Practical approach to vasculitides in adults: an overview of clinical conditions that can mimic vasculitides closely

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Abstract

Primary systemic vasculitides are rare diseases affecting blood vessel walls. The type and patterns of distribution of the organs affected usually reflect the size of the vessels predominantly involved, and the patterns of clinical manifestations are generally useful to reach a specific diagnosis. However, presenting symptoms may lack adequate specificity for a prompt diagnosis, leading to a diagnostic (and therapeutic) delay, often causing irreversible damage to the affected organs.

Due to their rarity and variable clinical presentation, the diagnosis of primary vasculitides could be challenging for physicians. Vasculitis mimickers, i.e. the clinical conditions that could be likely mistaken for vasculitides, need to be carefully ruled out, especially before starting the immunosuppressive therapy.

We present here a practical approach to the diagnosis of primary systemic vasculitides involving large, medium and small size vessels, and reviewed most of the conditions that could mimic primary systemic vasculitides.

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Introduction

Vasculitides are defined as inflammation of the blood vessels, often impairing the local blood circulation and leading to structural damage, tissue ischemia and necrosis.[1,2] The type and patterns of distribution of the affected organs usually reflect the predominant size of the vessels involved, suggesting one or more possible diagnoses of vasculitis.[3] Vasculitides may be caused by an underlying disease or occur as a primary process; in the latter case the precise pathogenic mechanisms is not yet fully understood.[1,2]

Because of their rarity, primary vasculitides are sometimes difficult to diagnose. In several cases, the presenting symptoms might lack adequate specificity for a prompt diagnosis, leading to a diagnostic (and, therefore, therapeutic) delay that could irreversibly damage the target organs.[4-6] In this respect, exhaustive medical history collection and an extended clinical examination constitute the first step of the work-up. When possible, a biopsy of an affected organ is recommended to confirm the clinical diagnosis.[7,8]

On the other hand, other clinical conditions that could be likely mistaken for vasculitides need to be carefully ruled out (*i.e.* vasculitis mimickers), especially before starting the immunosuppressive therapy.[9-12]

Here we outline a practical approach to the diagnosis of vasculitis and review most of the conditions that need to be rigorously recognized, when diagnosing the most common forms of primary systemic vasculitides involving large, medium and small size vessels.

When to suspect a vasculitis

Given the heterogeneous spectrum of clinical manifestations, it is not possible to outline an algorithm which reflects the complete diagnostic process for patients with suspected vasculitis.[13,14] However, several clues in medical history, physical examination, laboratory and imaging findings might be of help.[15] Specifically, vasculitis should be considered in all patients with constitutional symptoms (fever, fatigue, weight loss and/or musculoskeletal symptoms such as arthralgia or myalgia) in combination with evidence of vessel involvement in imaging (mostly for medium-large vessel vasculitis) or clinical evidence of single and/or multiorgan dysfunction (for all vasculitis).

There are classification criteria for vasculitides and a stepwise algorithm for classification of ANCA-associated vasculitis (AAV) specifically designed for epidemiological studies[7,13,16-20] The Chapel Hill Consensus Conference (CHCC) nomenclature, revised in 2012, categorizes vasculitides based on the size of the most affected vessels (*i.e.*, large, medium, and small vessel vasculitis) in order to dis-

tinguish the different forms of vasculitides into definable groups (Table 1).[21] Although these could be used by clinicians for the diagnosis, they do not have enough sensitivity and specificity, as diagnostic criteria. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) are currently working on the development of new diagnostic and classification criteria for systemic vasculitides, the *Diagnostic and Classification Criteria of Vasculitis* (DCVAS) study.[22]

Patterns of clinical manifestations and organ involvement are generally useful to reach a specific diagnosis. In particular, a positive history of nasal crusting, sinusitis, and/or scleritis might be suggestive of granulomatosis with polyangiitis (GPA).[23,24] Asthma, sinusitis with or without nasal polyps and peripheral blood hypereosinophilia suggest a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA).[25,26] Subtle and extensive neuropathies can occur in many forms of vasculitides, and an acute foot or hand drop may be due to a motor neuropathy due to small vessel vasculitis.[27-30] New-onset, severe headache, usually above the temple area, scalp tenderness and jaw claudication are highly suggestive of a diagnosis of giant cell arteritis (GCA).[31] Limb claudication, particularly of the upper limbs and in the presence of systemic symptoms, is suggestive of a large vessel vasculitis (LLV), as Takayasu's arteritis (TA) or GCA.[32-36] Absent, diminished, or tender pulses, bruits, or blood pressure discrepancies between arms may suggest LLV and particularly TA in the young females.[32-34,37] Oral and genital aphthoses with uveitis should strongly guide towards Behçet's Disease, possibly associated with other neurological or vascular symptoms.[38]

The combination of unexplained hemoptysis/alveolar hemorrhage and positive urinary sediment, especially if accompanied by acute kidney injury, should raise the suspicion of anti-glomerular basement membrane disease (anti-GBM) or MPA.[39,40] In general, palpable purpura is a solid sign of cutaneous leukocytoclastic vasculitis and is a common finding in many small-vessel vasculitides,[41,42] while subcutaneous nodules, livedo reticularis, and ulcers are more typical of polyarteritis nodosa (PAN).[43] The presence of skin purpura, abdominal pain, arthralgia/arthritis and glomerulonephritis, especially in teenagers or younger patients, should instead suggest a possible diagnosis of immunoglobulin A (IgA) vasculitis.[20]

Among laboratory findings, some confirm the suspicion of vasculitis or the organ involvement secondary to the disease; other may support the diagnosis of a specific vasculitis.

In LVV, especially GCA, common findings are elevated erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), although in a subset of active TA this could be normal. In SVV, blood and urine lab tests reflect the type of organ involvement, so they could widely vary among patients. It is recommended to screen any renal involvement in all suspected SVV. This could easily be done by testing serum creatinine and urinalysis with urinary sediment.

The presence of anti-neutrophil cytoplasmic antibodies (ANCA) directed against either protease 3 (PR3) or myeloperoxidase (MPO) is extremely specific for AAV diagnosis in patients with a compatible clinical picture, although it does not have any diagnostic value in itself.[44] Peripheral blood hypereosinophilia, defined as an eosinophil count >10% of leukocytes or >1500 cells/μL in absolute number, are characteristic in EGPA at onset before corticosteroid initiation or during disease relapse.[26,45] The presence of cryoglobulins and low serum complement 4 (C4) levels are highly specific of cryoglobulinemic vasculitis, that could be idiopathic or secondary to viral infections (in particular chronic hepatitis C viruses), lymphoproliferative disorders or underlying connective tissue diseases (46,47). A positive anti-nuclear antibody (ANA) test with or without the presence of rheumatoid factor (RF) may support a process secondary to HCV infection or an underlying systemic rheumatic disease, as primary Sjögren syndrome.[46,47] C3 and C4 levels are usually (but not always) normal in pauci-immune vasculitis like AAV, while they tend to be both reduced in hypocomplementemic urticarial vasculitis.

Overall, patients with conditions that can present with signs and symptoms mimicking primary systemic vasculitides should be carefully screened. There are several processes that need to be ruled out, including inflammatory and non-inflammatory diseases.[12,21] The vasculitis mimickers that should be taken into consideration vary according to the size of the vessels involved (Table 2).

Table 1. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides. *Adapted from Jennette* et al., *2013*.[22]

Large vessel vasculitis (LVV)
Takayasu arteritis (TAK)
Giant cell arteritis (GCA)
Medium vessel vasculitis (MVV)
Polyarteritis nodosa (PAN)
Kawasaki disease (KD)
Small vessel vasculitis (SVV)
Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
Microscopic polyangiitis (MPA)
Granulomatosis with polyangiitis (Wegener's) (GPA)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
Immune complex SVV
Anti–glomerular basement membrane (anti-GBM) disease
Cryoglobulinemic vasculitis (CV)
IgA vasculitis (Henoch-Schoenlein) (IgAV)
Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
Variable vessel vasculitis (VVV)
Behçet's disease (BD)
Cogan's syndrome (CS)
Single-organ vasculitis (SOV)
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Others
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable etiology
Hepatitis C virus–associated cryoglobulinemic vasculitis
Hepatitis B virus–associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated vasculitis
Others

Large vessel vasculitis

According to the recently revised Chapel Hill Consensus Conference,[15] LVV is considered vasculitis that affects large arteries more often than do other vasculitides. GCA and TA are the 2 major

variants. While TA usually affects aorta and its major branches, evidence of LVV occurs in GCA in 25% to 83% of patients,[36,48,49] depending on the imaging tool used. In this subset of GCA, cranial manifestations and vision loss are infrequent, and temporal artery biopsy is positive in approximately 50% of cases.[49,50] Overall, the diagnosis of LVV may be challenging, since clinical manifestations are largely unspecific and may overlap with other inflammatory and neoplastic conditions. Infective conditions (*i.e.* tuberculosis, syphilis) may rarely involve large vessels, while Quantiferon test and rapid test for the detection of treponemal antibodies are good screening tools for these conditions. Furthermore, other inflammatory or non-inflammatory conditions may be considered.[51-53]

Diffuse atherosclerosis

Atherosclerosis accounts for nearly half of the mortality worldwide and is a leading cause of adult disability.[54] In particular, peripheral arterial disease may potentially involve all the arterial districts of the body, leading to aneurysms (often of the abdominal aorta), and partial or total occlusions of limb arteries (often presenting with intermittent claudication or, in the worst case scenario, gangrene of the extremities).[55]

The increasing availability of 18-F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18-F-FDG-PET/CT) led to an increase of its use for the diagnosis of LLV and particularly LLV-GCA.[56,57] It has been shown that 18F-FDG PET/TC can identify metabolically active tissue, and specifically that the uptake of FDG within the artery wall correlates with macrophage accumulation in arterial plaques.[58,59] Therefore, large-vessel FDG uptakes due to non-specific, inflammatory-like, vascular remodeling due to atherosclerotic plaques might be an issue in elderly patients with suspected LVV.[58,59-74] The age at diagnosis of the patients affected by GCA or atherosclerosis is approximately the same, and they often share the same cardiovascular risk factors. Moreover, patients with GCA have an increased incidence of cardiovascular events compared to the age-matched healthy population.[75]

An initial assessment of the usual cardiovascular risk factors (such as known peripheral arterial disease, dyslipidemia, arterial hypertension and diabetes) may be advisable. Cardiovascular diseases may develop in patients affected by GCA. Normal CRP and ESR should suggest a different diagnosis than GCA, although 4% of the patients may have negative ESR and CRP at diagnosis.[62]

In PET/CT imaging, the main sites involved in atherosclerosis and LLV are different.[58] Lower abdominal aorta, popliteal arteries, descending thoracic aorta, carotid arteries are mainly affected in atherosclerosis, while thoracic vessels, subclavian arteries, axillary arteries and common carotid arteries (without the internal and external carotid arteries) are mainly affected in vasculitis. Moreover, atherosclerotic lesions are usually characterized by a less intense 18F-FDG uptake compared to vasculitic ones. Finally, the pattern differs substantially between the two diseases: atherosclerotic lesions typically present irregular and patchy 18F-FDG uptake while a linear and homogeneous pattern of 18F-FDG uptake over long vascular segments is more suggestive of vasculitis (Figure 1).[57,63]

Erdheim-Chester disease

TA and GCA often present with fever, fatigue, weight loss, and elevated acute-phase reactant levels potentially mimicking a neoplastic condition like Erdheim-Chester disease (ECD). The current consensus for the diagnosis of ECD relies on the identification of characteristic histological features in the appropriate clinical setting.[64] The presence of CD68-positive, CD1a-negative non-Langerhans histiocytes on histological samples, with foamy cytoplasm and lacking Birbeck granules confirm the diagnosis of ECD.[64]

Most of the vascular symptoms of ECD are not specific and are shared with other inflammatory conditions, particularly large vessel vasculitis or idiopathic periaortitis.[65,66] However, the *coated aorta*, a characteristic inflammatory fibrosis surrounding the aorta on CT

Table 2. Systemic vasculitis mimickers.

	Frequency
Conditions mimicking large vessel vasculitis	
Diffuse Atherosclerosis	Frequent
Erdheim-Chester disease	Very rare
Chronic idiopathic aortitis and IgG4-Related Disease (vascular district)	Very rare
Heritable collagenopathies (Ehlers-Danlos type IV, Marfan syndrome, Loeys-Dietz syndrome)	Rare
Conditions mimicking medium vessel vasculitis	
Fibromuscular dysplasia	Rare
Segmental arterial mediolysis	Very rare
Thromboangiitis obliterans (Buerger's disease)	Rare
Livedoid vasculopathy	Very rare
Conditions mimicking small vessel vasculitis	
Antiphospholipid syndrome	Rare
Emboli (cholesterol, cardiac myxoma, cardiac thrombus, endocarditis, mycotic aneurysm, others)	Very rare
Infection (endocarditis, disseminated intravascular coagulation, others)	Frequent
Hypereosinophilic syndrome	Rare
Calciphylaxis	Rare
IgG4-Related Disease (cranial district)	Very rare
Levamisole-induced vasculitis	Rare
Idiopathic diffuse alveolar hemorrhage, pulmonary alveolar proteinosis	Rare
Intravascular lymphoma	Very rare
Lymphomatoid granulomatosis	Very rare
Malignant atrophic papulosis (Degos disease)	Very rare
Thrombotic thrombocytopenic purpura	Very Rare

Frequency: disease considered frequent if >1% in the general population, rare if 0.01 -1% in the general population, very rare <0.01% in the general population.

scans, is a typical sign of ECD and may be confused with a thickened vessel wall like in aortitis.[67] Vascular involvement in ECD can be seen by 18-F-FDG-PET/CT scanning, which can be useful in assessing the burden of ECD lesions.[68]

Thoracic aorta (25% of cases), abdominal aorta (25% of cases) or the whole aorta (50% of cases) may be involved.[65,69] Perivascular infiltration is typically circumferential, regular, and without clear stenosis. Fibrosis is mainly located in the adventitia and only rarely infiltrates the vascular walls until the intima.[65] Involvement of aorta and its collateral are quite common in TA and GCA; unlike ECD, in GCA and TA inflammatory thickening involves primarily the vessel wall, from the adventitial to the intimal layer.[70] Moreover, stenosis, occlusions and sometimes aneurysms develop during follow-up in a quite high proportion of patients affected by TA and GCA, while they are fairly uncommon in ECD.[64]

Eventually, the presence of other extra-vascular findings helps the differential diagnosis between ECD and LLV: retroperitoneal fibrosis with hairy kidneys (*i.e.* a characteristic perinephric fat surrounding the kidney), bone pain with symmetric osteosclerosis of the long bones on technetium-99m bone scintigraphy, or the presence of central diabetes insipidus, concomitant to aortic involvement, are key elements and should suggest a diagnosis of ECD.[71]

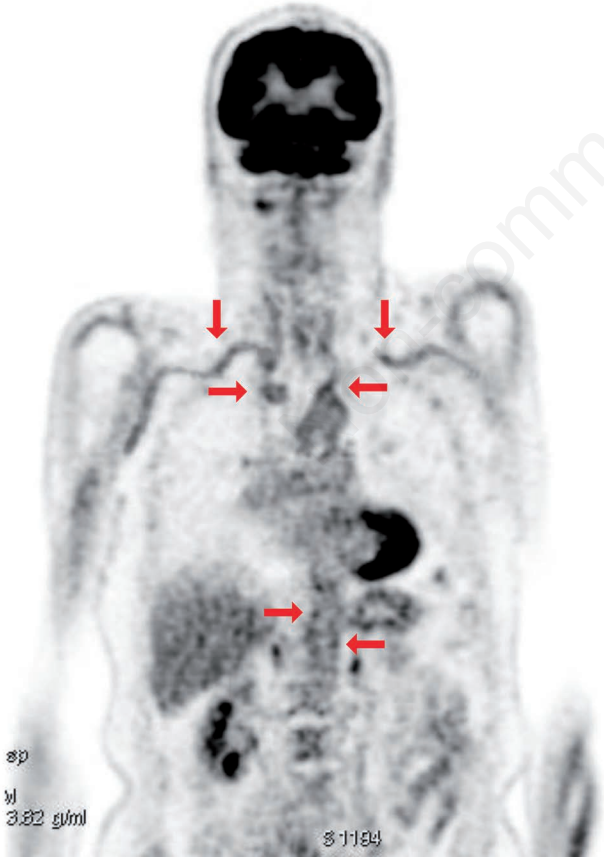

Figure 1. A 18F-FDG PET/CT scan of a patient with atherosclerosis. Arrows indicate the patchy, low grade FDG uptake at subclavian arteries and thoracic and abdominal aorta, suggestive of atherosclerosis.

Chronic idiopathic aortitis and IgG4-related disease

Both chronic idiopathic aortitis and IgG4-Related Disease (IgG4-RD) are characterized by the presence of vascular inflammation, mostly in the abdominal district, usually accompanied by retroperitoneal fibrosis.[72,73] In general, the concomitant retroperitoneal fibrosis, detected with CT scan or FED/PET, is a distinguishing features of chronic idiopathic aortitis/IgG4-RD, and should suggest a diagnosis different from GCA/TA.[74,75] FDG PET/CT also detects remote disease such as that seen in multifocal fibrosclerosis, occult cancers or infections, that might be secondarily associated with retroperitoneal fibrosis.[76,77]

Chronic idiopathic aortitis in the context of idiopathic retroperitoneal fibrosis is a rare condition characterized by a systemic inflammatory state (constitutional symptoms, elevated levels of (ESR and nCRP, *etc*.) with evidence of abdominal aortic aneurysms and perianeurysmal retroperitoneal fibrosis.[66,72] In this clinical scenario, aortic thickening seen in imaging is usually not circumferential like in ECD, but rather involves lateral and anterior sides of the aorta, usually sparing the posterior side.[66,72]

Aortitis in a context of IgG4-related disease usually presents with retroperitoneal fibrosis and only moderately acute inflammatory response; hence, it should be taken into consideration in differential diagnosis with GCA and TA (75)(78). Pancreas, salivary glands and retroperitoneum are among the more frequently affected anatomical sites, and aorta, its branches and the surrounding tissues may be involved.[78,79] It should be noted that IgG4-RD may also mimic inflammatory conditions usually seen in AAV, particularly when involving head and neck, such as hypertrophic pachymeningitis, retro-orbital masses or midline destructive lesions (erosive and/or tumefactive lesions of the of the nose, paranasal sinuses, and palate).[80] The presence of high levels of serum IgG4 (cut off 135 mg/dL), reported in about 60% of patients, is suggestive, yet not specific of a probable diagnosis of IgG4-RD.[81]

Medium vessel vasculitis

Fibromuscular dysplasia

Fibromuscular Dysplasia (FMD) is a non-inflammatory vasculopathy affecting primarily medium and small-sized arteries.[82] The prevalence of FMD in the general population is reported to be around 2% to 3%, with a significant predisposition in females in the adult population (female:male ratio 9:1).[83] The distal renal, internal carotid and vertebral arteries are more frequently affected (accounting for two-third of the total, approximately), followed by intracranial arteries, common carotid, external carotid subclavian, coronary, mesenteric, iliac, and limb arteries.[83-85] FMD patients have usually more than one vascular site affected, and findings reported are aneurysms, that could potentially complicate with dissections, and steno-occlusive lesions.[83,84] FMD is classified in 5 main types, based on the location of the process within the arterial wall, but medial fibroplasia accounts alone for more than the 90% of the cases.[86]

The presentation is heterogeneous and includes headache, lightheadedness, pulsatile tinnitus, neck pain, limb claudication, postprandial angina, renovascular hypertension and acute coronary syndrome. Sometimes patients are asymptomatic and lesions detected are incidental findings.[83,85,87,88] Pulse deficits, asymmetric blood pressure and vascular bruits are typically reported. Both spontaneous arterial dissections (often of the carotid arteries) and arterial aneurisms have been reported in up to 20% of the patients, more often in males.[83,85]

The diagnosis of FMD is usually made using vascular imaging, and the classic *string-of-beads* appearance on conventional angiography is highly suggestive of medial fibroplasia.[84] Clues that may help to differentiate FMD from TA, GCA and PAN include the presence of normal CRP and/or ESR (unless tissue infarction occurs); the absence of constitutional symptoms; and the absence of arterial wall thickening edema, or contrast uptake in imaging. Importantly, if FMD is suspected, patients should undergo screening of the cervical, intracranial, and renal arteries to identify potential concomitant lesions.[83,85,87,88]

Segmental arterial mediolysis

Segmental arterial mediolysis (SAM) is a rare, non-atherosclerotic, non-inflammatory arteriopathy that typically involves the splanchnic district.[89] This condition mainly affects adults and elderly, with a slight male predominance, and the pathogenesis is unknown. It is caused by occurrence of tissue vacuolization in the outer portion of the media, leading to lysis of the media artery wall.[90]

SAM often presents with acute-onset, self-limiting abdominal pain in late middle-aged and elderly patients.[90,91] Overall, patients deny history of rheumatic disease, fever, weight loss, purpura, respiratory or neurological symptoms. Physical examination does not reveal skin or mucosal alteration, neurological examination is typically negative and usually there are no pulse alterations or vascular bruits. Renal function and sediment and CRP are usually normal, unless complications occur (*e.g.* macroscopic hematuria, *etc.*), and auto-antibodies are absent.[90,91]

The diagnosis is typically made by vascular imaging, and classical lesions are arterial aneurysms, stenoses and occlusions, and the characteristic dissecting aneurysms in the splanchnic district (Figure 2).[90,92] Medium-sized arteries of the abdomen, and particularly the celiac trunk, the superior and inferior mesenteric arteries and their branches are involved in the majority of cases, followed by renal, coronary, carotid, and intracranial arteries.[89,92] The aorta is typically spared. Approximately one-third of patients present with hemoperitoneum or retroperitoneal bleeding due to aneurism rupture, which is associated with higher mortality.[93-95] The differential diagnosis is between TA, PAN and other hereditary collagenopathies.[90,91] Unless arterial rupture occurs, any invasive intravascular procedure (*e.g.* transarterial coil embolization) should be avoided, since it could trigger the arterial dissection.[89-91]

Thromboangiitis obliterans (Buerger's disease)

Thromboangiitis obliterans (TAO), also known as Buerger's disease, is a non-atherosclerotic inflammatory disorder of unknown etiology that affects small and medium-sized arteries and veins of the extremities.[96] Median age at diagnosis ranges between 25 and 45 years old and is strongly associated with smoking habits, which have to be investigated at presentation.[97,98]

The diagnosis is based on the typical clinical presentation and imaging, and it should be suspected, if ischemic lesions of the distal limbs without organ involvement are present (Figure 3A).[98] Despite the usual absence of systemic symptoms, there is not yet consensus on whether TAO should be considered a primary vasculitis or not.[99,100] For the differential diagnosis, it is necessary to take into consideration other diseases presenting with ischemic lesions at distal extremities, and a complete autoimmune and thrombophilic screening (including factor V Leiden, protein C and S levels, activated protein C resistance, homocysteine levels, and antiphospholipid antibodies, prothrombin mutation G20210A) is mandatory.[97,101] CT or conventional angiography of the aorta and its major branches and trans-thoracic echocardiography should be performed to exclude other sources of embolism.[100,102] The presence

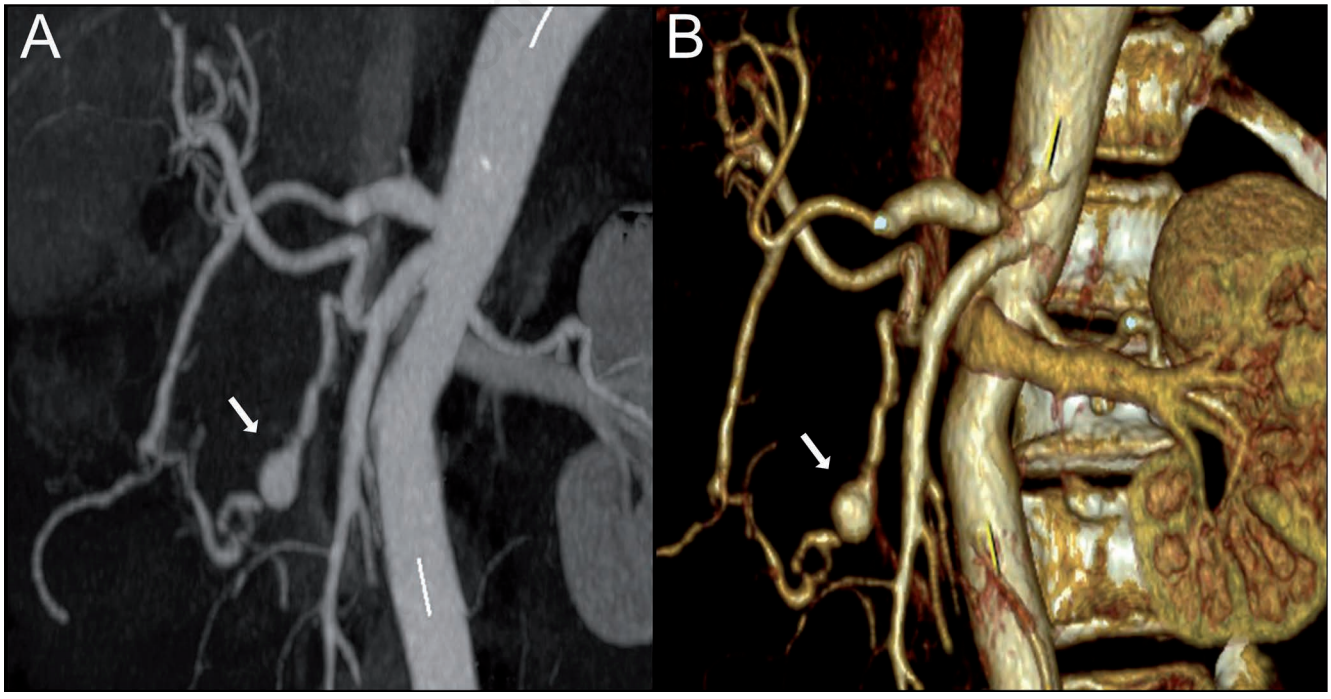

Figure 2. A case of segmental arterial mediolysis. Maximum intensity projection of the arterial phase of the angio-computed tomography (A) and volume rendering (B) showing a typical aneurism of the celiac-mesenteric trunk.

of collateral circles of the distal arteries with a *corkscrew* appearance (Martorell's sign), reflecting the slow progression of the disease and compensatory changes, is typical of TAO, although not pathognomonic.[99,103,104] Arteriographic abnormalities in unaffected (contralateral) limb are also a hallmark of the disease, since it is usually not limited to a single extremity. Unless atypical presentations, confirmatory biopsy showing highly inflammatory thrombi infiltrated with polymorphonuclear leukocytes is not strictly required for the diagnosis.[96] Although prostacyclin analogues and aspirin are moderately effective in healing ulcers and relieving pain, complete abstinence from tobacco has proven to be the only effective measure in preventing disease progression towards amputation (present in at least one-quarter of patients).[100,105]

Small vessel vasculitis

The *small vessel vasculitis* includes a wide variety of vasculitis syndromes, characterized by different pathogenic mechanisms, clinical manifestations, risk factors and prognosis, which are lumped together because of the involvement of the same vessel size.[21,106] Therefore, a huge number of inflammatory and non-inflammatory conditions may mimic small vessel vasculitis, depending on the specific type of vasculitis and the prevalent organ manifestation(s).[12] Here we review the forms that we believe are the most important mimickers of systemic small-vessel vasculitis.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder with a wide range of vascular and obstetric manifestations associated with thrombotic and inflammatory mechanisms, orchestrated by antiphospholipid (aPL) antibodies.[107] The disorder is significantly more common in middle-aged women, but it can potentially affect all age groups. APS may occur as a primary condition, or can be secondary to systemic autoimmune diseases, more frequently systemic lupus erythematous.[108] Arterial and venous thrombosis, along with repeated miscarriages or stillbirths, are the clinical hallmarks of the syndrome.[107] Usually, thrombosis involves deep veins of the lower extremities but, also the pulmonary, coronary and intracranial vessels. Several other non-criteria manifestations that could enter in differential diagnosis with small vessel vasculitis have been described.

Livedo reticularis is the most frequent skin manifestation; other cutaneous manifestations include livedoid vasculopathy (*atrophie blanche*), purpura, digital gangrene, circumscribed or extensive skin necrosis, subungual splinter hemorrhages, and superficial venous thrombosis (phlebitis).[10,109,110] Frequently, the dermatologic manifestations of APS are concomitantly present with other disease features, and livedo reticularis is significantly associated with the arterial subset of APS.[109] Overall, it might be difficult to distinguish these manifestations from PAN, AAV, cryoglobulinemic vasculitis, and Henoch-Schoenlein purpura.

Among pulmonary manifestations, diffuse alveolar hemorrhage caused either by capillaritis or bleeding diathesis is probably the main feature that is considered in the differential diagnosis with alveolar hemorrhage or alveolitis of AAV.[111] Cardiac valvular thickening and Libman-Sacks endocarditis, coronary artery disease, myocardial dysfunction, intracardiac thrombi for cardiovascular APS manifestations,[111,112] while gastrointestinal infarction and Budd-Chiari syndrome for the gastrointestinal APS manifestations[110] should be recalled in the differential diagnosis of vasculitis. Neurological involvement includes a wide spectrum of clinical conditions, from autonomic dysfunction to stroke, transient ischemic attack and cerebral vein thrombosis.[113]

Antiphospholipid nephropathy is characterized by non-inflammatory occlusion of renal blood vessels (renal arteries or veins, intraparenchymatous arteries and glomerular capillaries).[114,115] Renal abnormalities are present in approximately 9% of patients, mostly proteinuria, but creatinine increase has been reported. Lupus anticoagulant (LAC) is considered the most frequent antibody associated with APS nephropathy, and it can be associated with an otherwise unexplained mild to moderate thrombocytopenia as a consequence of thrombotic microangiopathy.[116] In contrast, platelets are usually not reduced in AAV, even if a subset of AAV with thrombotic microangiopathies has been described.[117]

Approximately 1% of patients with APS develop a widespread micro and macrovascular thrombotic disease, with multiorgan failure, referred as catastrophic APS (CAPS).[118] Patients with CAPS present with a systemic inflammatory response (*e.g.* fever and increase of CRP) and various combinations of signs and symptoms, such as encephalopathy, stroke, myocardial infarction, acute respiratory distress, pulmonary embolism, acute kidney injury, mimicking AAV with severe onset and other life-threatening thrombotic microangiopathy, such as thrombotic thrombocytopenic purpura.[118]

Overall, the key to differentiate APS from vasculitis is the presence of circulating aPL (anti-cardiolipin antibodies, anti-β2-glicoprotein1 antibodies, and lupus anticoagulant). A moderate/high level of one of the aPL (on two or more occasions, at least 12 weeks apart) is required for diagnosis. In addition, also the presence of a prolonged activated partial thromboplastin time (aPTT) because of the presence of lupus anticoagulant or a past history of a false positive serologic test for syphilis should raise the suspicion of APS.[111]

Histology, when performed, could contribute to the final diagnosis of APS, showing vascular thrombi with partial or complete obstruction of the small- to medium-sized vessels, with the disruption of the elastic lamina, suggesting minimal perivascular inflammation. In contrast, vasculitides show distinctive histologic abnormalities, and even when vascular thrombosis (secondary to inflammation) coexists, the inflammation of the vascular wall prevails (*e.g.* transmural inflammation, vascular wall fibrinoid necrosis, leukocytoclasia, *etc.*).[107,112-120]

Cholesterol emboli syndrome

Cholesterol emboli syndrome (CES) is due to small-vessel occlusion in the extremities or viscera by cholesterol crystals dislodged from atherosclerotic plaques.[120] This could be secondary to a endovascular procedure or surgery, angiogram, or trauma, or occur after anticoagulant or thrombolytic therapy, which weaken the fibrin clot that stabilizes the atheroma.[121,122] Rarely, it could be a spontaneous process. Cutaneous findings are present in the majority of the patients and are a hallmark of the syndrome; these include livedo reticularis (49%), gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%), purpura (9%), and the characteristic *blue toes* (Figure 3B).[10,123]

The onset may be acute (days to weeks), or subacute (weeks to months), when triggered by the anticoagulant therapy.[124] Elevated levels of ESR and CRP have been associated with CES, and sometimes positive ANA and ANCA tests have been found. The cause of ANCA positivity remains unknown, but neutrophil activation after vessel wall damage could represent a trigger.[10,120,124] Fundus-

copic identification of *Hollenhorst plaques*, cholesterol emboli with yellow orange appearance at bifurcations of retinal arteries, is a highly suggestive diagnostic clue of the presence of CES.[10,125]

Skin biopsy is the gold standard for diagnosis, with the evidence of intravascular, biconvex, needle-shaped cholesterol clefts occluding arterioles in around 90% of samples.[120,124] In some cases, especially when due to biopsy delay (days), skin biopsy could not be diagnostic, showing instead necrotizing vasculitis (pseudovasculitis) secondary to vessels destruction.[10,120]

Infective endocarditis

Infections, and in particular subacute infective endocarditis, could sometimes be associated with circulating ANCA titers (in the majority of cases c-ANCAs or PR3-ANCAs).[126] In a prospective cohort of infective endocarditis, a positive ANCA test at immunofluorescence has been reported in up to 18% of patients.[127] Fever and systemic symptoms are typically shared by both vasculitis and endocarditis. In addition, some patients with endocarditis have clinical manifestations mimicking AAV, in particular glomerulonephritis, followed by purpura, epistaxis, and sinus symptoms.[128-131] In the majority of cases, the bacteria reported as the cause of ANCA-positive, infective endocarditis are Bartonella Henselae and Streptococcal species.[126,127,129] The positivity of cANCA/pANCA was associated with younger age, more frequent occurrence of echocardiographic vegetations, and above-normal total IgG serum levels.[127]

The exact link between ANCA positivity and infective endocarditis is still unknown. Blood cultures should be performed to help exclude infections. In these case reports and series, the great majority of the patients recovered with the only use of an antibiotic therapy.[126,127,129]

Hypereosinophilic syndrome

Sustained elevated hypereosinophilia may be present in hypereosinophilic syndrome (HES), which is characterized by eosinophilic organ infiltration due to abnormal bone marrow proliferation (myeloproliferative form) or cytokine-driven hypereosinophilia (lymphocytic form).[132-135] In both cases, it is reported as a differential diagnosis of EGPA, since both conditions share blood and tissue eosinophilia.[26,136] From a clinical perspective, vasculitis is virtually never present in HES, and circulating MPO-ANCA, found in 40% of EGPA patients, are negative in HES.[132,137] Adenomegaly and splenomegaly are typical findings of HES, while surrogates of vasculitis as palpable purpura and peripheral neuropathy are highly suggestive of EGPA.[26,136,138] Asthma and rhinosinusitis with or without nasal polyps are usually associated with EGPA,[139,140] while lower level of CRP in patients with blood hypereosinophila and systemic symptoms is suggestive of HES rather than EGPA.[141] In selected cases, a bone marrow biopsy and the FIP1L1/PDGFRA testing on peripheral or bone marrow blood may be useful for the differential diagnosis.[132,133] Overall, it is important to keep in mind that other conditions, among others parasite infection, acute and chronic eosinophilic pneumonia, allergic broncopulmonary aspergillosis, drug allergy and hematological neoplasms, should be considered in the differential diagnosis of EGPA.[26,132]

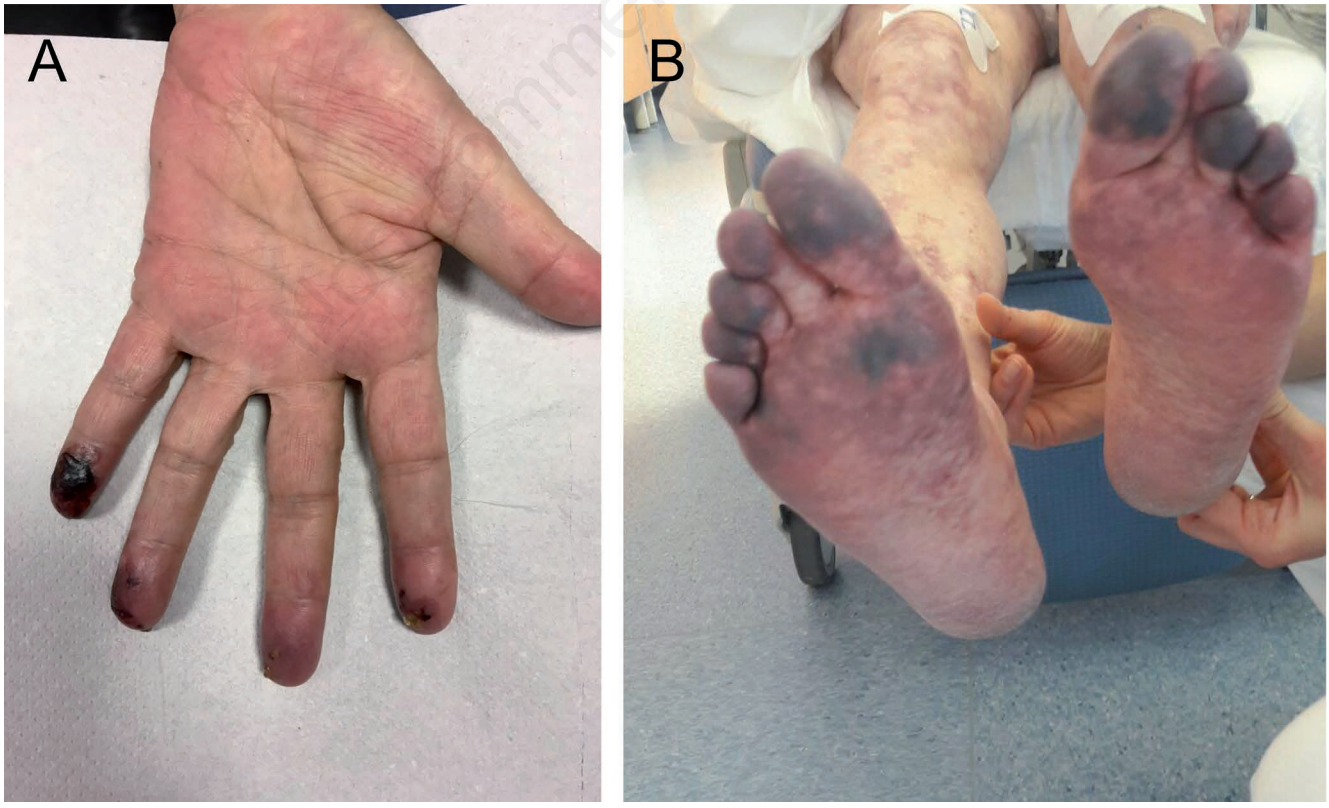

Figure 3. Digital ischemia in a patient with thromboangiitis obliterans (A). A patient with livedo reticularis and the characteristic *blue toes*, hallmark of cholesterol emboli syndrome (B).

Conclusions

Primary systemic vasculitides are sometimes difficult to diagnose: presenting symptoms may lack adequate specificity for a prompt diagnosis, leading to a diagnostic (and therapeutic) delay, often irreversibly damaging the affected organs. Classical patterns of clinical manifestations are generally useful to guide physicians towards the specific diagnosis. On the other hand, those clinical conditions that could be likely mistaken for vasculitides need to be carefully ruled out, especially before starting an adequate immunosuppressive therapy.

Here we discussed a practical approach to the diagnosis of vasculitis, and reviewed in detail most of the conditions that should to be considered and ruled out, while diagnosing the most common forms of primary systemic vasculitides.

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