Mimics of primary systemic vasculitides

The primary systemic vasculitides are well defined entities, but a number of diseases can imitate their clinical, laboratory, radiographic and histological features. The importance of awareness and recognition of these conditions lies in the initiation of correct therapy for the specific disease process and in the avoidance of unnecessary and potentially harmful immunosuppression. In this review, we have provided a comprehensive, but by no means complete, review of some of the imitators of the primary vasculitides. Every attempt must be made to establish the diagnosis before indicated therapy is commenced. This will help to avoid therapeutic misadventures when managing patients with these complex diseases.

KEYWORDS: differential diagnosis ■ mimics ■ vasculitis

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Learning objectives

Upon completion of this activity, participants should be able to:

- Identify reasons for distinguishing mimics from true primary vasculitides
- Describe the difference between vasculitis associated with syphilis and TB
- List inherited conditions that can be mimics of primary vasculitides
- Identify drugs and toxins associated with mimics of primary vasculitides
- Describe clinical features of antiphospholipid syndrome

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The vasculitides are defined by histological inflammation of blood vessels in various tissues. They are classified as primary or secondary and have their identifiable causes such as infectious agents, drug reactions, systemic autoimmune diseases or malignancy. However, in addition, there are myriad conditions that can mimic true vasculitis clinically, on laboratory testing, on radiography and at histopathology. Distinguishing vascular inflammation from nonvasculitic disorders has significant therapeutic implications, since immunosuppressive therapy directed at the primary systemic vasculitides may be associated with significant toxicities, and a failure to recognize a vasculitis mimic may delay the initiation of effective therapy for the disorder in question. For purposes of this review, the term 'mimic' will include conditions that may or may not result in true vascular inflammation ('vasculitis') but present similarly to the defined primary systemic vasculitides. We will discuss the key categories of disease that may mimic the primary systemic vasculitides, focusing on a few important entities in each category; however, a detailed discussion of all potential vasculitis mimics is beyond the scope of this article.

Infections

Diseases caused by infectious agents can mimic any of the primary systemic vasculitides and may affect vessels of all sizes. Acute bacterial or viral infections or chronic infections with bacteria, viruses, mycobacteria, fungi or parasites may mimic vasculitis. While in many cases the infectious agents discussed can cause a true secondary vasculitis rather than being a vasculitis mimic *per se*, they remain a critical exclusion in the evaluation of a patient with suspected primary systemic vasculitis, not least because of the potential of causing significant harm to patients with active infection if they are inappropriately treated with immunosuppressive therapy. For example, syphilitic affection of the aorta results in true vascular inflammation but it is still considered to 'mimic' the primary large vessel vasculitides and is treated differently. The clinical, imaging and histopathological appearance of vascular disease caused by infectious agents may resemble the primary systemic vasculitides. However, infectious agents have been listed here as a 'mimic' since they are distinct entities in terms of well-defined etiologies, pathogenic mechanisms and therapeutic approaches. The presence of true vascular inflammation in these conditions has also led to their being classified as 'secondary' vasculitides.

Syphilis

Syphilis is invoked most commonly in the differential diagnosis of the aortic and aortic branch involvement of the large vessel vasculitides. Cardiovascular syphilis occurs as part of the tertiary manifestations of syphilis, caused by the spirochete *Treponema pallidum*. Cardiovascular syphilis presents with inflammation of the aorta resulting in aortic wall thickening, aneurysm formation, aortic valvular incompetence and coronary artery disease. Approximately 11% of untreated patients progress to develop cardiovascular syphilis [1]. Aortic aneurysms occur most commonly in the ascending aorta where they may be symptomatic (from pressure on the surrounding structures) but less commonly they can affect the descending thoracic and abdominal aorta where they are often asymptomatic. The prevalence of abdominal aortic aneurysms varies and most commonly involves the suprarenal aorta. Rare reported manifestations of cardiovascular syphilis include involvement of the pulmonary arteries and great vessels arising from the aortic arch, hepatic artery and renal artery [2]. Histopathologically, syphilitic aortitis is characterized by the collection of lymphocytes and plasma cells in the perivascular spaces surrounding the vasa vasorum in the adventitia of the root of the aorta, a lack of 'skip lesions', plasma cell microabscesses and the rare occurrence of fibrinoid necrosis and sclerotic lesions (sometimes mildly inflammatory) with or without thrombosis [3]. The sensitivity of the Venereal Disease Research Laboratory (VDRL) test for cardiovascular syphilis is 73% and for the fluorescent treponemal antibody (FTA-ABS) test sensitivity is 96%. Co-existent neurosyphilis may provide a clue to the diagnosis. Syphilis can also rarely confound the diagnosis of a small vessel vasculitic process affecting the lungs. Syphilitic involvement of the lungs resulting in necrotizing vasculitis with gumma in the pulmonary parenchyma presenting as mass lesions has been reported [4].

Mycobacterial infections

TB (caused by *Mycobacterium tuberculosis*) can result in granulomatous arteritis leading to vessel wall thickening, aneurysm formation and stenoses that can affect the aorta and its branches, thereby mimicking large vessel vasculitis [5]. Moreover, vasculitis may be seen at histopathology in the region of tuberculous granulomas. Involvement of the descending aorta or renal artery may resemble Takayasu's arteritis (TAK), especially in clinical settings where this

pattern of aortic involvement from TAK is common [6]. Four types of TB arterial disease have been described:

- Miliary TB of the intima
- TB polyps attached to the intima
- TB involving the vascular wall
- TB aneurysm [7]

Tuberculous aortitis may be differentiated from TAK owing to its tendency to cause erosion of the vessel wall with the formation of true or false aneurysms, particularly affecting the descending thoracic and abdominal aorta in contrast with arterial stenoses that are more typical of TAK [8]. The diagnosis may be suggested by the co-existence of extrapulmonary TB. Atypical mycobacteria (*Mycobacterium avium intracellulare*) have been reported to result in granulomatous and vascular pulmonary disease and positive antineutrophil cytoplasmic antibodies (ANCA). The ANCA in these patients are often of the perinuclear (P-ANCA) pattern and are reactive to nonmyeloperoxidase (MPO) antigens [9]; however, MPO-reactive P-ANCA have been reported in this situation [10].

Infective endocarditis

Infective endocarditis (IE) has the ability to mimic the entire spectrum of vasculitides clinically, radiologically and at histopathology. IE can cause mycotic (infected) aneurysms affecting the aorta and its branches and pulmonary arteries, as well as small vessel inflammation in various organs either from direct infection (septic vasculitis) or through immune complex-mediated (purpura, glomerulonephritis [GN]) or embolic mechanisms. The presence of cutaneous findings, such as 'splinter hemorrhages', may also be seen in both IE and small vessel vasculitis. In one series of patients who underwent surgical repair for aortic aneurysms, the prevalence of mycotic aneurysms was 2.3% [11]. Mycotic aneurysms can occur in any arterial location, resulting in symptoms related to organ-specific or multiorgan ischemia and inflammation. The aneurysms occur at major branches of the aorta, most frequently the femoral artery and abdominal aorta, followed by the thoraco–abdominal and thoracic aorta [12]. Transesophageal echocardiography can provide valuable information by visualizing IE affecting the cardiac structures, as well as the root of the aorta and ascending aorta [13]. Blood cultures are useful in identifying the responsible organism as well. GN observed in the setting of IE is typically associated with 'granular' immune complex deposits (immunoglobulin and complement) on the subepithelial or subendothelial glomerular basement membrane seen by electron microscopy and immunofluorescence [14] in contrast with GN, occurring from primary systemic small vessel vasculitides, such as Wegener's granulomatosis (WG) and microscopic polyangiitis, which are classically associated with few to absent immune deposits (referred to as pauci-immune GN).

Viral hepatitis

Hepatitis A infection is rarely associated with cutaneous vasculitis and cryoglobulinemia [15]. Hepatitis B (HBV), and less commonly, Hepatitis C viruses (HCV), are well known to cause a medium vessel vasculitis resembling polyarteritis nodosa (PAN). The strict definition of PAN as a primary vasculitis at this time excludes the PAN-like diseases caused by viruses [16]. In a study of 115 patients with HBV-associated PAN [17], renal involvement was always accompanied by vasculitis in the absence of GN. ANCA was negative in all cases. Relapses were rare and never occurred after seroconversion. A combination of antiviral therapy and immunosuppression resulted in the best outcomes. The major cause of death was gastrointestinal tract involvement [17]. Orchitis, gastrointestinal and renal artery involvement resulting in hypertension are common in HBV-associated PAN, whereas cutaneous and pulmonary involvement is rare [18]. HCV can also cause cryoglobulinemic vasculitis – an immune complex-mediated small vessel disease (purpura and GN) with mixed cryoglobulinemia. In a study of 1200 patients with chronic HCV infection, cryoglobulins were observed in 40% of patients and vasculitis developed in 1% of patients (all with cryoglobulins) [19]. The histopathology of cutaneous vasculitis from HCV-associated cryoglobulinemia shows leukocytoclastic vasculitis with inflammatory infiltrates and, in some cases, fibrinoid necrosis of the arteriolar walls and luminal thrombi. Renal involvement from mixed cryoglobulinemia classically results in Type I membranoproliferative GN. Other described pathologies include focal and mesangioproliferative GN, membranous GN and thrombotic microangiopathy [20].

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) presents with progressive cognitive decline, altered mental status, neurologic deficits became apparent upon physical examination and

subcortical white matter changes on MRI of the brain, which can mimic the presentation of CNS vasculitis. It is a rapidly progressive, generally fatal, neurological disease owing to reactivation of the John Cunningham (JC) virus polyoma virus. It has been observed in patients with malignances on immunosuppressive therapy, but systemic lupus erythematosus (SLE) may bear an independent predisposition to PML, even in patients on minimal immunosuppression owing to immune dysregulation [21]. PML must be considered in the differential diagnosis of immunosuppressed patients presenting with progressive neurological deficits, regardless of the intensity of immunosuppression, and especially if worsening occurs after increasing immunosuppression. The diagnosis can be confirmed by testing the cerebrospinal fluid for JC virus by PCR; however, brain biopsy may be needed if clinically indicated and PCR testing is negative.

Inherited disorders

Disorders of the connective tissue matrix

Marfan's syndrome

Vascular involvement in Marfan's syndrome, an autosomal dominant disorder of connective tissue caused by mutations in the gene for fibrillin-1 (*FBN1*), is characterized by abnormalities in the wall of the thoracic aorta leading to aortic aneurysms and dissection. Aortic regurgitation occurs in 15–44% of patients [22]. Thoracic aortic involvement from Marfan's syndrome can mimic other etiologies of aneurysm including giant cell arteritis and Takayasu's arteritis. The large vessel vasculitides can be differentiated from Marfan's syndrome based on their tendency to cause arterial stenoses, their pattern of vascular involvement, a lesser likelihood of causing arterial dissection and a lack of other accompanying features of Marfan's syndrome (i.e., ocular, skeletal and cutaneous). *FBN1* mutations have also been described in patients with thoracic aortic aneurysms and dissection without the typical marfanoid body habitus [23].

Ehlers–Danlos syndrome type IV

Ehlers–Danlos syndrome type IV is another autosomal dominant arterial wall matrix disorder that results from mutations in the type III procollagen gene (*COL3A1*) and may be complicated by arterial dissection or rupture, bowel perforation or organ rupture. Arterial involvement is most commonly seen in the thoracic or abdominal arteries, but carotico-cavernous fistulas, carotid artery dissection, aneurysm and rupture have been reported [24]. Again, in this disease, arterial wall thickening or stenoses were not observed. The histopathology of the arterial wall in both Marfan's syndrome and Ehlers–Danlos syndrome type IV is cystic medial necrosis, which clearly differs from the granulomatous inflammation seen with the primary large vessel vasculitides. However, this distinction may be difficult to make as evidence of active inflammation is generally only found in approximately half of surgical specimens from patients with large vessel vasculitides [25,26] since surgery is usually performed in these patients when the disease is considered quiescent.

Loeys–Dietz syndrome

Loeys–Dietz syndrome is characterized by a triad of arterial tortuosity and aneurysms, hypertelorism and bifid uvula or cleft palate owing to mutations in the TGF-β receptors (TGFBR 1 and 2). Thoracic and abdominal aortic dissections are the leading causes of death in Loeys–Dietz syndrome. The reported mean age of dissection is 26 years and the mean age for surgical intervention for ascending aortic aneurysm or dissection is 20 years. Other arteries that can be affected by aneurysms include the thoracic, head and neck and abdominal vessels [27]. The bicuspid aortic valve has also been associated with aortic dissection from the possible overactivity of matrix metalloproteinases [28].

Genetic testing is available for mutations in *FBN1*, *COL3A1* and *TGFBR1/2* and helps to establish the diagnosis in suspected cases.

Other inherited disorders

Neurofibromatosis type I

Neurofibromatosis type I is also an autosomal dominant disorder that may affect large- or medium-sized vessels. Large vessel involvement can lead to aortic dissection and rupture [29]. The most common vascular involvement in neurofibromatosis type I is renal artery stenosis resulting in hypertension. Other lesions include cerebrovascular involvement, pulmonary artery stenosis and intra-abdominal vessel involvement [30]. Vascular involvement has been classified as pure intimal, advanced intimal, intimal aneurysmal and nodular. Histopathology of the intimal subtype shows marked, concentric intimal proliferation of spindle cells with or without fibrosis and a thinned media. The aneurysmal subtype demonstrates marked fibrous intimal thickening, irregular loss of media smooth muscle and elastic fragmentation in small-sized arteries [31].

Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) is a non-inflammatory vascular disease characterized by stenoses and aneurysm formation in multiple vascular territories, usually from medium-sized vessel involvement. Histopathologically, FMD is classified as intimal, medial or perimedial based on the predominant, but not exclusive, arterial wall layer involvement. Renal and carotid arteries are most commonly involved, but other arteries may be involved in 10% of cases. Angiographically, FMD has been classified as multifocal ('string-of-beads' appearance), tubular, focal and mixed [32]. Depending on the vascular territory and vessel size involved, FMD can mimic polyarteritis nodosa or TAK. An autosomal dominant inheritance has been suggested for renal artery involvement from FMD in a French study [33].

Grange syndrome

Grange syndrome is a recently described hereditary disorder characterized by a variable combination of multiple arterial stenoses and aneurysms, brachysyndactyly, bone fragility, learning disability and cardiac defects [34]. Arterial involvement can mimic FMD, manifesting with hypertension and angiographic 'beading'. No clear genetic defect has yet been discovered in Grange syndrome, but an autosomal recessive inheritance pattern has been observed.

Moyamoya disease/syndrome

Moyamoya disease is a vasculopathy of unknown etiology that most commonly affects the cerebrovascular circulation predisposing a stroke. The classical involvement results in bilateral internal carotid artery stenosis resulting in a florid collateral circulation that, given the appearance of 'a puff of smoke' on the angiogram, the Japanese term for this appearance is 'Moyamoya'. However, the arteries comprising the circle of Willis may also be commonly involved with 'spontaneous occlusion'. Moyamoya disease occurs most commonly in the Asian–American population in children and middle aged adults with a female predominance. The symptoms typically arise as a consequence of vascular ischemia or hemorrhage from the collaterals. Vascular smooth muscle cell hyperplasia and thrombosis are described at histopathology, with no evidence of vascular inflammation. Renal artery stenosis has been reported in Moyamoya syndrome. A genetic basis has been suggested based in family studies revealing increased linkage analysis (chromosomes 3p24.2-p26, 17q25, 8q23, 6) and occurrence of certain haplotypes (HLA-B35 in the Korean population) [35].

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is considered a typical monogenic inherited cause of stroke resulting from mutations in the *Notch3* gene [36]. Recurrent strokes may eventually cause multi-infarct dementia. Other presentations include migraine and psychiatric disturbances. MRI reveals white matter and a diffuse small vessel ischemia pattern within the periventricular white matter, basal ganglia, thalamus, internal capsule and pons. This widespread vascular involvement and stroke/dementia-like presentation mimics the presentation of primary CNS vasculitis. The angiographic picture can also be similar due to the appearance of arterial stenoses. Histopathology reveals degeneration and loss of smooth muscle in middle- and small-sized arteries, basophilic granular degeneration of the media, vessel fibrosis, hyalinization and enlargement of perivascular spaces. The presence of granular osmophilic material in the medial layer on electron microscopy is pathognomonic and corresponds to the extracellular domain of the protein coded by the *Notch3* gene on immunohistochemistry [37]. CADASIL should be suspected in the right clinical context and if a family history is suggestive of this condition [38].

Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is a hereditary or sporadic disorder characterized by deposition of extracellular eosinophilic material (amyloid) in the cerebral vessels. Hereditary forms of CAA result from mutations in various amyloid proteins (such as cystatin C, presenilin, prion protein, transthyretin and gelsolin). Clinical presentations of CAA include stroke (both ischemic and hemorrhagic), subarachnoid hemorrhage, transient neurologic phenomena, cognitive impairment and dementia [39]. Histopathology demonstrates thickening of the small- and medium-sized arterial and arteriolar walls (and less often veins), resulting from deposition of an amorphous, intensely eosinophilic material on light microscopy with a characteristic 'apple-green' birefringence on polarized microscopy after Congo red staining [40]. The incidence of CAA increases with age and even in the hereditary forms of the disease, a large variation in the age of presentation is reported.

Box 1. Vasculitis mimics.

Infection
- Treponema pallidum
- HIV
- Hepatitis B virus
- Hepatitis C virus
- Hepatitis A virus
- Mycobacteria
- Herpes viruses
- Infective endocarditis
- Mycotic aneurysms
- John Cunningham virus
- Protozoa

Inherited disorders
- Disorders of connective tissue matrix
  - Marfan's syndrome
  - Ehlers Danlos syndrome type IV
  - Pseudoxanthoma elasticum
  - Loeys–Dietz syndrome
- Other inherited disorders
  - Neurofibromatosis type I
  - Fibromuscular dysplasia
  - Grange syndrome
  - Moyamoya disease
  - Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
  - Cerebral amyloid angiopathy

Drugs/toxins
- Cocaine
- Sympathomimetics

Atherosclerosis & arteriolosclerosis
- Hypercoagulable states
  - Thrombotic thrombocytopenic purpura
  - Antiphospholipid syndrome

Vasospastic disorders
- Reversible cerebral vasoconstriction syndrome
- Reversible posterior leukoencephalopathy syndrome

Immunodeficiency disorders
- Common variable immunodeficiency
- HLA class I deficiency

Malignancies
- Leukemia
- Lymphoma
- Glioma
- Angiocentric lymphoma

Multisystem inflammatory disease
- Sarcoidosis
- Susac's syndrome

Miscellaneous
- Degos disease
- Segmental arterial mediolysis
- Cardiac myxoma
- Calciphylaxis
- Cholesterol emboli syndrome
- Postradiation therapy
- Paraneoplastic

Miscellaneous noninherited disorders

Segmental arterial mediopathy

Segmental arterial mediopathy (SAM), originally called segmental mediolytic arteritis, was first described by Slavin in 1976 in three patients at autopsy who were found to have large abdominal muscular arteries affected by dissecting aneurysms, partial or total mediolysis accompanied by linear fibrin deposits between the media and adventitia and a variable inflammatory infiltrate [41]. SAM commonly affects medium-sized vessels in various territories (most commonly in the abdomen) and presents as arterial dilatation, solitary aneurysm, multiple aneurysms, arterial dissections with hematomas, and arterial stenoses and occlusions. Most patients with SAM are middle aged to elderly individuals with an equal male/female distribution. Patients typically present with abdominal pain or retroperitoneal hemorrhage owing to rupture of a visceral artery aneurysm. SAM is hypothesized to be a part of the pathological continuum from an initial vasospastic process that may eventually evolve into a PAN-like disease [42,43]. Radiographic [44] and clinical [43] long-term follow up studies indicate that SAM is most likely to be an acute disorder with resolution or unchanged arterial involvement over time.

Drugs/toxins

A wide variety of drugs may result in mimics of vasculitis or indeed cause a true vasculitis. A number of drugs, such as minocycline and hydralazine, may be associated with positive ANCA testing, and in some cases may be associated with a vasculitic syndrome [45]. However, cocaine use may be a particularly elusive mimic of WG. Cocaine use may result in nasal mucosal irritation and necrosis, intense vasoconstriction leading to nasal septal perforation and collapse with a saddle-nose deformity. These patients can present with facial pain, epistaxis and constitutional symptoms. In addition, they can have a classical-ANCA pattern on immunofluorescence and positive antiproteinase 3 (PR3) testing by immunoassay, compounding the diagnostic confusion with WG. PR3-ANCA has been reported in up to 50% of patients with cocaine-induced midline destructive lesions [46]. However, the epitope on the PR3 molecule for ANCA in patients with cocaine-induced lesions is different from that of patients with WG. The antigen for ANCA in patients with cocaine-induced lesions is human neutrophil elastase (HNE); antibodies

directed against HNE were found in patients with cocaine-induced midline destructive lesions by one assay in 84%, by two assays in 68%, and by all three assays in 36% (indirect immunofluorescence, direct and indirect capture ELISA) but were not observed in patients with WG [46]. The ANCA reacting with both HNE and PR3 demonstrate a P-ANCA pattern on indirect immunofluorescence [46]. Evidence for multisystem disease should be carefully sought and clearly favors a diagnosis of WG. However, the absence of the antibodies does not preclude a diagnosis of WG. Sustained use of other vasoconstrictor medications, such as oxymetazoline and phenylypropanolamine, can also result in similar injury to the nasal mucosa through ischemia and also mimic chronic sinusitis owing to the occurrence of rebound phenomena such as rhinitis medicamentosa, but will not typically be associated with positive ANCA testing.

Atherosclerosis & arteriolosclerosis

Atherosclerosis is a well-defined inflammatory vascular disease [47], distinct from vasculitis. It is influenced by genetic factors modified by metabolic risk factors such as diabetes mellitus, hypertension, hyperlipidemia and smoking. Atherosclerosis results in aortic aneurysms (most commonly in the infrarenal aortic segment), aortic valve sclerosis and stenoses in the aortic branches and medium-sized arteries. It can mimic vasculitis clinically (symptoms from tissue ischemia and infarction, absent or weak pulses and bruits) and angiographically (focal, short segmental or diffuse arterial narrowing and aneurysms). At histopathology, atherosclerosis is characterized by 'plaques' consisting of lipids, inflammatory cells and platelets with or without thrombus. The clinical suspicion for atherosclerosis should be heightened in the relevant clinical setting in a patient with a typical clinical risk factor profile and presentation. Arteriolosclerosis is a systemic noninflammatory small vessel (arteriolar) disease characterized by hyalinization of the intima (hyalinosis) with proliferation and hypertrophy of the media. It is usually silent, associated with ageing, diabetes mellitus and hypertension and is most commonly described in the renal [48] and cerebral microvasculature [49]. Histopathology of arteriolosclerosis consists of subendothelial protein deposits staining bright magenta with periodic acid-Schiff stains and has a glassy texture (hyaline). Inflammatory changes do not occur distinguishing it from true vasculitis.

Hypercoagulable states

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a microvascular angiopathy that may be familial, idiopathic or secondary to medications, infections or organ transplantation. It is clinically characterized by microangiopathic hemolytic anemia, consumptive thrombocytopenia, renal failure, fever and altered mental status or other neurological deficits [50]. All features do not need to be present to make the diagnosis. Microvascular thromboses in multiple vascular territories are associated with tissue infarction and hence, invoke the differential diagnosis of vasculitis. The pathogenesis of TTP involves deficient activity of a metalloproteinase (ADAMTS13) resulting in von Willebrand factor multimers with resultant platelet aggregation [51,52]. Histopathology of tissues in patients with TTP typically demonstrates thrombi composed predominantly of platelets, with little fibrin deposited in the myocardial microcirculation and variable involvement of the circulation in the kidney, pancreas, brain and adrenal glands [53]. Microangiopathic hemolytic anemia (evidenced by schistocytes on the peripheral blood smear), thrombocytopenia and histological findings (platelet thrombi) help differentiate TTP from primary systemic vasculitis.

Antiphospholipid syndrome

Antiphospholipid syndrome is an autoimmune hypercoagulable disorder, clinically characterized by recurrent arterial and venous thrombotic events, pregnancy loss, thrombocytopenia and persistently positive anticardiolipin or lupus anticoagulant antibodies. Pathogenetic mechanisms underlying the thrombotic manifestations include activation of endothelial cells, monocytes or platelets, complement activation and inhibition of protein C [54]. Multifocal thrombotic events with angiographic appearances of arterial narrowing secondary to luminal thrombi can mimic the clinical and angiographic appearance of vasculitis. Antiphospholipid syndrome can occur as a primary disorder or in association with diseases such as SLE. Other manifestations include hematologic (hemolytic anemia), neurologic (transverse myelopathy or myelitis, multiple sclerosis-like involvement, chorea and migraine), cutaneous (livedo reticularis/racemosa, atrophie blanche), cardiac (thrombotic endocarditis and valvular disease) and hypertension from renal involvement. The diagnosis can be confirmed by serial testing for antiphospholipid antibodies in the right clinical context.

Vasospastic disorders

Reversible cerebral vasoconstriction syndromes

Reversible cerebral vasoconstriction syndromes (RCVS) are vasospastic disorders of unknown etiology affecting the cerebral vasculature that are usually associated with acute onset and severe, recurrent headaches, with or without additional neurological signs and symptoms. RCVS may be idiopathic or triggered by pregnancy, medications, illicit drug use, metabolic disorders, trauma, postneurosurgery or catheter-based vascular intervention. The typical presentation is with recurrent episodes of acute onset of severe (thunder-clap) headache, with or without associated nausea, vomiting, photosensitivity and transient or permanent visual or neurological deficits as a result of intense vasoconstriction in that particular cerebral vascular territory. The vasoconstriction can be severe enough to result in stroke (either ischemic or hemorrhagic) and even death. The diagnosis is made based on the clinical history, normal or near normal cerebrospinal fluid findings and evidence of multifocal segmental arterial narrowing ('beading') with reversal within 12 weeks (on magnetic resonance angiography or conventional dye angiography) [55]. In patients with suspected RCVS without the typical clinical presentation of headache and with neurologic deficits and diffuse parenchymal abnormalities on MRI, and/or absence of reversibility on follow-up angiography, a brain biopsy to exclude true CNS vasculitis may be indicated. There is limited data regarding brain biopsy findings in patients with true RCVS, but the available data reports demonstrate no evidence of vasculitis. Observational data regarding treatment includes calcium channel blockers and short courses of glucocorticoids, with subsequent reversal of the vascular abnormalities at serial imaging, providing the greatest retrospective confirmation of RCVS is apparent.

Reversible posterior leukoencephalopathy syndrome

Reversible posterior leukoencephalopathy syndrome, first described in 1996, is a vasoconstrictive disorder associated with headache, seizures, confusion, visual disturbances and a pattern of predominantly posterior cerebral edema on imaging. It can occur in isolation or in the context of other diseases such as SLE, WG and systemic sclerosis [56], pre-eclampsia, severe hypertension, when taking medications (ciclosporin, tacrolimus and methotrexate), and as a result of infection/sepsis and organ transplantation [57]. Three imaging patterns of reversible posterior leukoencephalopathy syndrome on computed tomography/MRI have been reported: holohemispheric watershed, superior frontal sulcal and dominant parieto-occipital [58]. Angiography demonstrates irregular vascular abnormalities of constriction and dilatation, but these are reported to reverse at future follow-up imaging. Histopathology on brain biopsy demonstrated edema of the white matter consistent with that observed on MRI [59].

Immunodeficiency disorders

Common variable immunodeficiency

Common variable immunodeficiency [60] may mimic WG, as it can manifest with pansinusitis, recurrent pneumonia, multisystem and pulmonary granulomatous involvement and inflammatory polyarthritis. However, it can be differentiated from WG by its features of qualitative and quantitative defects in cellular and humoral immune function, which include cytopenias, impaired lymphocyte proliferation with mitogenic stimulation, decreased immunoglobulin levels, specific antibody nonresponsiveness to protein and/or polysaccharide antigens, autoimmune phenomena (such as thrombocytopenia and hemolytic anemia) and absence of ANCA. Diagnosis can be established with laboratory evaluation of immune function although genetic testing may be necessary to identify the exact responsible defect in an individual patient.

HLA class I deficiency

Manifestations of HLA Class I/transporter-associated protein deficiency can mimic signs and symptoms of WG. These patients present with granulomatous skin lesions, cutaneous vasculitis and recurrent bacterial sinus and pulmonary infections [61,62]. The diagnosis may be suspected based on the presence of recurrent infections or may sometimes be made retrospectively-based on the response to immunosuppression. The diagnosis can be confirmed by reverse transcriptase PCR and DNA sequence analysis [63].

Miscellaneous conditions

Calciphylaxis

Calciphylaxis is a noninflammatory vasculopathy resulting from calcification of the small-sized arterial vessels with consequent tissue ischemia and infarction. Calciphylaxis is seen most commonly, but not exclusively, in patients with advanced chronic kidney disease ('calcific

uremic arteriopathy'). Other risk factors include female gender, elevated phosphate levels, elevated alkaline phosphatase, hypoalbuminemia, obesity, liver disease, systemic glucocorticoid use and calcium phosphate product greater than 70 mg^2/dl^2 [64,65]. Patients usually develop severe pain in the muscles or skin breakdown, but other presentations such as rhabdomyolysis, or involvement of the cardiac, penile, pulmonary, pancreatic and ocular vasculature have been described [66]. The proposed pathogenesis of calciphylaxis involves a switch of the vascular smooth muscle phenotype to an osteoblastic phenotype. Histopathology shows small vessel calcification, intimal proliferation, endovascular fibrosis and intravascular thrombosis. Vascular inflammation is not seen.

Cardiac myxoma

Cardiac myxomas are the most common primary cardiac tumors that are benign, occur most commonly in the left atrium and can produce symptoms due to valvular obstruction, embolization or paraneoplastic effects. They are most commonly observed in middle-aged females. Paraneoplastic manifestations of myxomas include fever, arthralgias and weight loss that can mimic the constitutional symptoms seen with systemic vasculitis. Recurrent embolic phenomena can lead to tissue infarction with digital ischemia, cutaneous infarcts, limb claudication, hemoptysis (pulmonary infarction), hematuria (renal infarction) and stroke (cerebral infarction). Elevated MPO-ANCA that normalized after surgery has been reported in a patient with cardiac myxoma [67]. Transesophageal echocardiography or computed tomography/MRI can be used to diagnose myxomas, and surgical resection with reconstruction improves prognosis [68].

Cholesterol emboli syndrome

Cholesterol embolization (atheroembolism) can occur from the arterial wall as a result of trauma from catheter manipulation, direct trauma, surgery, anticoagulation or thrombolysis. It most commonly affects the extremities where it manifests with symptoms of limb ischemia with a livedo reticularis-like rash and normal pulses. Other cutaneous findings include purpura, ulcers, nodules, cyanosis and frank gangrene [69]. Renal involvement can result in acute renal failure, sometimes necessitating dialysis. Treatment is largely supportive and renal function may be irrecoverably lost [70]. Other sites of embolization include the gastrointestinal tract and CNS. Bedsides, ophthalmoscopy may reveal retinal cholesterol emboli. A deep skin biopsy shows cholesterol crystals (identified by 'cholesterol clefts') in the cutaneous microvessels. The skin biopsy can be diagnostic in as many as 92% of cases [71]. Elderly male patients with pre-existing renal disease have a worse prognosis and this condition is associated with significant mortality [72].

Future perspective

Greater awareness of vasculitis mimics will facilitate diagnosis and additional study of these entities. Future development of more reliable biomarkers, novel genetic markers and advances in diagnostic imaging modalities may provide better tools to characterize known vasculitis mimics and to distinguish them from the primary systemic vasculitides. With advances in the understanding of the pathophysiology of known infectious agents and the future discovery of novel infectious agents, it is likely that additional infectious agents with the ability to mimic vasculitis will be identified. However, the most important consideration will always be to separate these entities from the primary systemic vasculitides due to the consequent therapeutic and prognostic implications.

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Executive summary

- The primary systemic vasculitides are rare diseases and are generally less common than secondary forms of vasculitis and the vasculitic mimics.
- Many of the vasculitic mimics are noninflammatory and treating with immunosuppressive therapy is not only unnecessary, but is also potentially hazardous.
- An attempt must always be made to establish a diagnosis using the best risk–benefit strategy and therapy is then instituted accordingly.
- The diagnosis of primary systemic vasculitis should always be re-appraised in the event of failure to respond to immunosuppressive therapy.

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1. Which of the following best describes reasons for distinguishing mimics from true primary vasculitides?

- ☐ **A** Avoid adverse effects of immunosuppressive drugs
- ☐ **B** Avoid missing treatable conditions
- ☐ **C** Identify causes of vasculitis
- ☐ **D** All of the above

2. A patient presents with secondary vasculitis that is thought to be associated with syphilis or TB. Which of the following clinical features would most likely distinguish the two conditions?

- ☐ **A** Effect on ascending versus descending aorta
- ☐ **B** Presence of aneurysms
- ☐ **C** Involvement of vessels of the lung
- ☐ **D** Presence of large-vessel vasculitis

3. Which of the following vasculitis mimic conditions is least likely to have an autosomal dominant inheritance?

- ☐ **A** Fibromuscular dysplasia
- ☐ **B** Ehlers–Danlos syndrome
- ☐ **C** Grange's syndrome
- ☐ **D** Marfan's syndrome

4. Which of the following toxins or drugs is most likely to be associated with pathology that mimics Wegener's granulomatosis?

- ☐ **A** Minocycline
- ☐ **B** Cocaine
- ☐ **C** Oxymetazoline
- ☐ **D** Hydralazine

5. A 36-year-old woman presents with recurrent pregnancy losses, hypertension and hemolytic anemia, and a vasculitis is suspected. Which of the following features is least likely to be associated with a diagnosis of antiphospholipid syndrome?

- ☐ **A** Transverse myelopathy
- ☐ **B** Migraine
- ☐ **C** Livedo reticularis
- ☐ **D** Thrombocythemia