Exploring the Labyrinth: Imaging in Systemic Vasculitis

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Abstract
Systemic vasculitis is an immune-mediated group of disorders broadly classified based on the involved vessel type. It has myriad clinical presentations, adding to the challenge of timely diagnosis and management. Thus, imaging has taken center stage in the diagnosis of these disorders as there is a lack of definitive clinical diagnostic markers. Various available imaging modalities can be used for diagnosis and follow-up on these patients.

The coronavirus disease 2019 (COVID-19) has added a new dimension to the already existing problem of vasculitis. The virus has shown great affinity for the vascular endothelium, leading to multisystem organ vasculitis. There has been a spike in vasculitis cases in the COVID-19 pandemic era, thus necessitating more research and studies in this field for a better understanding of the disease.

In this review, we wish to summarize the various imaging spectrums of classical systemic vasculitis along with the new addition of COVID-19-related vasculitis to the already long list.

Introduction
Vasculitis is a multisystem disorder that causes immune-mediated inflammation of the blood vessel walls. In 1994, the Chapel Hill Consensus Conference (CHCC) gave a classification system based on the size of the predominantly involved vessel (Fig. 1). The International CHCC in 2012 proposed nomenclature for previously poorly defined systemic vasculitis classification adopted since 1994. It has been classified into three broad categories based on the affected vessel size, namely large vessel vasculitis (LVV), medium vessel vasculitis (MVV), and small vessel vasculitis (SVV). The basic concept states that any type of vasculitis can affect a vessel of any size; only the predominantly involved vessel has been included in the definition.

Role of Imaging
A suspected case of vasculitis needs a comprehensive clinical and radiological evaluation for confirmation of the diagnosis as well as for following up on the disease. Ultrasonography (USG) and contrast-enhanced ultrasound (CEUS) help in both structural and functional evaluation of the disease. Computed tomography (CT), computed tomography angiography (CTA), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) help better demonstrate the vessel wall pathology, viz circumferential mural thickening, areas of stenoses, occlusions, and aneurysmal dilatations. Positron emission tomography (PET) CT and CEUS can tell us about disease activity and, hence, can play an important role in patient follow-up. Digital subtraction angiography (DSA) has been the best investigation for diagnosis with the added advantage of its role in intervention. However, it is invasive, with an additional risk of radiation exposure.

Thus, these imaging techniques play a great role in assessing the distribution patterns as well as the extent of the disease with numerous advantages as well as limitations as described in Table 1.

Large Vessel Vasculitis
Large vessel vasculitis (LVV) usually involves the aorta and its main branches, excluding the most peripheral branches. It is the most common primary vasculitis, and it includes giant cell arteritis (GCA) and Takayasu arteritis (TKA). There is considerable overlap between the distribution patterns and histopathology of both GCA and TKA with atypical involvement of small- and medium-sized arteries as well as the coronary arteries in TKA (Table 2).

Giant Cell Arteritis
Giant cell arteritis (GCA) is considered a rare entity in the Indian subcontinent population, but the involved population shows a higher rate of ophthalmic complications resulting from ischemia, such as permanent vision loss. Temporal artery biopsy was considered the gold standard for the diagnosis of GCA, but it is still important for the diagnosis of cranial GCA. With the advancement in imaging, temporal artery biopsy has largely been replaced by imaging. However, European League against Rheumatism (EULAR) has recommended biopsy in cases of GCA that have not been confirmed in clinical, laboratory, and imaging studies.

Imaging
On USG, hypoechoic circumferential wall thickening is seen, known as the “halo sign.” On Doppler, vessel stenosis and occlusions with consecutive alterations in flow velocities are seen.

Magnetic resonance imaging (MRI) of the cranial arteries shows mural thickening, contrast enhancement, stenosis, occlusion, and aneurysmal dilatations. The EULAR recommends USG of the temporal artery along with the auxiliary artery to look for noncompressibility and halo sign. MRI is advised in cases where USG is not feasible in cranial arteries to look for mural inflammation. CT and PET are not currently recommended for assessment. For extracranial GCA, USG, CT, PET, and MRI are advised. USG, however, has a lesser role among all these modalities due to the limited accessibility of the thoracic aorta.

On CEUS, grading between vascularization and carotid intima–medial thickness (IMT) can be performed. No current role of DSA has been described in the diagnosis of LVV.

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Takayasu Arteritis

Takayasu arteritis (TKA) affects the younger age group, which is fewer than 40 years of age, with a female preponderance. It is more common among Asian and African people than among Europeans, and it was first described in Japan. Most of the clinical manifestations that are similar to GPA include asymmetry of pulses, pulselessness, or difference in blood pressure in both limbs. Aorta, common iliac arteries, and external iliac arteries may show changes in stenosis with collateral formation. The coronary and pulmonary arteries are frequently involved as compared to GCA. EULAR recommends MRI as the initial investigation for evaluation of TKA changes. Alternatively, USG, CT, or PET may also be used. USG has a limited role in the assessment of the thoracic aorta. Digital subtraction angiography (DSA) plays both diagnostic and therapeutic roles. It is not very useful in early diagnosis as it can’t detect the early vasculitis changes of the vessel wall. Due to other disadvantages such as exposure to ionizing radiation, invasive nature, and use of iodinated contrast, it is mainly being used for endovascular treatment rather than in diagnosis. Based on angiographic appearance, Hata et al. divided TKA into five types. Type I includes the involvement of major arch branches, IIA is the involvement of the ascending aorta, arch, and its branches, and IIB is IIA includes the descending thoracic aorta as well. Type III is the involvement of the descending thoracic aorta, including the abdominal aorta as well, with or without the involvement of the renal vessels. Type IV includes the involvement of the abdominal aorta with or without the involvement of the renal arteries. Type V is the entire thoracic and abdominal aorta, with or without the involvement of the renal arteries.

Imaging

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Contrast-enhanced ultrasound (CEUS) is a noninvasive modality without the risk of nephrotoxicity, which can improve the visualization and quantification of vessel wall vascularization. CEUS, contrast-enhanced ultrasound; CT, computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PET, positron emission tomography; USG, ultrasonography.
than 4 mm can be virtually seen on PET, but smaller arteries, like temporal or renal arteries, cannot be visualized. In active disease, the inflamed vascular wall shows increased tracer uptake in a linear fashion (Figs 5A to D). For semiquantitative estimation of tracer uptake, a scale known as the Meller scale has been devised, in which vessel uptake is compared to the uptake in the liver.

Medium vessel vasculitis mainly consists of two entities, namely polyarteritis nodosa (PAN) and Kawasaki disease (KD).

Table 2: Difference between TKA and GCA

<table>
<thead>
<tr>
<th>Finding</th>
<th>TKA</th>
<th>GCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20s–30s</td>
<td>After 50s</td>
</tr>
<tr>
<td>Incidence</td>
<td>2/million</td>
<td>20/100,000</td>
</tr>
<tr>
<td>Vessels involved</td>
<td>Large elastic arteries; spare temporal artery</td>
<td>A predilection for carotid artery branches in neck and temporal arteries; typically spares intracranial vessels</td>
</tr>
<tr>
<td>Large vessel involvement</td>
<td>Long narrowed segments; mural thickening; dilatation and thrombosis are more frequent</td>
<td>Long stenotic segments; mural thickening; dilatation and thrombosis</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>More</td>
<td>Less</td>
</tr>
</tbody>
</table>

Magnetic resonance imaging/angiography (MRI/MRA) is the recommended investigation in the younger age group as it provides better soft tissue resolution and is free of ionizing radiation. The use of fat suppression and black blood sequences further improves the visualization of contrast enhancement and helps in the assessment of disease activity and burden. MRA helps in recognizing the disease extent and vessel status. MRI T2 weighted images show hyperintensity in the vessel wall, suggesting mural edema, which, if it shows contrast enhancement, suggests active inflammation. Diffusion-weighted imaging (DWI) helps differentiate chronic disease from active disease (Figs 4A to F). This is due to the impaired diffusion in the aortic wall in the acute phase of the TKA.

Positron emission tomography (PET) CT is highly sensitive for measuring disease activity. All vessels with a diameter of more than 4 mm can be virtually seen on PET, but smaller arteries, like temporal or renal arteries, cannot be visualized. In active disease, the inflamed vascular wall shows increased tracer uptake in a linear fashion (Figs 5A to D). For semiquantitative estimation of tracer uptake, a scale known as the Meller scale has been devised, in which vessel uptake is compared to the uptake in the liver.

Medium vessel vasculitis (MVV) mainly consists of two entities, namely polyarteritis nodosa (PAN) and Kawasaki disease (KD).

Polyarteritis Nodosa
It necrotizes arteritis in medium and small vessels. In CHCC’s 1994 classification, ANCA was thought to be associated with PAN; however, in the 2012 update, ANCA-associated vasculitis and PAN were declared separate entities, though they can appear clinically and pathologically similar. It is seen commonly in men in their 50s–70s with male preponderance. An association between HIV, hepatitis B virus, and PAN has been proposed, but the exact etiology is not known.

Figs 2A and B: Takayasu arteritis: (A) CEUS with corresponding grayscale images of a carotid artery demonstrating minimal intimal contrast enhancement in an active disease (arrow) (B) As compared to a posttreatment inactive disease showing no obvious uptake in the hypoechoic intima layer; CEUS, contrast-enhanced ultrasound
involved lymph nodes, along with the absence of involvement of the VB nodes. Computed tomography angiography (CTA) and MRA help in the noninvasive delineation of coronary artery aneurysms (Figs 7A and B) along with the classification of the aneurysms based on their size, which helps in prognosis. Small aneurysms have a diameter of <5 mm, medium-sized aneurysms are 5–8 mm in size, and large-sized aneurysms have a size of >8 mm. Smaller aneurysms may eventually regress; however, larger aneurysms are more prone to thrombosis. Cardiac MR may help in better assessment of myocardial perfusion and function.

Smaller vessel vasculitis (SVV) is a necrotizing inflammation affecting intraparenchymal small arteries along with arterioles, capillaries,
Peripheral nerves, and skeletal muscles. Venules in skin, lungs, intestines, and mesenteries in the peak age of 50s–60s without any obvious sex predilection. Variable neutrophilic cytoplasmic granular proteins in the presence of autoantibodies against vasculitis. ANCA-associated vasculitis shows immune complex-associated small vessel vasculitis in the vessel walls. Vasculitis with few or no immune complexes in the vessel wall is called antineutrophilic cytoplasmic antibody (ANCA) associated vasculitis, and the other type is called immune complex-associated vasculitis. ANCA-associated vasculitis shows the presence of autoantibodies against neutrophilic cytoplasmic granular proteins, proteinase-3, and myeloperoxidase. Variable vessel vasculitis and vasculitis associated with systemic diseases have also been included in this category. It occurs in the peak age of 50s–60s without any obvious sex predilection.

Imaging
Chest radiographs are done for the initial workup; USG can help diagnose pleural and renal pathologies, whereas disease extent can be better evaluated on CT. CT further helps in looking at the abnormalities of the heart, sinonasal cavities, and lungs. Intracranial, orbital, and sinonasal involvement is better appreciated on MRI. Antineutrophilic Cytoplasmic Antibody-associated Small Vessel Vasculitis It has three subtypes viz granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic GPA (EGPA). Granulomatosis with polyangiitis: Granulomatosis with polyangiitis (GPA), earlier known as Wegener’s granulomatosis, is characterized by upper respiratory involvement (100%), lower respiratory involvement (90%), and glomerulonephritis (80%).

Sinonasal involvement in CT scans is seen in the form of mucosal thickening, erosions, and new bone formation. The most common site for erosions is the anterior ethmoidal region. Punctate areas of bone erosions may be seen in the midline septum, with turbinate extending into the adjacent antra and other sinuses. The concurrent bony destruction and new bone formation are characteristic of GPA. Disease from the sinonasal and orbital location can extend into the skull base, resulting in cranial neuropathy; however, intracranial involvement is rare. Serous otitis media can result from temporal bone involvement.

Common CT findings in most patients with pulmonary involvement are nodules and masses. The characteristic finding is the waxing and waning of nodules, which are randomly distributed. Larger nodules are more prone to cavitation and are seen in up to 50% of the cases. Surrounding hemorrhage can result in the formation of ground glass opacities (GGOs). Adjacent organizing pneumonia can give rise to the “reverse halo sign.” Pleural effusions are the most common pleural abnormality. Other rare forms of involvement may be thickening, nodularity, and pneumothorax (Figs 8A and B).

Computed tomography (CT) is also an excellent modality to document the larynx and tracheal involvement. The most commonly involved location is subglottic. Involvement may be a short segment or multifocal, smooth, or nodular. Differentials include relapsing polychondritis, tracheobronchopathia osteochondroplastica, and amyloidosis.

The most common orbital manifestation of the GPA is the orbital pseudotumor. Unilateral and extraconal diffuse inflammatory infiltrate is seen. Enophthalmos can result from diffuse fibrotic tissue, leading to orbital contracture. Eosinophilic granulomatosis with polyangiitis: Eosinophilic GPA (EGPA) is also known as Churg-Strauss syndrome. Lungs are most commonly affected, resulting in CT appearance of GGOs, consolidations, nodules, interstitial thickening, and bronchial wall thickening. The predominant pattern of involvement is subpleural and lobular distribution, which most commonly involves the lungs. (Figs 9A to D). Cardiovascular complications include myocarditis, coronary arteritis, pericarditis, and pericardial effusion, for which MRI may be warranted.

Microscopic polyangiitis: Microscopic polyangiitis commonly involves the kidneys, lungs, skin, and gastrointestinal system. Kidney involvement is in the form of necrotizing glomerulonephritis. GGOs, consolidations, and diffuse alveolar hemorrhage are noted in pulmonary involvement. It cannot be differentiated from EGPA on imaging.

Immune Complex Small Vessel Vasculitis Immunoglobulin A (IgA) vasculitis (Henoch–Schoenlein purpura) is the prototype of immune complex SVV. It presents with purpuric skin rash, gastrointestinal bleeding, abdominal pain, and glomerulonephritis. Ultrasound helps diagnose epipodymal orchitis, hydroscele, and funiculitis. CT may
help in case of gastrointestinal bleeding and ischemia.  

Variable Vessel Vasculitis

Behçet’s disease is the prototype of variable vessel vasculitis with multiorgan involvement. It presents with recurrent aphthous oral ulcers, uveitis, and genital ulcers, along with other multisystem involvement. The most common form of vascular involvement is venous stenosis, followed by arterial stenosis and aneurysm. Sudden death can occur due to rupture of large aortic or arterial aneurysms.  

Vasculitis Associated with Systemic Diseases

Vasculitis associated with systemic diseases is systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) related vasculitis. Systemic lupus erythematosus (SLE) is an autoimmune disease with a peak age in the 20s–40s, in which there is complex immune deposition and inflammation involving multiple systems. The respiratory system is relatively commonly involved, leading to symptoms of dyspnoea and poor physical activity tolerance in 40–57% of the patients, either secondary to infection or pulmonary edema from renal failure. CT may show pleural effusion due to serositis, lymphadenopathy, and areas of ground glass opacity (Figs 10A and B). Recurrent infections lead to bronchiectasis and respiratory dysfunction.  

Rheumatoid arthritis (RA) is a multisystem disease that commonly can involve the lungs and is the cause of significant morbidity. Pulmonary vasculitis occurs in severe forms of RA. Another rare presentation is diffuse alveolar hemorrhage, which occurs in association with capillaritis or vasculitis (Figs 11A and B).

Coronavirus Disease 2019-related Vasculitis

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread across the countries since its first report in December 2019 from China. During this pandemic, there has been an emergence of COVID-19-associated multisystem inflammatory vascular disease. It leads to endothelial cell inflammation, dysfunction, and apoptosis. Younger age groups, including children, have shown multisystem inflammatory syndrome (MIS-C), which mimics KD. Cytokine-related inflammatory disorder is commonly seen within 2 weeks of infection in adults; however, in children, MIS-C is seen after 2 weeks.
Coronary artery abnormalities in the form of dilatation and small aneurysms have been found in 9–24% of the patients (Figs 12A to D). Some association between COVID-19 and other IgA-related diseases has also been found, which could be the cause of coronary involvement.

Pulmonary vasculitis presents as vessel dilatation with mosaic perfusion patterns. Perfusion abnormalities may also be demonstrated on dual-energy CT. Hanafi et al. reported neurologic complications of COVID-19, which include cerebral vasculitis leading to extensive cerebral small-vessel ischemic lesions, hemorrhage, and punctate postcontrast enhancement pattern.

Another key aspect of imaging in COVID-19 is to decrease the exposure to the technicians and medical personnel, so imaging should be done in a controlled environment and with proper precautions. Ultrasound can be avoided in the initial diagnosis to avoid direct exposure, so CTA and MRA may be more useful in such patients.

**Conclusion**

Due to advancements in imaging techniques, radiology has taken center stage in the diagnosis, follow-up, and treatment of systemic vasculitis. These modalities, combined with clinical pictures, help assess the disease status, thus helping the patient manage the disease in the long term. Imaging and management should be performed by well-trained specialists and multidisciplinary teams. Further refinement is needed in the currently followed protocols of imaging in vasculitis patients to better elucidate the role of imaging in disease monitoring, precise management, and individualized tailoring of treatment protocols. The COVID-19 pandemic has added a new dimension to the already existing problem of vasculitis, and radiologists must be aware of this new emerging clinical entity.
Exploring the Labyrinth

**References**


