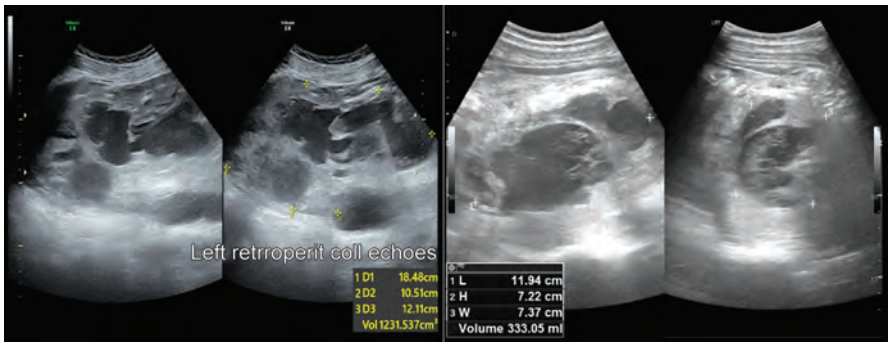

Fig. 2: USG abdomen 28th and 30th September 2023

Table 1: Hematology and biochemistry for initial 6 days

	28th September 2023	*29th September 2023*	*30th September 2023*	*1st October 2023*	*2nd October 2023*	*3rd October 2023*
CRP (0–5 mg/L)	26.5					
D-dimer (<255 ng/mL DDU)	626			534		
Ferritin (13–150 ng/mL)		8903		2214		
BUN (6–20 mg/dL)	61	77	87	102	120	103
Creatinine (0.5–0.9 mg/dL)	2.20	2.90	3.15	3.60	3.61	2.91
S. electrolytes (meq/L)	148/4.81	151/4.81	156/5.88 158/5.98	158/4.86	163/4.30 162/4.78	149/4.59
Uric acid (3.4–7 mg%)	13.7	17.6	13.0	13.7	12.8	7.5
Hb (gm/dL)	5.3 (11 am) 4.4 (7.15 pm)	8.0 (1 am) 7.2 (5.45 am) 5.6 (2.30 pm)	6.2 (1 am) 6.4 (6 am) 5.8 (4.20 pm) 6.8 (10.30 pm)	7.5 (6.10 am) 7.8 (3.15 pm) 9.3 (6.35 pm)	10.0 (6.15 am)	8.8 (7 am) 10.6 (5.30 pm)
HCT (PCV)% (@ time as for Hb)	15.8 13.5	23.7 20.4 16.0	17.5 18.6 17.2 20.6	23.1 23.8 xxx	30.7	27.8 33.2
TLC (10^3/mm^3) (@ time as for Hb)	10.9 17.7	11.1 10.3 9.8	10.9 10.7 10.3	10.0 11.9 xxx	15.8	13.4 xxx
DLC (%) (@ time as for Hb)	P77L19 P68L24S4	P76L12S8 P82L13 P84L12	P84L12 P82L14 P74L13S11	P83L13S0 P86L12S0 P10L90	P89L8S0	P90L6
Platelets (10^3/mm^3) (@ time as for Hb)	150 150	150 155 150	150 150 150	150 150	120	90
SGOT/SGPT (<32 U/L)	2351/1214	1656/862	976.3/655	927/726		490/412
S. bilirubin T/D (<1.2 mg/dL)	1.04/0.76		1.83/1.24			
S.ALP (40–129 U/L)	46		90			
S. protein/alb. (6.4–8.3 gm/dL)	4.2/2.5		5.4/3.2			
GGT (5–36 U/L)	70		102			
LDH (135–225 U/L)	2531		1780			
PT/INR	30.6/2.34	20.6/1.52	17.7/1.29	12.3/0.87		
APTT (control 25.9 seconds)				26.2		
Procalcitonin ng/mL (*N* < 0.046)	21.0			11.08		
S. fibrinogen		198 332				
Amylase (28–100 U/L)	1054			215		
Lipase (13–60 U/L)	18					
NT-proBNP (pg/mL)	1055					
CK MB (0.30–6.22 IU/L)	24.9					
CPK (39–308 U/L)	2815		5974	5090	6734	
Trop T (<14 pg/mL)	140.3			232.2		

CRP, C-reactive protein; Hb, hemoglobulin; HCT, hematocrit; TLC, total leucocyte count; DLC, differential leucocyte count; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate pyruvate transaminase; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; LDH, lactic dehydrogenase; PT-INR, prothrombin time–International ratio; aPTT, activated partial thromboplastin time; CK-MB, creatine kinase–myocardial band; CPK, creatine phosphokinase; Trop T, troponin T

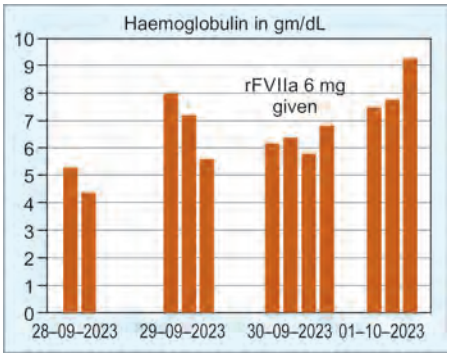

Fig. 4: Daily hemoglobin level and stabilization after administration of rFVIIa. (Refer to Table 1 for time chronology of Hb)

FFP for coagulopathy, and cryoprecipitate for hypofibrinogenemia. In addition, he received supportive treatment, airway management, fluid and electrolyte therapy, and appropriate antibiotics according to the clinical manifestations and culture reports. When all efforts failed to control ongoing bleeding with falling hemoglobin, off-label use of rFVIIa was considered, and a 6 mg dose was given on 30th September 2024. After the dose, hemoglobin stabilized (Fig. 4). The efficacy of bleeding control was assessed as "effective" as the ongoing bleeding episode completely stopped. No clinical evidence of thromboembolic or other complications was observed. He was observed until 11 days after giving rFVIIa and did not have a recurrence of bleeding related to DHF. However, a week later, he developed erosive gastritis with melena and required 2 units PRBC transfusion. ARDS and other complications were considered to be related to the disease course. He could not be observed afterward as he took discharge for further care at a government facility.

It is proposed that rFVIIa has localized hemostatic effects and helps in forming a firm fibrin clot locally at the site of vascular injury by enhanced thrombin generation.[15] Further, earlier initiation of rFVIIa in DHF yields a higher effective response than delayed initiation in the stage of DSS.[13] In this case, its use as an adjunctive treatment improved the efficacy of bleeding control.

In conclusion, based on this case study and our previous case report,[14] rFVIIa appears to be useful as an adjunctive treatment to blood component replacement therapy in restoring hemostasis in patients with DSS presenting with life-threatening bleeding manifestations. Nevertheless, there is a need for further research and studies on the use of these therapeutic agents and to establish the optimal dose regimen of rFVIIa in DHF.

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CASE REPORT

Refractory Pericardial Effusion in a Patient with Rosai–Dorfman Disease

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Abstract

Rosai–Dorfman disease (RDD) is an extremely rare, histiocytic proliferative disorder most commonly presenting as lymphadenopathy in young adults and children. Although it may present with a wide range of extranodal manifestations, involvement of the cardiovascular system is extremely rare. The etiopathogenesis of RDD is poorly understood. Sporadic RDD is mostly a self-limited disease and has a good clinical outcome. There is a lack of standardized, evidence-based recommendations to treat multifocal extranodal disease. Poor prognostic factors include autoimmune cytopenias as well as disseminated organ involvement, including kidneys, heart, lower respiratory tract, liver, etc. We report a case of a 54-year-old gentleman who presented with refractory pericardial effusion, orbital disease, and lymphadenopathy, with a good clinical response to immunosuppressive therapy.

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Case Description

We report a case of a 54-year-old gentleman who presented initially to his family physician with swelling of the left eye. He also developed swelling of the right eye and progressive loss of vision in the left eye over the following 6 months. Eye examination revealed bilateral proptosis, conjunctival chemosis, and diffuse bilateral upper and lower lid swelling (Figs 1A and B). The lid swelling felt hard on palpation, and the lid lumps appeared to be attached to the deeper structures. MRI of the orbit confirmed diffuse soft tissue masses replacing orbital fat bilaterally, compressing the intraorbital part of the optic nerve (Fig. 2). There was no history of headache or focal neurological deficit. He started to experience chest pain, low-grade fever, and exertional shortness of breath and was reviewed by a cardiologist, at which point a large pericardial effusion was diagnosed with no evidence of cardiac tamponade. Thereafter, he required four consecutive hospital admissions over a period of 5 months, during which large-volume pericardiocentesis was performed, draining 1200, 800, 1700, and 400 mL of exudative pericardial fluid on different dates. He also required a pericardial window due to worsening chest discomfort and breathlessness associated with refractory pericardial effusion. Pericardial biopsy was performed. Infection screening, including tuberculosis, and autoimmune screening were negative. He denied any history suggestive of xerophthalmia, xerostomia, arthralgia, swelling of the legs, skin rash, lymphadenopathy, or significant weight loss. A computed tomography of the chest revealed small-sized mediastinal lymphadenopathy. Biopsy from bilateral orbital tissue and pericardium (Figs 3A and B) demonstrated sheets of histiocytes and foamy macrophages, a few emperipolesis, scattered lymphocytes and plasma cells, and lymphoid aggregates suggestive of Rosai–Dorfman disease (RDD). He was treated with pulsed methylprednisolone followed by a tapering regimen of oral prednisolone and methotrexate, with a good clinical response. Over the next few months, he experienced significant improvement of proptosis and vision involving both eyes, with no further relapse of pericardial effusion during follow-up.

Discussion

Rosai–Dorfman disease is an uncommon, benign nonLangerhans cell histiocytosis characterized by the accumulation of abundant CD68-positive, S100-positive histiocytes in various tissues or organs of the body. The estimated incidence of RDD is around 100 new cases per year, with a prevalence of 1:2,00,000 in the United States.[1,2] There are ambiguities about the etiology of RDD, although associations with viral infections such as Epstein–Barr virus,

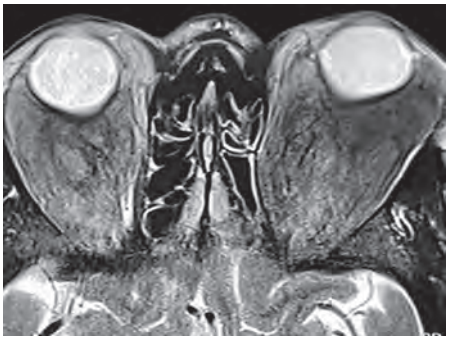
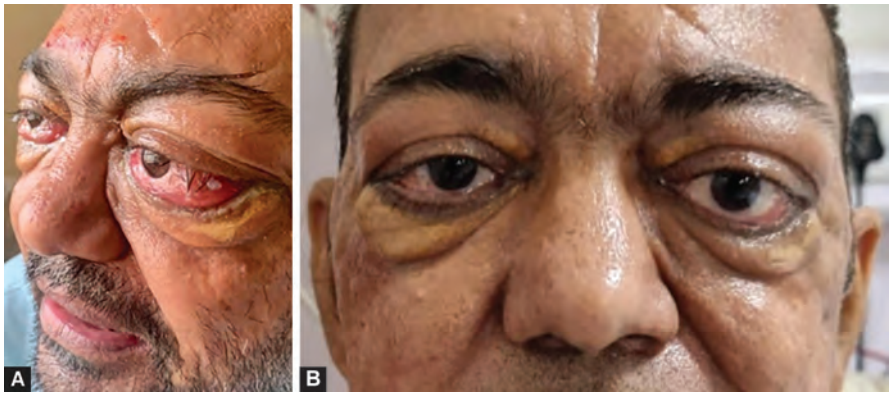


Fig. 2: MRI of orbit showing diffuse soft tissue masses replacing orbital fat bilaterally compressing the intraorbital part of optic nerve



Figs 1A and B: Proptosis of both eyes and conjunctival effusion. (A) Prior to treatment; (B) Following treatment

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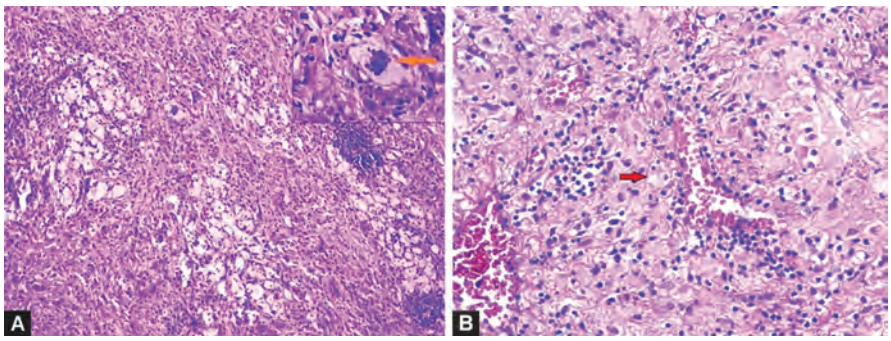

Figs 3A and B: Histopathology section showing sheets of histiocytes and foamy macrophages with occasional lymphoid aggregates (H&E 10×). Inset showing emperipolesis (H&E 40×). (A) Orbital tissue; (B) Pericardial tissue

herpesviruses, HIV, and cytomegalovirus have been reported in several studies.[3] RDD has also been associated with inherited conditions (familial histiocytosis, pigmented hypertrichotic dermatosis with insulin-dependent diabetes, etc.), neoplastic conditions (lymphoproliferative diseases, myelodysplastic syndromes, etc.), autoimmune diseases (idiopathic juvenile arthritis, systemic lupus erythematosus, autoimmune hemolytic anemia, etc.), and IgG4-related RDD. Garces et al.[4] have observed *KRAS*, *NRAS*, *ARAF*, and *MAP2K1* mutations in affected tissues, raising the possibility of a neoplastic process.

The clinical spectrum of RDD is wide and depends on the extent of the disorder and the specific organ systems involved. It usually affects children, adolescents, or young adults, with a slight male predominance. The most common organs involved are the skin and subcutaneous tissue, followed by lymph nodes and extranodal tissues, including the salivary glands, upper respiratory tract, bones, eyes, and orbits.[5] In rare cases, the central nervous system (CNS), digestive system, heart, and kidneys may be affected.

Cardiac involvement in RDD is an extremely rare presentation, occurring in 0.1–0.2% of cases. Three patterns of cardiac involvement have been identified: (1) an intracardiac mass with or without underlying infiltration, (2) pericardial or epicardial involvement, and (3) a pulmonary arterial mass, with the most common manifestation being an intracardiac mass.[6] The unique feature in this case was the initial clinical presentation with refractory pericardial effusion and orbital involvement in a patient with RDD.

A comprehensive medical history, thorough physical examination, and focused diagnostic strategy are therefore essential for the appropriate assessment of disease activity and evaluation of associated medical conditions such as autoimmune disorders, malignancies, etc. The therapeutic approach is multidisciplinary and should be customized according to clinical circumstances. Around half of patients with cutaneous or nodal disease will have spontaneous remissions, and no therapy will be indicated. Corticosteroid therapy is recommended to optimally control nodal size, CNS, orbital, and bone diseases, as well as autoimmune hemolytic anemia, although the responses have been variable. Immunosuppressive therapies such as methotrexate, azathioprine, vincristine alkaloids, lenalidomide, and rituximab have shown variable beneficial effects in several studies.[7] However, the optimal duration of corticosteroid therapy or other immunosuppressive agents for RDD remains a matter of debate. Radiotherapy may be beneficial in orbital bone disease with visual impairment or refractory airway obstruction. Surgical resection is indicated for unifocal disease or an intracardiac mass. Debulking surgery may be warranted for spinal cord compression, severe upper airway obstruction, or large lesions causing end-organ dysfunction.

There is a paucity of evidence to determine the prognosis of RDD. Sporadic RDD, nodal, and cutaneous disease are usually self-limiting and have a favorable outcome. Multifocal and extranodal RDD, especially involving the lower respiratory tract, liver, and kidneys, seem to have an unfavorable prognosis.

Conclusion

The unique feature of this case is refractory pericardial effusion and significant orbital disease in a patient with RDD. Being a rare disease, the clinical profile and prognosis of RDD are not clearly defined. A high index of suspicion and accurate histopathological diagnosis are warranted for early diagnosis and the institution of optimal therapeutic intervention. Advancements in biological and molecular research are needed for characterization of the spectrum of molecular alterations in RDD, to prognosticate the clinical profile and investigate novel therapies for RDD.

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CASE REPORT

Opercular Syndrome without Involvement of Opercular Area—An Uncommon Presentation of Stroke: A Case Report

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Abstract

Foix Chavany Marie syndrome (FCMS), or opercular syndrome, is a rare type of pseudobulbar palsy characterized by paralysis of bilateral facio-linguovelo-masticatory and pharyngeal muscles with automatic-voluntary dissociation. This syndrome was first described by Magnus in 1837 and further defined by two French neurologists, Charles Foix and Jean Alfred Emile Chavany, along with one French pediatrician, Julie Marie, who reported it first in 1926. Since then, a few cases have been reported across the world. We hereby report a case of FCMS in a 61-year-old male patient who presented to us with two different cerebrovascular events.

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Introduction

Foix Chavany Marie syndrome (FCMS), or opercular syndrome, also known as cheiro-oral syndrome (COS), is characterized by the inability of the patient to open or close the mouth or eyes, that is, loss of voluntary bulbar movements. It is a severe form of pseudobulbar palsy that occurs due to bilateral lesions involving the opercular region, the perisylvian cortex, or the subcortical connections, causing paralysis of bilateral facio-linguo-masticatory-pharyngeal muscles innervated by lower cranial nerves (CNs) including CNs V, VII, IX, X, and XII.[1,2] Comprehension in these patients is intact, allowing them to follow commands. There is no weakness or paresis of the extremities, enabling them to perform routine tasks, and their reflexes are well preserved. A phenomenon called automatic-voluntary dissociation is observed in these patients, meaning their emotional response to a particular stimulus is intact and appropriate. However, they cannot elicit the same response voluntarily when asked to do so in the absence of a stimulus. For instance, these patients can yawn spontaneously, smile and laugh in response to an entertaining joke, and cry in response to distressing news. However, when asked to yawn, smile, or cry voluntarily, they are unable to do so.

Case Description

A 61-year-old male patient, a security guard by profession, presented with chief complaints of difficulty speaking and eating for 1 day. On the previous morning, after waking up at 11:00 AM, he experienced palpitations and choking followed by difficulty speaking. He had a similar episode 9 hours earlier during his night duty, which resolved spontaneously after a few minutes. Along with difficulty speaking, he also noticed difficulty opening his mouth, chewing food, and swallowing water, which was associated with severe coughing whenever he attempted to do so. There were no complaints of limb weakness, vertigo, falls, loss of consciousness, abnormal body movements, decreased hearing, bladder or bowel incontinence, difficulty walking, or head injury. He was an occasional alcohol drinker and a tobacco chewer. His past medical history included hypertension for 5 years, for which he was noncompliant with antihypertensive medications.

On physical examination, the patient was fully conscious, oriented to time, place, and person, and cooperative. His vitals were normal. His speech was slurred, lacked clarity, and showed improper articulation of words. This was associated with hoarseness and decreased volume of speech, with no scanning or nasal twang. He was able to understand and comprehend instructions and could respond by writing on paper. Examination findings revealed severe cortical dysarthria with bilateral facial weakness, orolabial, lingual, masticatory, and pharyngeal paralysis, and severe oropharyngeal dysphagia, accompanied by constant drooling of saliva from his mouth (Fig. 1). He cried when emotional and smiled upon seeing his family members; however, he was unable to smile voluntarily when asked. There was no aphasia or limb weakness. Sensory, autonomic, and cerebellar examinations were within normal limits, and there was no gait abnormality.

Blood investigations revealed moderate anemia with normal white blood cell and platelet counts. Liver and kidney function tests, as well as the chest X-ray and electrocardiogram (ECG), were normal. Fundus examination showed drusens (extracellular yellowish deposits under the retina made up of lipids and proteins) in the macular area bilaterally. Noncontrast computed tomography (NCCT) of the head showed multiple chronic lacunar infarcts bilaterally in the ganglio-capsular region, the right corona radiata, and the right thalamus (Fig. 2). Contrast-enhanced magnetic resonance imaging (CEMRI) of the brain and magnetic resonance (MR) angiography revealed both acute and chronic infarcts. Acute infarcts were observed in the corona radiata, body of the caudate nucleus, internal capsule, and putamen on the left side. Chronic lacunar infarcts were identified in the ganglio-capsular region, corona radiata, and thalamus on the right side (Fig. 3). There was no evidence of arterial stenosis or aneurysm in the cerebral arteries or their branches.

Fig. 1: The image shows bilateral facial weakness and the patient's inability to fully open the mouth

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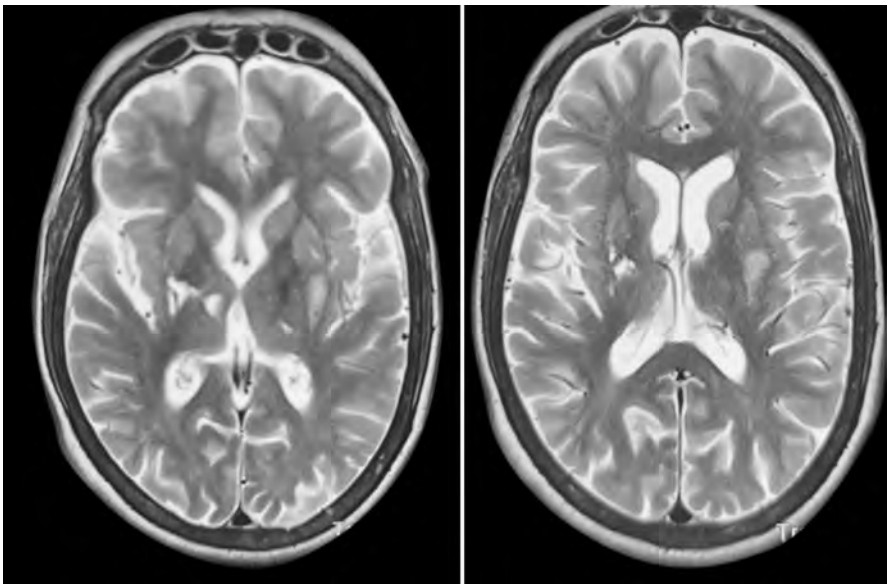
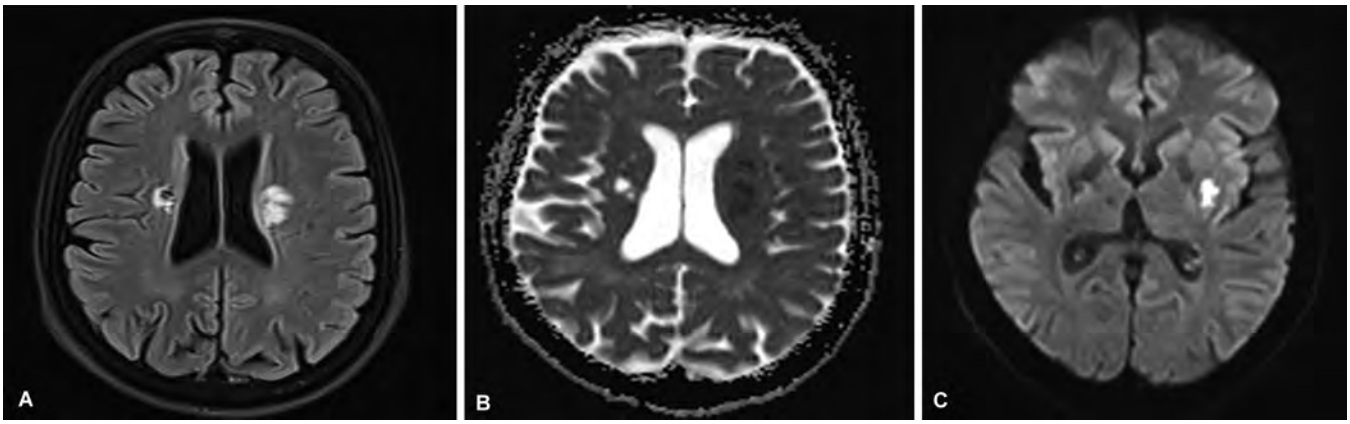


Fig. 2: T2-weighted MRI sequences (axial section) showing acute lacunar infarcts in the corona radiata, body of the caudate nucleus, internal capsule, and putamen on the left side, as well as chronic lacunar infarcts in the ganglio-capsular region, corona radiata, and thalamus on the right side



Figs 3A to C: (A) Axial image (T2/TIRM); (B) ADC; and (C) DWI images showing diffusion restriction in the body of the caudate nucleus, putamen, internal capsule, and corona radiata on the left side, suggestive of acute infarcts, and without diffusion restriction in the ganglio-capsular region, corona radiata, and thalamus on the right side, suggestive of chronic infarcts

He was managed conservatively with Ryle's tube feeding, antihypertensives, antiplatelets, and statins. Thrombolysis was not performed due to late presentation. After 11 days of conservative management, there was marked improvement in his symptoms. He was discharged on the same treatment, and speech therapy was initiated. At follow-up after 2 months, 70–80% improvement in his symptoms was observed, and he was able to eat and speak.

Discussion

FCMS occurs due to bilateral lesions of the opercular cortex surrounding the insula, the perisylvian cortex, or their subcortical connections. In our patient, neuroimaging studies showed ischemic lesions in the caudate nucleus, putamen, internal capsule, and corona radiata, suggesting involvement of subcortical connections and descending tracts from the opercular area to CN nuclei. This led to bilateral involvement of lower CNs, paralyzing the face, lips, tongue, jaw, and pharyngeal muscles. Automatic-voluntary dissociation was also present in our patient. The features of FCMS resemble the bulbar form of Guillain–Barré syndrome (GBS) and botulism, but the symptoms are more severe, with the characteristic feature of automatic-voluntary dissociation. The most common etiology is cerebrovascular accidents, with other causes including central nervous system (CNS) infections (human immunodeficiency virus and herpes simplex encephalitis), multiple sclerosis, neurodegenerative diseases, Moyamoya disease, vasculitis, and traumatic brain injury. Diagnosis is made by combining clinical examination with neuroimaging studies, and management is based on the etiology of the disease. The incidence of FCMS is very rare, with fewer than 150 cases reported in the literature to date.[3]

Conclusion

Foix-Chavany-Marie syndrome is a rare and severe type of pseudobulbar palsy observed in patients with sequential strokes involving the bilateral opercular regions, perisylvian cortex, or subcortical connections. Immediate recognition of this syndrome is crucial, and prompt revascularization therapy should be initiated.

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CASE REPORT

Demodex Folliculorum Causing Necrotizing Fasciitis in a Patient of Autoimmune Myelofibrosis and Type 2 Diabetes: A Rare Case Report

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Abstract

Demodicosis is a skin disease caused by the *Demodex* mite. It commonly involves areas in or near pilosebaceous units. Infestation with *Demodex* is asymptomatic but may have a pathogenic role in immunocompromised individuals or when present in high densities. We hereby report a case of a 36-year-old fruit seller, a known case of diabetes, rheumatic heart disease, and autoimmune myelofibrosis, who presented with progressive right periorbital swelling with blackish discoloration, purulent discharge, and fever. Incision and debridement were performed repeatedly, and tissue was sent for microbiology, which revealed *Demodex folliculorum*. The patient was treated with IV antibiotics, IV amphotericin B empirically, and oral ivermectin for *Demodex*.

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Introduction

Demodex mite, belonging to the phylum Arthropoda, is a tiny parasitic mite found in or near hair follicles of mammals, with two species, namely *Demodex folliculorum* and *Demodex brevis*, typically residing in humans. *Demodex* infestation is common in healthy adults, with a prevalence of 23–100%.[1,2] Men are more likely to be heavily infested compared to women.[3] Demodicosis involves pilosebaceous units, predominantly found in the follicles of the eyelids, nose, and nasolabial folds.[2] Immunosuppressed patients are known to have a more extensive variety of manifestations of this disease compared to immunocompetent individuals.[3] The conditions [human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), cancer, diabetes] and medications (steroids, chemotherapy) affecting humoral or cellular immunity can contribute to the proliferation of *Demodex* mites.[4]

Case Description

We hereby report the case of a 36-year-old male, a fruit seller by occupation, known case of type 2 diabetes mellitus for 10 years, rheumatic heart disease postaortic valve replacement on warfarin, and autoimmune myelofibrosis on low-dose prednisolone. He presented with swelling and black discoloration around the right eye, which started as a small papule on the lower eyelid 10 days ago and gradually progressed over the next few days to a large swelling with black discoloration and purulent discharge from the same. The swelling was accompanied by a low-grade fever for the last 7 days. There was no history of recent trauma, blurring/reduced vision, discharge from the eye, cough/cold, discharge from the nose, sore throat, abdominal pain, diarrhea, vomiting, headache, neck stiffness, altered behavior, or abnormal movements. There was no history of similar swelling in the past or at any other site in the body.

On examination, the patient was conscious and oriented. He had tachycardia [heart rate (HR)–110/minute) with a blood pressure of 92/70 in the right arm in the supine position, peripheral capillary oxygen saturation (SpO_2) was 98% on room air, and the axillary temperature was 98.2°F. On examination of the right eye, a large periorbital swelling around the right eye was noted, with blackish discoloration and surrounding erythema. Purulent discharge was noted from the swelling (Fig. 1).

The rest of the systemic examination was within normal limits. A clinical diagnosis of necrotizing fasciitis was made with a possible fungal etiology. Initial investigations revealed anemia [hemoglobin (Hb)—8 gm/dL], normal total leukocyte count (TLC) (7000/mm^3), and low platelets (10000/mm^3), with bicytopenia attributed to underlying autoimmune myelofibrosis. Liver function test (LFT) and kidney function test (KFT) were normal (Table 1). Inflammatory markers were raised: erythrocyte sedimentation rate (ESR)—120 mm/hour, C-reactive protein (CRP)—227 mg/L, and procalcitonin—27 ng/mL. Hemoglobin A1c (HbA1C) was 8.5%. HIV Ab was negative. Four units of random donor platelets were transfused, and an urgent incision and debridement of the tissue was performed, with removal of the sloughed tissue and debridement of the necrotic margins. Pus pockets extending into the right cheek and forehead were drained (Fig. 2).

Pus and tissue were sent for Gram stain, KOH for fungus, ZN staining for AFB, *Mycobacterium* gene Xpert, and routine and fungal cultures, all of which were negative. A wedge biopsy from the margin of the wound was taken and sent for histopathology, which was inconclusive.

Microbiology reported *D. folliculorum*, which was considered an infestation. Blood and urine cultures were sterile. He was started on empirical antibiotics, antifungals (amphotericin B), and other supportive therapies. The patient underwent multiple debridements over the next few days, and each time microbiology reported *D. folliculorum* from every tissue sent (Fig. 3).

The case was discussed with a microbiologist, and he reported that it was very unusual to see such heavy growth of *D. folliculorum* and should not be ignored as an infestation. A decision to treat *Demodex* with ivermectin was made, and the wound actually started healing. The patient was discharged in stable condition with advice to follow-up.

Discussion

Demodex mites are the most commonly found ectoparasites in humans.[4] Approximately, 65 species of *Demodex* have been studied, of which two species, that is, *D. folliculorum* and *D. brevis*, are considered pathogenic for humans and are collectively referred to as *Demodex*.[2] *D. folliculorum* was first identified by Simon in

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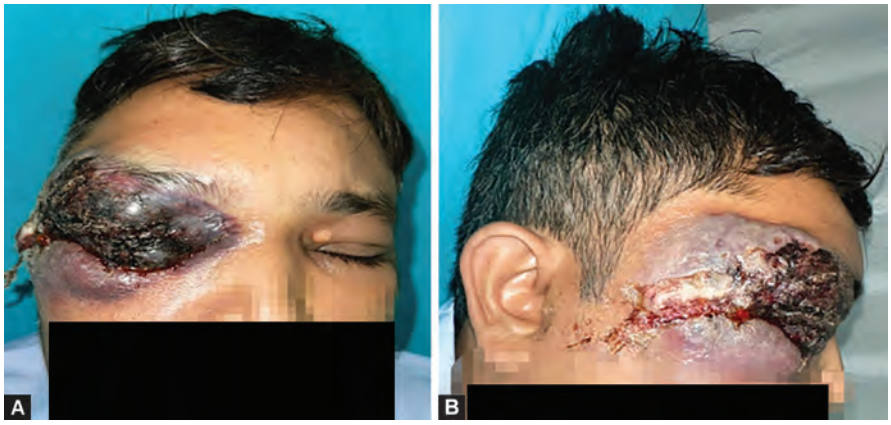

Figs 1A and B: Large periorbital swelling around right eye with blackish discoloration and surrounding erythema

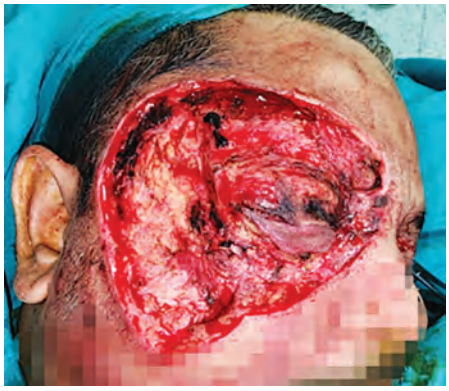

Fig. 2: Postdebridement wound with necrotic and sloughed base

Table 1: Routine investigations

Complete blood count (CBC)	Hb	8 g/dL
	TLC	7000/mm^3
	Platelets	10000/mm^3
KFT	Creatinine	0.68 mg/dL
	Na/K	136/4.1 meq/L
LFT	Total/direct bilirubin	1.1/0.5 mg/dL
	Total protein/albumin	5.01/2.5 g/dL
	SGOT/SGPT	33/22 IU/L
	ALP/GGT	71/46 IU/L

Fig. 3: *Demodex folliculorum* seen in microscopic examination of the tissue

1841–42,[5] and *D. brevis* by Akbulatova in 1963.[6] Adult *D. folliculorum* and *D. brevis* are 0.3–0.4 mm and 0.15–0.2 mm in length, respectively, with eight short, segmented legs that move at a rate of 8–16 mm per hour at night, as bright light causes mites to recede into follicles.[2] *Demodex* is an ectoparasite of the pilosebaceous unit and, therefore, infests seborrheic regions, with *D. folliculorum* predominantly localized to the face and *D. brevis* on the neck as well as the chest. *D. folliculorum* is the more prevalent species, usually found in the upper canal of pilosebaceous units and utilizes skin cells as well as sebum for nourishment.[7] *D. brevis*, on the contrary, is less common but has a wider distribution over the body. It burrows deeply into sebaceous glands and ducts, hence feeding on the gland cells.[8]

In most of the population, *Demodex* mites are only carriers and do not develop clinical symptoms. Demodicosis is considered to be a multifactorial disease, with immunosuppression being one of the most important factors for the transition from asymptomatic mite infestation to symptomatic disease.[9] Both primary (hereditary defect of T cells) and secondary immune suppression (corticosteroid use, HIV, cytotoxic therapy, malignancies) have been shown to predispose individuals to demodicosis.[9] Apart from immunosuppression, demodicosis may also be related to genetic predisposition[10] and may also be associated with various types of human leukocyte antigen (HLA), although some of them are considered resistant to demodicosis.[11] The exact pathogenesis of demodicosis is poorly understood, with altered immune response—especially in immunosuppressed individuals—being considered one of the most possible hypotheses.[12]

Infestation may remain clinically inapparent, but under favorable conditions, it multiplies rapidly, causing pathogenic conditions. An increase in mite density has been found in skin conditions like rosacea, nonspecific facial dermatitis, androgenetic alopecia, madarosis, dissecting folliculitis, peri-oral dermatitis, acariasis blepharoconjunctivitis, Grover's disease, eosinophilic folliculitis, papulovesicular facial eruptions, papulopustular scalp eruptions, pityriasis folliculorum, pustular folliculitis, *Demodex* abscess, and demodicosis gravis (granulomatous rosacea-like demodicosis).[13] It is still unknown whether *Demodex* is a cause of the abovementioned conditions or if the density of mites increases secondary to inflammation of affected follicles.[14] One possibility is that blockage of hair follicles may lead to inflammation, allergic reactions, or may act as a vector for other microorganisms.[15]

Treatment of demodicosis includes topical permethrin, topical/oral metronidazole, oral ivermectin, doxycycline, and erythromycin.[3] Our patient was diabetic and on steroids for autoimmune myelofibrosis, which are predisposing factors for the development of demodicosis. Additionally, the lesion started as a papule and progressed to a massive black periorbital swelling. It cannot be clearly confirmed that the lesion was solely due to *Demodex*, but repeated cultures from the tissue did not reveal any bacteria or fungi and persistently showed densely infiltrated *Demodex* in every microscopy. To the best of our knowledge, this is the first case report of *Demodex* causing necrotizing fasciitis. The patient was treated with broad-spectrum antibiotics, antifungals, ivermectin, and topical permethrin, and he responded to the treatment.

Conclusion

Demodicosis should be kept in mind when considering the differential diagnosis for skin lesions, especially on the face, in immunosuppressed individuals. This may aid in early diagnosis and timely treatment, thus being helpful for the patient as well as cost-effective.

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Announcement

DR JC PATEL AND DR BC MEHTA BEST PAPERS AWARD 2024

1st Prize for Best Original Article entitled – Neutrophil-to-lymphocyte Ratio as a Marker for Diagnosis and Prognostication of Sepsis – Rakesh Bhadade[1], Isha Naik[2], **Minal Harde**[3]*, Rosemarie de Souza[4] – [1]Professor, Department of Medicine; [2]Assistant Professor, Department of Medicine; [3]Professor, Department of Anaesthesialogy; [4]Professor and Head, Department of Medicine, Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital, Mumbai – *J Assoc Physicians India 2024;72(6):33–38.*

2nd Prize for Best Original Article entitled – To Access Knowledge Regarding Organ Donation among Healthcare Workers and Their Willingness toward Organ Donation – Kapil Zirpe[1], Sushma Gurav[2], **Subhal Dixit**[3]*, Prajakta Pote[4], Abhijeet Deshmukh[5], Anand Tiwari[6], Prasad Suryawanshi[7], Surekha Joshi[8], Khalid Khatib[9], Lochana Jadhav[10], Manasi Gole[11], Sinu Mathew[12], Raeena L Shaikh[13] – [1]Director, Department of Neurotrauma, Intensive Care Unit, Ruby Hall Clinic; [2,4–7]Consultant, Department of Neurotrauma; [3]Director, Department of Critical Care, Sanjeevan Hospital; [8,10,11]Social Worker, Department of Neurotrauma, Intensive Care Unit, Ruby Hall Clinic; [9]Consultant, Department of Critical Care, Smt Kashibai Navale Medical College & General Hospital; [12–13]Patient Coordinator, Department of Neurotrauma, Intensive Care Unit, Ruby Hall Clinic, Pune, Maharashtra – *J Assoc Physicians India 2024;72(1):56–62.*

2nd Prize for Best Original Article entitled – Evolution of Metabolic Syndrome in Newly Diagnosed Type 2 Diabetes Mellitus Asian–Indian Patients Over the Last 15 Years using Adult Treatment Panel III of the National Cholesterol Education Program, World Health Organization, and International Diabetes Federation Criterion – **Harshpreet Singh Tuteja**[1]*, Nikhil Nassikar[2], Krish Panikar[3], Mangesh Tiwaskar[4], Sanhita Walwalkar[5], Ishita Sachdev[6], Sunil Kamble[7], Parveen Kadir[8], Aditi Mahajan[9], Shashank Joshi[10], Vijay Panikar[11] – [1]Consultant, Department of Medicine, SRS Hospital, Ambikapur, Chhattisgarh; [2]Associate Professor, Department of Medicine, BKL Walawalakar Medical College, Mumbai, Maharashtra; [3]Resident, Department of Endocrinology, Amrita Institute, Cochin, Kerala; [4]Consultant Physician & Diabetologist, Shilpa Medical Research Centre; [5,6]Consultant, Dr Panikar Diabetes Care; [7]Consultant, Dr Kamble Diabetes Care; [8,9]Resident; [10]Consultant; [11]Consultant and HOD, Department of Endocrine, Lilavati Hospital, Mumbai – *J Assoc Physicians India 2024;72(6):39–43*.

1st Prize for Best Case Report entitled – Pulmonary Radiological Manifestations of Paraquat Poisoning: A Pictorial Essay – Ekta Mishra[1], **Rekha Gupta**[2]*, Gursimran Singh Anand[3], Gurkamal Kaur Toor[4] – [1,3]PGJR; [2]Associate Professor, Government Medical College and Hospital, Chandigarh; [4]Consultant, IVY Hospital, Mohali, Punjab – *J Assoc Physicians India 2024;72(03):100–104.*

2nd Prize for Best Case Report entitled – A Case Report of Larsen's Syndrome, Antiphospholipid Syndrome, Diaphragmatic Hernia, and a Colon Polyp: A Hidden Association or a Mere Coincidence – Shashwat Mallik[1], **Shahin Khan**[2]*, Aayushi J Rajani[3], Juhi Amin[4], Darshankumar Manubhai Raval[5] – [1,2]Intern Doctor; [3]Medical Officer, Department of Medicine; [4]Senior Resident, Department of Obstetrics and Gynecology, Government Medical College Baroda, Vadodara, Gujarat, India; [5]Research Fellow, Department of Infectious Disease, Mayo Clinic, Jacksonville, Florida, United States – *J Assoc Physicians India 2024;72(11):e47–e49.*

1st Prize for Best Correspondence entitled – Supraventricular Tachycardia: An Uncommon Cause of Chronic Cough – **Ambika Sharma**[1], Kanhaiya Lal Meena[2], Raghuveer Singh[3]; [1]Assistant Professor; [2,3]Junior Resident, IRD Hospital, SMS Medical College, Jaipur, Rajasthan, India – *J Assoc Physicians India 2024;72(04):103*.

2nd Prize for Best Correspondence entitled – Tissue Biopsy to the Rescue: The Art of Modern Medicine – **Rahul Kumar**[1], Pooja Khosla[2], Vinus Taneja [3], Manuj Sondhi[4] – [1]DNB Trainee; [2]Senior Consultant; [3]Associate Consultant; [4]Clinical Assistant, Department of Internal Medicine, Sir Ganga Ram Hospital, Delhi, India – *J Assoc Physicians India 2024;72(04):103*.

CASE REPORT

Lest We Miss Hansen Arthritis: Case Series of Combo Articular Manifestations; One of Acute Lepra Reaction with Chronic Arthritis, and Another of Swollen Feet and Hand Syndrome besides Acute Lepra with Chronic Arthritis

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Abstract

Hansen's disease is an infectious granulomatous disease with classical cutaneous and neurological profile and varied musculoskeletal manifestations. Poor awareness and low specificity of symptoms lead to a delay in the diagnosis of a treatable disease, culminating in worsening morbidity. A rare case series of Hansen's arthritis, showing complex, diverse, and rare combinations of musculoskeletal manifestations of acute lepra reaction over chronic arthritis, besides cutaneous and neurological manifestations, must be understood for early diagnosis and treatment to avoid debilitating complications.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.0753

Introduction

The musculoskeletal involvement is observed in 75%[1] of patients with leprosy (Hansen's), an infectious granulomatous disease caused by *Mycobacterium leprae*, mainly seen in developing countries with a classical neurocutaneous profile. Even with typical neurocutaneous manifestations, Hansen's arthritis perplexes rheumatologists. Despite being treatable, it is debilitating due to late diagnosis, primarily because of poor awareness among physicians, even in endemic regions like India[2] and the low specificity of clinical symptoms.

Case Report 1

A 35-year-old female presented with multiple joint pains lasting 3 years, beginning after her last delivery. The waxing and waning arthritis involved the knees, ankles, and small joints of all four limbs. She had hyperpigmented lesions on both legs for 2 years, intermittent fever for 1 year, and multiple nodular skin lesions (Fig. 1) for 1 year. She experienced an acute exacerbation of swelling and pain in small joints for 1.5 months. She had generalized lymphadenopathy [preauricular, submandibular, upper jugular, epitrochlear, inguinal (matted)], hyperpigmented patches, and multiple small red painful nodules on the extensor aspects of the limbs and face, some pustular and eroded, in addition to livedo reticularis on the shins (Fig. 2). Synovial thickening was present in the aforementioned joints.

Investigation showed leukocytosis [total leukocyte count (TLC) = 15,800], skin biopsy, and histopathology positive for acid-fast bacilli (AFB), bacillary index: 4+ (Fig. 3), reactive lymphadenitis on fine needle aspiration cytology (FNAC) from the inguinal lymph node, and neutrophilic vasculitis with Langerhans giant cell granuloma in the histopathology of the cervical lymph node biopsy.

Discussion

Our patient had chronic multiple joint pain and acute flaring of symptoms during an epidemic of viral polyarthritis (chikungunya), which started in eastern Uttar Pradesh in September 2023. As the duration was >6 weeks and >10 joints were involved, rheumatoid arthritis[3] was considered as a second differential; however, dermatological manifestations and lymphadenopathy indicated Hansen's arthritis (Table 1) as the provisional diagnosis, and a bacillary index of 4+ confirmed it.

A rare atypical insidious onset lepra reaction [involving the knee in addition to the typical ankle, metatarsophalangeal (MTP), proximal interphalangeal (PIP),

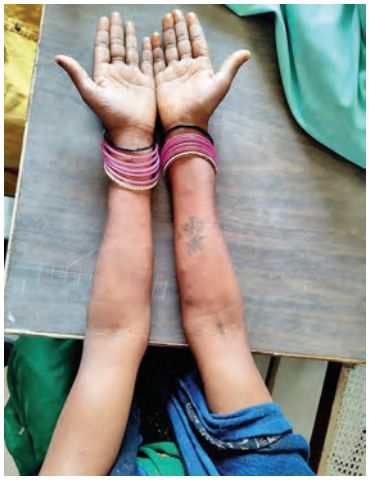

Fig. 1: Case 1 showing multiple nodules on the forearm

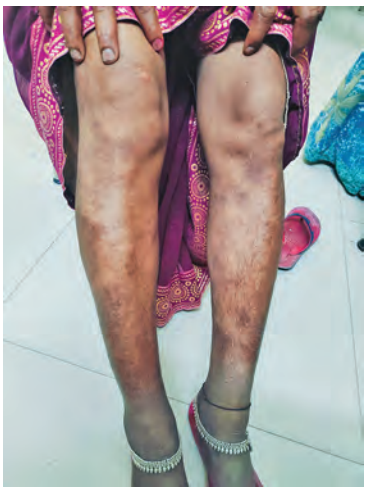

Fig. 2: Skin of case 1 showing a hyperpigmented patch and livedo reticularis on the shins of the lower limbs

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and metacarpophalangeal (MCP)] was not considered, as she had an acute presentation of lepra reaction over insidious chronic arthritis.

In leprosy, hypopigmented, anesthetic macules, plaques, papules, or nodules are typically seen,[1] while our patient presented with hyperpigmented lesions, nodules, livedo reticularis, in addition to generalized lymphadenopathy with thickened ulnar nerves.[3,4]

The pathogenetic mechanism of musculoskeletal leprosy is not yet known, but the proposed precipitating factors are intercurrent infections, anemia, stress, puberty, pregnancy, parturition (as in our case), and surgery.[1]

Our patient had lepra reaction type 2 [erythema nodosum leprosum (ENL)], evidenced by fever, leukocytosis, painful nodular lesions, lymphadenopathy, neutrophilic vasculitis with Langerhans giant cell granuloma,[5] and perineural inflammation in the histopathology of the inguinal lymph nodes; insidious-onset chronic symmetrical relapsing polyarthritis, including knee joint involvement (characteristic of chronic Hansen's arthritis) for 3 years without morning stiffness.

Hansen's disease should be diagnosed early, as disease-modifying antirheumatic drugs (DMARDs) [which mimic rheumatoid arthritis (RA)] and biologics can be deleterious.[2]

As our case turned out to be multibacillary erythema nodosum leprosum (ENL), a type 2 lepra reaction on chronic arthritis, rifampicin 600 mg, clofazimine 100 mg once monthly, and dapsone 100 mg/day were given along with steroid prednisolone 0.5mg/kg body weight tapered by 10mg over 1st two weeks followed by reducing 5mg every two weeks and gradually stopped. She experienced marked relief within 10 days in all her symptoms; pain and even livedo reticularis subsided. All her pain subsided, and her lesions turned hyperpigmented post-inflammatory.

Case Report 2

A 55-year-old postmenopausal female presented with knee joint pain for 1 year, fever, and erythematous anesthetic scaly skin lesions for 3 months. She had swollen, painful feet and hands for 1 month, which were affecting her gait markedly.

Physical examination showed erythematous anesthetic scaly lesions on the extensor surfaces of the elbows, forearms, and trunk (Fig. 4); subcutaneous nodules on the forearm were seen along with markedly swollen feet (Fig. 5) and thickened non-tender ulnar nerves. Investigation showed leukocytosis (TLC = 16,000). Histopathology of the skin nodules showed lymphoplasmacytic inflammatory infiltrate in the upper dermis, while the mid dermis showed epithelioid cell granuloma along with multinucleated giant cells and lymphohistiocytic collection. In addition, AFB was positive with a bacillary index of +1, suggesting ENL in borderline tuberculoid leprosy.

Discussion

This patient presented with chronic arthritis, swollen painful feet, and numb skin lesions. After ruling out other causes of swollen feet, the diagnosis of Hansen's disease with swollen feet and hand syndrome[1] and ENL on

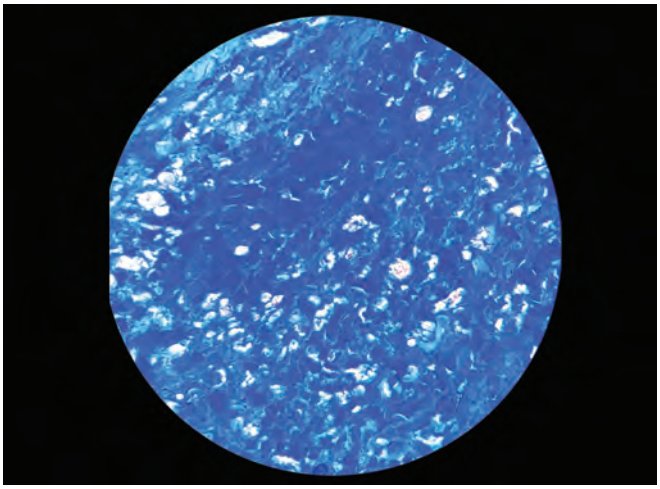

Fig. 3: Histopathology of skin biopsy showing AFB positive in case 1

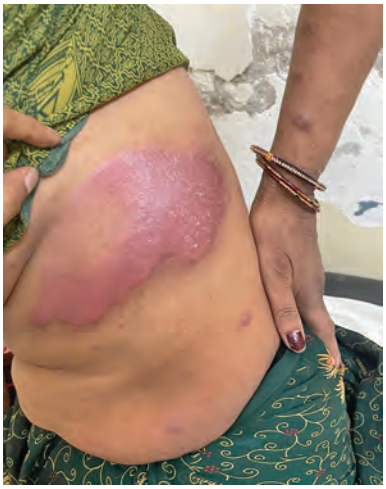

Fig. 4: Skin of case 2 showing erythematous anesthetic scaly lesions on the trunk

Table 1: Characteristics of different forms of articular involvement in leprosy[1]

	Onset	*Symmetrical*	*Polyarthritis*	*Joints involved*	*Erosions*	*M. leprae in synovium*	*Response to MDT*
Lepra reaction	Acute	Yes	Yes	Wrist, MCP, PIP, ankle, MTP	±	Yes	Good[a]
Swollen hands and feet syndrome	Acute	Yes	Yes	Ankle, wrist, feet, MCP, PIP	No	Yes	Good
Chronic arthritis	Insidious	Yes	Yes	Wrists, MCP, PIP, knee, MTP	+	±	Moderate
Charcot's arthropathy	Insidious	No	Mono- to polyarticular	Hand and foot joints, ankle, knee, wrist	+	No	No role
Tenosynovitis	Acute to insidious	±		Extensor tendons of hands and feet		Yes	Good

[a]Requires glucocorticoid therapy in addition to MDT

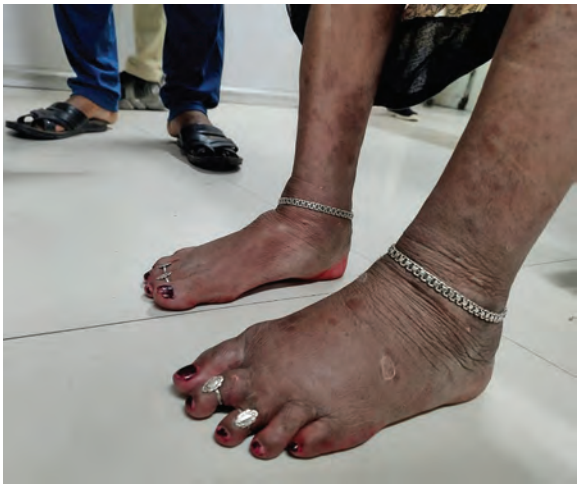

Fig. 5: Case 2 showing markedly swollen feet suggestive of swollen feet and hand syndrome

chronic arthritis was made. ENL is commonly seen in multibacillary borderline, borderline lepromatous, and lepromatous leprosy, but our case had paucibacillary borderline lepromatous leprosy. The patient responded dramatically in her neurocutaneous symptoms and chronic arthritis but gradually in swollen feet to multidrug therapy (MDT). Steroid was also given initially and later gradually tapered.

Conclusion

The cases illustrate the diverse combination of acute ENL on chronic Hansen's arthritis in the first multibacillary case and the same with the added rare swollen feet and hand syndrome in the second paucibacillary case, besides highlighting the critical need for awareness among clinicians to ensure timely diagnosis and treatment, thus avoiding devastating debility in the future.

Public and Patient Involvement

Both patients involved in the case reports were informed about the rarity of their cases and that the disease, if not treated early, can lead to devastating debility. It is important to make physicians aware of this dreadful disease worldwide for the early start of treatment, as it is a treatable disease. The patients were also asked to disclose other nearby patients with similar illnesses to help uproot the disease and hinder transmission, as it is a communicable disease, for the benefit of the community.

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An Uncommon Etiology of Photographic Negative of Pulmonary Edema in an Undifferentiated Connective Tissue Disorder Patient

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Introduction

Connective tissue diseases (CTDs) comprise a class of immunologically occurring inflammatory disorders with unclear causes. In addition to the rheumatological system, they affect a variety of other organs like the renal and pulmonary systems. People with CTD are commonly predisposed to lung illnesses, mainly interstitial lung disease (ILD). Also, the association of CTD with lung cancer has been a topic of controversy.[1] The gamut of diseases associated with diffuse pulmonary infiltrates in such a scenario is enormous and often poses a challenge to clinicians. However, the distinctive imaging finding of a photographic reverse batwing appearance has been characteristically considered a sine qua non of inflammatory conditions, mainly chronic eosinophilic pneumonia (CEP) or organizing pneumonia.[2] Here, we discuss a case of a 40-year-old lady with undifferentiated connective tissue disease (UCTD) who had a typical textbook radiographic picture but an unusual cause for this radiographic pattern. In view of such masqueraders, the authors wish to highlight the stepwise approach to diagnosis, including histopathological evidence and follow-up in such cases.

Case Description

A woman in her 40s, a nonsmoker, initially presented to the rheumatologist with complaints of polyarthralgia and a history suggestive of Raynaud's disease of 4 years' duration. On investigations, her antinuclear antibody (ANA) by immunofluorescence assay (IFA) was 3+ tested on two separate occasions. She was diagnosed as having UCTD and was started on mycophenolate mofetil 750 mg twice a day and steroids (tab prednisolone 40 mg once a day), which were subsequently tapered to 5 mg/day. She was on regular follow-up at the rheumatology OPD and had symptomatic relief. After 2 years postinitial diagnosis, she started having complaints of progressive breathlessness (mMRC grades I–III) and cough over a period of 3 months. She had copious expectoration. She had no fever, hemoptysis, or chest pain. She was referred to the pulmonology department for evaluation. On clinical examination, she had tachycardia with a pulse of 118 beats per minute, tachypnea (with a rate of 30 per minute), and a saturation of 92% on the pulse oximeter. She had grade III clubbing. Her chest auscultation revealed bilateral crackles and bronchial breath sounds in the right infrascapular area. Other systemic examinations were unremarkable. On investigations, basic laboratory studies revealed normal blood counts (hemoglobin of 13 gm/dL, total leukocyte count of 8,000/mm^3, with neutrophils of 70%, lymphocytes of 20%, and eosinophils of 5%). Her kidney function tests and C-reactive protein (CRP) were within range. Her electrocardiogram revealed sinus tachycardia, and her echocardiogram did not depict any cardiac issues or pulmonary hypertension. A chest radiograph revealed peripheral consolidation in both lungs with hazy borders (Fig. 1, panel A). High-resolution computed tomography (HRCT) of the thorax exhibited peripheral, subpleural confluent consolidation in both lung fields with central sparing involving each lobe of the right lung and predominantly the lingula and lower lobes on the left side (Fig. 2). A possibility of CEP or chronic organizing pneumonia was given by the radiologist based on imaging findings.

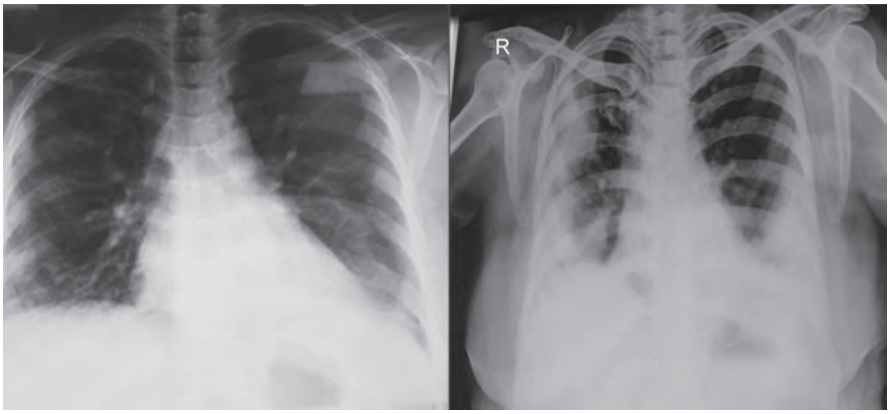

Fig. 1: Chest X-ray depicting marginal opacities in both lungs which are photographic negative of pulmonary edema and show subsequent progression

Q) What is the radiological diagnosis and other differentials?

A) Diagnosis: The radiographic presentation is that of a photographic negative of pulmonary edema. Though CEP is the commonest cause of this radiological picture, additional rare causes include cryptogenic organizing pneumonia, sarcoidosis, eosinophilic granulomatous polyangiitis, bronchoalveolar carcinoma (BAC), and localized radiation damage to the chest.

The patient subsequently underwent a bronchoscopy and bronchoalveolar lavage (BAL). Her BAL sample stains and cultures were negative for bacterial and fungal infections, and her cartridge-based nucleic acid test was negative for tuberculosis.

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The BAL's eosinophil count was 5%. She underwent a computed tomography (CT)-guided transthoracic biopsy, which showed a lymphocytic infiltrate with inflammation, but no conclusive or definite diagnosis was given. Based on her clinico-radiological picture in the background of UCTD, a diagnosis of organizing pneumonia was suspected, and she was initially prescribed oral corticosteroids. However, despite 2 months of therapy, the patient showed no clinical response and had radiological progression (Fig. 1, panel B). She underwent a positron emission tomography (PET)-CT, which showed bilateral peripheral consolidation with a standard uptake value (SUV) max of 2.5. A repeat CT-guided biopsy was executed, and a histopathological conclusion was achieved (Fig. 3). The CT-guided biopsy in this case revealed adenocarcinoma *in situ* (lepidic pattern). Subsequently, she was evaluated by an oncologist for further management and was thereafter started on chemotherapy.

Discussion

Radiologic opacities in pulmonary illnesses can manifest in a variety of distinct ways that are frequently ambiguous and challenging to define exactly to indicate a specific diagnosis. However, in certain conditions, the radiographic patterns have been characteristically attributed to specific etiologies, like the "reverse batwing" sign.[2] This emblematic imaging configuration of principally outer consolidation was first labeled by Gaensler and Carrington and is regarded as a hallmark of CEP. These patterns have been explicitly defined by many authors, such as diffuse subpleural parenchymal cloudy densities.[3] Crofton et al. elucidated them as billows of smolder arising due to an explosion in the vicinity of the hilum and wandering marginally.[4] Felson referred to these characteristic opacities as the reverse butterfly array. Pleural effusions are rarely described in this radiographic picture; however, due to the basal predominance of these opacities in the vicinity of the chest wall, they may be wrongly reported as effusions.[5] BAC, now known as adenocarcinoma *in situ* (AIS), presents with a gamut of varied imaging patterns, extending from discrete to more widespread involvement. The radiological array of this malignancy has largely remained divided into three characteristic forms: (i) single nodules; (ii) limited consolidation; and (iii) multicentric or widespread arrangement.[6] Although PET scan studies for diffuse BAC are confined to mere case series, a study consisting of seven cases of multifocal BAC reported a negative scan in only one patient. Characteristically, in our case, the lesions did not exhibit significant uptake on the PET scan. BAC is often called the masquerader. Diffuse pulmonary infiltrates radiologically mimicking infectious processes may masquerade as pneumonia or other inflammatory conditions in actual cases of adenocarcinoma of the lung.[7] Since, BAC is a rare cause of reverse batwing appearance on chest radiography, the diagnosis is usually missed or delayed. Though CEP and organizing pneumonia are common causes of this radiographic presentation, a failure to respond to steroids should alert the physician to look for an alternative diagnosis. Early detection of lung cancer will undoubtedly lead to a better rate of survival. The association between CTDs and malignancy has been an area of debate for ages. Whether this relationship is casual or causal has been questioned by many authors.[8] The most common lung cancer seen in CTD has been adenocarcinoma *in situ*, followed by adenocarcinoma.[9]

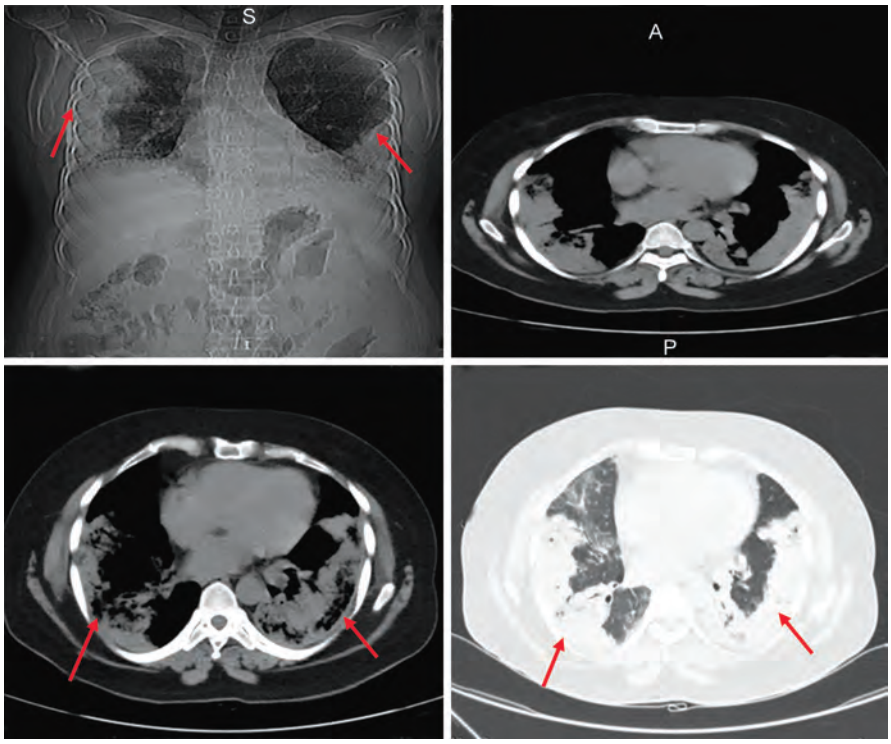

Fig. 2: HRCT chest sagittal and coronal view depicting peripheral patchy consolidation

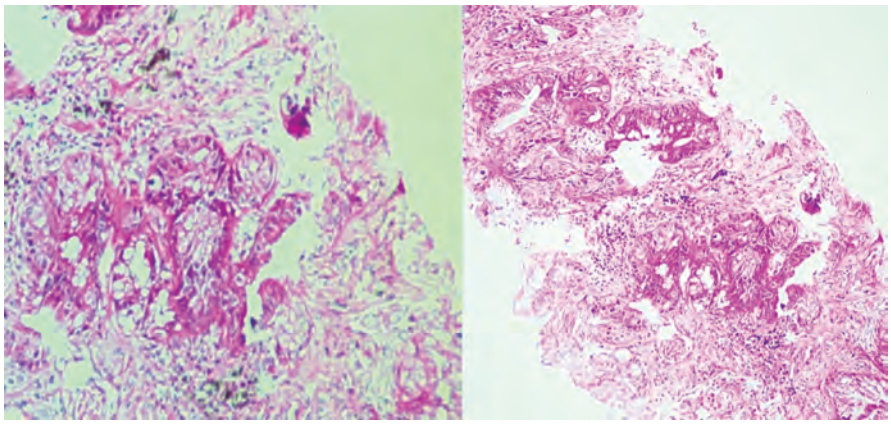

Fig. 3: Histopathological examination of CT guided biopsy showed adenocarcinoma (lepidic pattern)

Conclusion

In the background of connective tissue disorders, though the radiographic picture of the reverse batwing sign suggests an inflammatory disorder, the establishment of a tissue diagnosis is still of paramount importance. Prompt bronchoscopy with lavage, transbronchial lung biopsy, or CT-guided biopsy should be considered to establish a tissue diagnosis. Nonresolving pneumonia needs detailed evaluation,

and malignancy should be considered as a differential diagnosis in addition to inflammatory disorders, rather than relying solely on the radiological picture, even in classical textbook radiological presentations.

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Otto Warburg and Cellular Respiration

Jayant V Pai-Dhungat

Otto Warburg. Maxi card (reduced), Federal Germany, 1983

3rd World Protozoology Conference, Leningrad, Stamp USSR, 1969

Otto Heinrich Warburg (1883–1970) was born in Freiburg, Baden. He studied chemistry under Emil Fischer and obtained his PhD in chemistry for his work on polypeptides in 1906. He then obtained his medical degree at Heidelberg in 1911. Warburg served as an officer in the cavalry during World War I (WW I). He was appointed professor at the Kaiser Wilhelm Institute for Biology in Berlin in 1918 and headed the Max Planck Institute for Cell Physiology from 1931 until his retirement.

Much of his work was on intracellular respiration. He devised a thin U-shaped manometric tube and a flask (Warburg's tube) in 1923 to measure the consumption of oxygen while studying living tissue. This research on oxygen consumption in sea urchin eggs showed that, after fertilization, the oxygen consumption increased by as much as sixfold. Warburg suspected that a group of enzymes were involved in a reaction that consumed oxygen within cells. In 1928, he eventually proved that certain types of heme groups of cytochromes containing iron grasped the oxygen. This was quite distinct from hemoglobin, which carried oxygen in the blood. He concluded that the respiration enzyme he was looking for was a red ferrous protein related to hemoglobin in the blood.

Warburg's methods involved detailed studies on the assimilation of carbon dioxide in plants and the chemical constituent of the oxygen-transferring respiratory ferment. Warburg gave a complete account of the oxidations and reductions in the living world, where cell nutrients are broken down to release energy. For his discovery of the nature and mode of action of the respiratory enzyme, he was awarded the Nobel Prize in Physiology or Medicine in 1931. This discovery opened up new ways in the fields of cellular metabolism and cellular respiration. He showed, among other things, that cancerous cells consumed less oxygen and could live even in the absence of oxygen.

His later research was on coenzyme-1, leading to the discovery of the flavines and the PP factor (nicotinamide). He also showed that vitamins were enzyme components. Warburg's contribution to cancer research remains influential; it was he who discovered that industrial and car exhaust gases can trigger cancer.

Warburg's personality was controversial: he was intolerant of opposing scientific views yet tolerant toward Nazi abuses. His later career was marred by his increasingly intolerant attitude, which eventually isolated him.

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An Unusual Presence of Atypical Ligature Mark in a Case of Complete Hanging

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Sir,

The pressure abrasions caused by the ligature mark play an important role in understanding and investigating the mode and mechanism of injury in hanging.[1] Here, we report an atypical pressure abrasion consistent with a ligature mark that occurred as a result of complete hanging of a suicidal nature. We obtained consent from the patient for the publication of this important finding.

A 48-year-old male, following an attempted suicidal hanging from the ceiling using a rope, presented to the emergency department with loss of consciousness [Glasgow Coma Scale (GCS): E1V1M3]. He was rescued by family members within 4 minutes of the hanging being noticed. The investigation revealed findings of complete hanging, with the body fully suspended in the air when discovered. On external examination, the ligature mark was noted below the thyroid cartilage, running obliquely upwards and backwards, completely encircling the neck, with the knot positioned in the midline of the neck posteriorly (Figs 1A to C). The airway was secured by immediate tracheal intubation, and vitals were stabilized. He was later transferred to the critical care unit. Within 90 minutes of oxygenation and ventilation, his GCS improved to E2V1M5. He was then sedated and mechanically ventilated overnight. X-ray of the cervical spine did not reveal any fracture or displacement of the cervical vertebrae. On the following day, his GCS improved to E4V1M6, after which tracheal extubation was performed. Upon 24 hours of observation, he remained stable and was subsequently discharged for psychiatric evaluation and psychological counseling.

Complete hanging leads to early unconsciousness and accelerates death due to nonperfusion of the brain.[2] The entire body is suspended by the ligature, with no part of the body touching the ground. In suicidal hanging, the ligature mark is usually situated above the thyroid cartilage and below the chin, directed obliquely upwards on both sides of the neck. In typical hanging, the knot is situated in the midline of the neck posteriorly, causing symmetrical bilateral occlusion of the large neck vessels. On the contrary, in atypical hanging, the knot is placed elsewhere other than the posterior midline, causing unilateral compression of blood vessels, which is less commonly observed.[1] We reviewed an autopsy study (n = 634) of suicidal hangings, where 92% of cases of complete hanging (n = 456) had the ligature mark situated above the thyroid cartilage and oblique in shape; only 8% of cases had the ligature mark situated across the thyroid cartilage, whereas none of the cases had the ligature mark situated below the thyroid cartilage.[3] Our case is unique because the ligature mark was situated below the thyroid cartilage, though directed obliquely upward and backward, with the knot positioned in the midline of the neck posteriorly. Initially, the pattern of the ligature mark raised the suspicion of homicide. However, the self-admittance of suicide by the patient clarified the investigation. Thus, our report highlights an important finding of an atypical ligature mark following complete hanging. Furthermore, not all cases suffer irreversible brain damage after complete hanging if rescue is performed as early as possible. Timely resuscitation by securing the airway, maintaining oxygenation and ventilation, and ensuring stable hemodynamics with frequent neurological examinations is key.

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Figs 1A to C: Ligature mark from the front placed above the thyroid cartilage (A), directed obliquely upward and backward [left lateral—(B); right lateral—(C)]

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