Challenging Mimickers of Primary Systemic Vasculitis

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KEYWORDS

• Mimicker • Vasculitis • IgG4-related disease • Livedoid vasculopathy
• Segmental arterial mediolysis • Lymphomatoid granulomatosis
• Fibromuscular dysplasia • Degos disease

KEY POINTS

- Immunoglobulin G4–related disease is a common mimicker of small vessel and medium vessel vasculitides, particularly granulomatosis with polyangiitis, but it can also cause a true vasculitis of large vessels, requiring distinction from giant cell arteritis, among other vasculitides.
- Arterial instrumentation should be avoided whenever possible in cases of segmental arterial mediolysis and fibromuscular dysplasia, because such procedures can lead to arterial dissections.
- Calciphylaxis typically involves adipose tissues (eg, the thighs, buttocks, abdomen, and flanks).
- The myeloproliferative form of hypereosinophilic syndrome can be detected with examination of the bone marrow in addition to blood or bone marrow aspirate testing for FIP1L1/PDGFRA fusion, which is present in a subset of such patients.
- Of livedoid vasculitis begin as tender erythematous nodules that then rapidly ulcerate and scar with atrophie blanche. The ulcers have an irregular shape and are extremely painful.

Among the most challenging aspects of evaluating and caring for patients with systemic vasculitis is the need to distinguish rigorously between vasculitis and a host of conditions that can mimic vasculitis closely (**Box 1**). The treatment approaches for vasculitis mimickers are varied and often differ substantially from those required to treat vasculitis. This article reviews 9 challenging vasculitis mimickers: fibromuscular dysplasia (FMD), calciphylaxis, segmental arterial mediolysis, antiphospholipid syndrome (APS), hypereosinophilic syndrome, lymphomatoid granulomatosis (LMPG), malignant atrophic papulosis, livedoid vasculopathy, and immunoglobulin (Ig) G4–related disease (IgG4-RD).

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Box 1
Systemic vasculitis mimickers: a comprehensive list

Conditions mimicking small vessel vasculitis
- Antiphospholipid antibody syndrome[a]
- Atheroembolic disease
- Calciphylaxis[a]
- Hypereosinophilic syndrome[a]
- Emboli (cardiac myxoma, cardiac thrombus, endocarditis, mycotic aneurysm, others)
- Idiopathic diffuse alveolar hemorrhage
- Infection (endocarditis, disseminated intravascular coagulation, Rocky Mountain spotted fever, others)
- Intravascular lymphoma
- Levamisole-induced vasculitis
- Lymphomatoid granulomatosis[a]
- Malignant atrophic papulosis (Degos disease)[a]
- Thrombotic thrombocytopenic purpura[a]

Conditions mimicking medium vessel vasculitis
- Livedoid vasculopathy[a]
- Fibromuscular dysplasia[a]
- Segmental arterial mediolysis[a]
- Thromboangiitis obliterans (Buerger disease)

Conditions mimicking large vessel vasculitis
- IgG4-related disease[a]
- Erdheim-Chester disease
- Ehlers-Danlos type IV
- Loeys-Dietz syndrome
- Marfan syndrome

Conditions affecting a single organ
- Reversible cerebral vasoconstriction syndrome[a]

[a] Discussed in this article.

FIBROMUSCULAR DYSPLASIA

FMD is a noninflammatory vasculopathy of small and medium-sized arteries that can lead to aneurysm, stenosis, occlusion, and dissection.[1,2] This disease may occur in any age group, but mainly affects children and individuals more than 50 years of age.[3,4] The prevalence of FMD in the general population is estimated to be around 2% to 3%.[4,5] Women comprise up to 90% of cases in adults.[3,6] Approximately 10% of patients with FMD report a family member carrying the same diagnosis.[3,7]

The most commonly affected vascular sites are middle and distal portions of the renal, internal carotid, and vertebral arteries (~65% of the cases).[3] Lesions are detected less frequently in the intracranial, common carotid, external carotid,

subclavian, coronary, mesenteric, iliac, and limb arteries.[3,8] Aortic disease has rarely been reported. More than half of the patients have 2 or more vascular territories involved, and bilateral distributions of disease are common.[4] The etiopathogenesis of FMD is poorly understood, but genetic, biomechanical, and hormonal factors have been implicated.[9]

FMD is classified in 5 main types, based on the histologic characteristics and the location of the process within the arterial wall. These types are: (1) medial fibroplasia (~90%), (2) intimal fibroplasia (~10%), (3) perimedial fibroplasia (<1%), (4) medial hyperplasia (<1%), and (5) adventitial (periarterial) hyperplasia (<1%).[5] The specific FMD type correlates well with the radiologic findings in a given case (discussed later).

The presentation of FMD is determined primarily by the distribution of the arteries that are involved. The presentations vary from incidental findings in asymptomatic individuals to a diverse array of clinical manifestations such as renovascular hypertension (the most common presentation), headache, lightheadedness, pulsatile tinnitus, neck pain, limb claudication, postprandial angina, and acute coronary syndrome.[3,5,6,10] The physical examination may reveal pulse deficits, asymmetric blood pressure readings, and vascular bruits. At times, patients present with rupture of an aneurysm (eg, subarachnoid hemorrhage). Embolization of intravascular thrombi from aneurysmal segments can also occur, leading to amaurosis fugax, transient ischemic attack, stroke, and cyanotic toes.[3] Spontaneous arterial dissections, most frequently of the carotid arteries, occur in up to 20% of the patients.[3] Arterial aneurysms are seen in approximately 20% of the cases as well. Both dissections and aneurysms seem to be more prevalent in men.[11]

The diagnosis of FMD is typically made with vascular imaging. Duplex ultrasonography is a reasonable first-line screening technique, followed by noninvasive studies such as computed tomography angiography (CTA) or magnetic resonance angiography (MRA) as confirmatory tests. However, conventional angiography remains the gold standard for diagnosis.[5] The classic string-of-beads appearance on angiography generally corresponds with the medial fibroplasia FMD type (**Fig. 1**). In contrast, unifocal lesions described as focal concentric narrowing and diffuse tubular stenosis correlate more closely with the intimal and periadventitial fibroplasia FMD types.[6]

The differential diagnoses of FMD from a rheumatologic perspective are Takayasu arteritis (TAK), giant cell arteritis (GCA), and polyarteritis nodosa (PAN). Clues that may help to differentiate FMD from vasculitides include the presence of normal inflammatory markers (unless severe ischemia leads to tissue infarction); the absence of arthralgias, fever or constitutional symptoms; and the absence of arterial wall thickening, edema, or contrast uptake on cross-sectional vascular imaging. On diagnosis, patients with FMD should undergo screening of the cervical, intracranial, and renal vasculature to identify potential synchronous lesions.[3,12]

The treatment of FMD may include medical therapy and surveillance, endovascular procedures, and surgery.[5] However, disease-modifying agents have not been identified. Patients with renovascular hypertension require antihypertensive therapy. Hypertension in this setting is secondary to upregulation of the renin-angiotensin-aldosterone system,[13] therefore the drugs of choice are angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs). Close monitoring of kidney function is required during the initiation of ARBs or ACEIs because a subset of patients with FMD develop abrupt decline in the glomerular filtration rate, requiring drug discontinuation. More than 1 pharmacologic agent is frequently needed for adequate blood pressure control.

For patients with hypertension who respond poorly to medical therapy or for those with hemodynamically significant lesions in the renal arteries or in other vascular

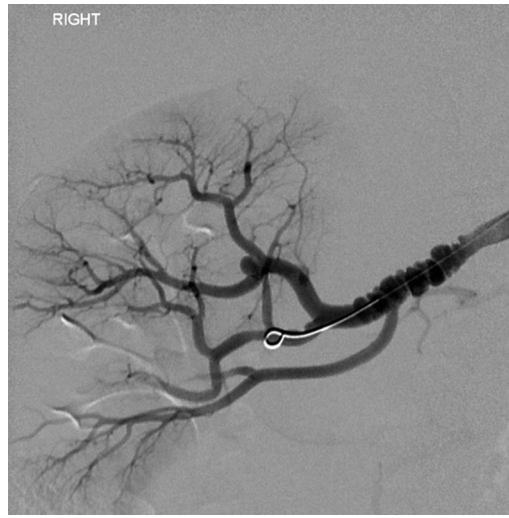

Fig. 1. Fibromuscular dysplasia. Conventional angiography in a patient with FMD showing a classic string-of-beads lesion affecting the distal portion of a right renal artery. (*Courtesy of* Dr George Oliveira, Massachusetts General Hospital.)

territories, revascularization is indicated. Endovascular treatment options include percutaneous transluminal balloon angioplasty (PTA) with or without stenting (eg, stenoses, dissections, and aneurysms) or coiling (eg, aneurysms). Surgical interventions are reserved for restenosis after PTA, complex lesions, or lesions that are difficult to reach by PTA (eg, renal artery branches). Unlike atherosclerotic disease, resolution of hypertension is common after revascularization of FMD-related renal artery stenosis.[14]

Monitoring via imaging is required after PTA or surgery to assess the short-term and long-term patency of revascularized arterial segments. If no revascularization is indicated, longitudinal imaging surveillance is also advisable to monitor the progression of disease and determine the indication and timing of revascularization. Experts recommend heparin therapy acutely followed by 3 to 6 months of anticoagulation with warfarin for patients who develop arterial dissection.[15] However, high-quality evidence supporting this practice is still not available.[16] In addition, identification and correction of concomitant cardiovascular risk factors (eg, smoking, dyslipidemia, and diabetes) is strongly recommended.[5]

CALCIPHYLAXIS

Calciphylaxis is a noninflammatory vasculopathy characterized by ectopic calcification within the wall of small and medium-sized arteries. This potentially serious process can lead to vascular occlusion, ischemia, and necrosis of the skin and subcutaneous tissues.[17] Calciphylaxis is observed in up to 4% of patients undergoing hemodialysis and is therefore sometimes termed calcific uremic arteriolopathy.[18] However, the disease can also occur in nonuremic patients.

Calciphylaxis has been described in the context of primary hyperparathyroidism, malignancy, chronic liver disease, acute kidney injury, inflammatory bowel disease, warfarin anticoagulation, and systemic autoimmune disorders (eg, systemic lupus erythematosus, Sjögren syndrome, polymyositis, rheumatoid arthritis, APS, sarcoidosis,

and GCA).[19–22] The disease is usually seen in the fifth or sixth decade of life, and is most frequent in women.[22,23] Some studies indicate that obesity, hypoalbuminemia, and the use of corticosteroids are also risk factors.[17,19]

The etiopathogenesis of calciphylaxis is poorly understood. Disturbances of calcium-phosphate homeostasis are clearly central to the disease process, as shown by the increased prevalence in patients with end-stage renal disease (ESRD)[24] and parathyroid dysfunction. Moreover, parathyroid hormone (PTH) or vitamin D administration is known to induce soft tissue calcification and skin necrosis in experimental models.[25] Additional research suggests that deficiency of circulatory and tissue calcium and phosphate binding proteins (eg, fetuin-A, matrix Gla protein),[26,27] inflammation, and alteration of the coagulation (eg, protein C and S deficiency)[28] and the RANK (receptor activator of nuclear factor kappa-B)/osteoprotegerin systems[29] might also be involved in the pathogenesis of the disease.

Calciphylaxis typically involves adipose tissues (eg, the thighs, buttocks, abdomen, flanks). A variety of cutaneous lesions can be evident: violaceous, indurated plaques and nodules; ulcerations; necrotic eschars; and lesions that mimic the purpura of vasculitis (**Fig. 2**).[22] Skin lesions are extremely painful and easily become infected. Skin contractures, penile involvement, myopathy, or cardiopulmonary calcification may rarely develop.[30–32] The diagnosis is usually made by skin biopsy, which shows medial calcification, intimal hyperplasia, intimal fibrosis, and superimposed thrombosis affecting dermohypodermic arterioles and venules (**Fig. 3**). Vascular obstruction leads to ischemia, necrosis, and secondary inflammation (calcifying septal panniculitis).

In patients with ESRD, the serum levels of PTH, calcium, and/or phosphate tend to be increased. However, most nonuremic calciphylaxis cases have no obvious abnormalities of those parameters.[19] Radiography and computed tomography of the affected areas may reveal vascular and extravascular calcium deposits. In addition, 3-phase technetium methylene diphosphate bone scans can help to define the extension of the disease and also monitor response to therapy.[31,33] The differential diagnosis of calciphylaxis not only includes systemic necrotizing vasculitides (eg, PAN, cryoglobulinemia, and antineutrophil cytoplasmic antibody (ANCA) associated vasculitis),[22] but also warfarin-induced skin necrosis, primary skin and soft tissue infections, cholesterol atheroembolism, APS, neutrophilic dermatosis, and nephrogenic systemic fibrosis.

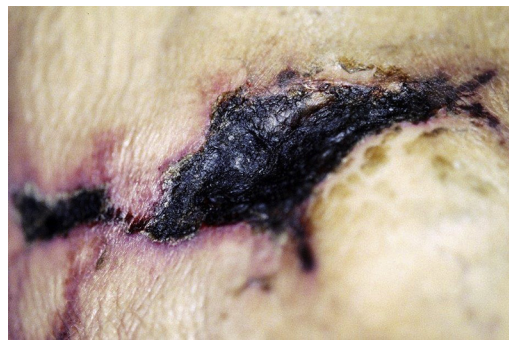

Fig. 2. Calciphylaxis. An eschar over the lateral thigh of a woman who self-administered excessive doses of vitamin D and calcium in the belief that she needed such doses for enhanced health. She developed deep ulcerative lesions over her thighs and buttocks, and some of the lesions evolved eschars such as this one. She died of infection because of compromise of her integument.

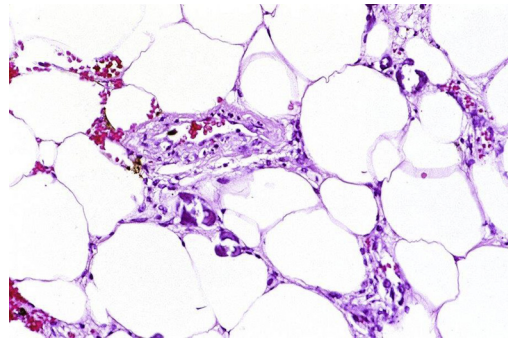

Fig. 3. Calciphylaxis. Calcium deposits within blood vessels of the subcutaneous fat. Irregular purple spicules of calcium are shown within vessel walls.

Treatment of calciphylaxis remains largely empiric because of its rarity, the incomplete knowledge with regard to its etiopathogenesis, and the absence of therapies showing clear-cut efficacy. Stopping possible offending agents (eg, calcium and vitamin D supplements) and adequate pain control are essential measures. When identified, hypercalcemia and hyperphosphatemia should be corrected to a target calcium $\times$ phosphate product less than 55 mg^2/dL^2. The use of corticosteroids in calciphylaxis remains controversial.[17,19,34] Agents such as bisphosphonates, cinacalcet, and tissue plasminogen activator have been tried with mixed results.[35–38] Nonpharmacologic interventions like hemodialysis intensification with low-calcium dialysates, parathyroidectomy, and hyperbaric oxygen have also been used with variable outcomes.[23,39–41] Unless otherwise indicated, anticoagulation is not generally indicated. More recently, encouraging preliminary results have been obtained with intravenous administration of sodium thiosulfate (STS).[31,39,42–44] Although good response to STS is typically heralded by rapid improvement of the cutaneous pain, complete resolution of the skin lesions can take up to several months.[36,42] Possible complications of this therapy include the development of metabolic acidosis. However, the mortality of calciphylaxis commonly exceeds 50% and is usually caused by sepsis.[19,34,42] Therefore, aggressive wound care such as surgical debridement when necessary, and prompt antibiotic therapy for superinfected lesions are perhaps the most important therapeutic interventions.[17,39,40]

SEGMENTAL ARTERIAL MEDIOLYSIS

Segmental arterial mediolysis (SAM) is a rare noninflammatory arteriopathy of unknown cause.[45] This condition has been described in all age groups, but mainly affects adults and elderly individuals, with a slight male predominance. The disease is characterized by the occurrence of vacuolization of tissue in the outer portion of the media. This vacuolization leads to tearing and separation of the media from the adventitia (mediolysis). As the lesion progresses, the internal elastic lamina and the intima are destroyed, creating gaps that allow the blood-filled lumen to dissect into the adventitia. The blood then dissects the vessel wall through the media, presumably because of the action of hemodynamic forces, creating intramural hematomas and dissecting aneurysms. Dissecting aneurysms is a unique arterial lesion combining luminal stenosis with dilatation of the blood vessel diameter. Superimposed thrombosis and arterial rupture are frequently seen.

SAM mainly targets medium-sized arteries within the abdominal cavity. The aorta is almost never involved in SAM, but the celiac trunk, the superior and inferior mesenteric

arteries, and their branches are involved in more than 80% of cases.[45] Less frequently, the renal, coronary, carotid, and intracranial arteries are affected.[46] The typical clinical picture consists of acute-onset abdominal pain; usually self-limited. Renal infarctions may prompt further evaluation in either SAM or FMD. Other manifestations of SAM include hematochezia, lumbar or flank pain, gross hematuria, acute coronary syndrome, pancreatitis, subarachnoid hemorrhage, and stroke.[47–49] Catastrophic presentations caused by arterial rupture, resulting in hemoperitoneum or retroperitoneal bleeding, occur in less than 30% of patients but are associated with high mortality.[50,51] In addition, SAM can also be subclinical and is sometimes identified incidentally when subjects are imaged for other reasons.[52]

In the absence of easily accessible tissue for biopsy, the diagnosis of SAM relies on identifying representative vascular imaging abnormalities (ie, angiography, CTA, and MRI/MRA) and excluding other entities. Angiographic findings comprise nonspecific arterial aneurysms, stenoses and occlusions, and the characteristic dissecting aneurysms (**Fig. 4**).[47,50,53] The differential diagnosis of SAM includes vasculitides (mainly PAN, Behçet disease, and TAK), mycotic aneurysm, and noninflammatory vasculopathies such as FMD, Ehlers-Danlos syndrome type IV, cystic adventitial artery disease, and cystic medial necrosis (eg, Marfan syndrome).[54,55] No serum or genetic biomarker is available for the diagnosis of SAM.

The treatment of SAM depends on the clinical manifestations. Many presentations resolve spontaneously without major consequences and can be managed conservatively. For cases of arterial rupture and hemorrhagic shock, either intravascular (eg, transarterial coil embolization) or surgical interventions are indicated depending on the gravity of the case.[56,57] Arterial instrumentation should be avoided whenever possible, because such procedures can lead to arterial dissections.

ANTIPHOSPHOLIPID SYNDROME

The APS is a condition characterized by thrombosis and pregnancy morbidity in the context of circulating antiphospholipid antibodies (aPL).[58] APS can affect all age groups in both genders, but is significantly more common in middle-aged women.

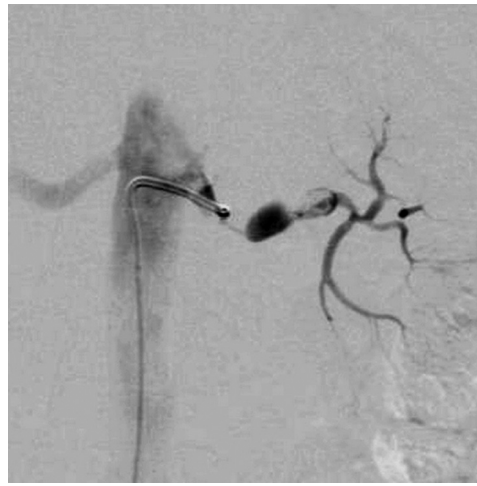

Fig. 4. SAM. Conventional angiography in a patient with SAM showing aneurysmal dilatation of the right renal artery. (*Courtesy of* Dr George Oliveira, Massachusetts General Hospital.)

The disorder may occur in isolation (ie, primary APS) or in the setting of systemic autoimmune diseases such as SLE.[59–61]

aPL are a heterogeneous group of immunoglobulins directed against anionic phospholipids or plasma proteins bound to anionic phospholipids (eg, β-2 glycoprotein I or prothrombin). On binding to their antigen, aPL trigger both the clotting and complement cascades and activate cell receptors (eg, apolipoprotein E receptor 2) on the surface of platelets, endothelial cells, and leucocytes.[59,62] Arterial and venous thromboses are the major features of the syndrome.[63] The most common vascular beds affected are the deep veins of the lower extremities, and the pulmonary, coronary, and intracranial circulation. In addition, several noncriteria clinical features have been described, including thrombocytopenia, hemolytic anemia, valvular heart disease, seizures, cognitive impairment, transverse myelitis, movement disorder (eg, chorea), brain white matter lesions, and renal and skin manifestations (discussed later).[63,64] An aPL-associated vasculopathy has also been described in association with the mammalian TORC (mTORC) pathway.[65] Some clinical data suggest that sirolimus (rapamycin), an inhibitor of the mTORC pathway, may have therapeutic utility in some APS cases, but this hypothesis requires confirmation. A small percentage of patients with APS develop diffuse alveolar hemorrhage either caused by capillaritis or bleeding diathesis (eg, antithrombin antibodies).[66–68] Leukocytoclastic vasculitis and responsiveness to the combination of rituximab and anticoagulation have been described in such cases.

APS skin manifestations such as livedo reticularis, livedoid vasculopathy (atrophie blanche), lower extremity ulcers, cutaneous necrosis, digital gangrene, and pseudovasculitic nodules and macules can be difficult to differentiate from PAN, ANCA-associated vasculitis, cryoglobulinemic vasculitis, and Henoch-Schönlein purpura.[64,69–72] The distinction between vasculitis and APS is of paramount importance given its therapeutic implications (ie, anticoagulation). aPL nephropathy, which comprises thrombotic microangiopathy and to a lesser extent membranous nephropathy, can represent a challenging differential diagnosis as well. Approximately 1% of patients with APS develop a particularly severe form of disease referred as catastrophic APS (CAPS).[63] Patients with CAPS present with systemic inflammatory response (eg, fever, tachycardia) and widespread macrovascular/microvascular clotting that may lead to encephalopathy, stroke, myocardial infraction, acute respiratory distress, pulmonary embolism, acute kidney injury, and intra-abdominal thrombosis.[68] The clinical picture then may resemble severe sepsis, thrombotic thrombocytopenia purpura, and disseminated intravascular coagulopathy. The mTORC pathway has also been implicated in CAPS.[65]

The key to differentiating APS from vasculitis relies on the presence of persistently circulating aPL (ie, anticardiolipins, anti–β-2 glycoprotein 1 antibodies, and lupus anticoagulant), and the histologic features of the different conditions. Although vasculitides show distinctive anatomopathologic abnormalities (eg, vascular wall fibrinoid necrosis, mural inflammation, immune complex deposition, and even vascular thrombosis as a result of inflammation), the characteristic finding of APS when it affects medium and small vessels is a bland thrombus with absent or minimal vascular or perivascular inflammation.[59] In addition, other serologic markers such as ANCA and cryoglobulins contribute importantly to the approach to diagnosis. The treatment of APS usually requires intravenous heparin followed by oral warfarin.[59] In addition to anticoagulation, patients with CAPS might benefit from high doses of corticosteroids and, at times, plasma exchanges and additional immunosuppression (eg, rituximab, cyclophosphamide).[68] Sirolimus has been proposed for patients with APS-associated vasculopathy in the kidneys and for those with CAPS, but this approach requires further testing.[65]

HYPEREOSINOPHILIC SYNDROME

Hypereosinophilic syndrome (HES) is a group of rare disorders mediated by eosinophil-driven end-organ damage. The diagnosis requires the presence of persistent eosinophilia (>1500 $\times$ 10^9/L for 6 months) typically accompanied by eosinophilic infiltration of end organs.[73] Men are more commonly affected than women and the condition typically affects adults in the third to sixth decade of life.[74] A commonly encountered diagnostic challenge is distinguishing HES from conditions associated with hypereosinophilia, such as eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome), sarcoidosis, systemic mastocytosis, and inflammatory bowel disease.[73] This article focuses on the differentiation between HES and EGPA, because these syndromes have many similar presenting features but differ markedly in their treatment.

HES can present with cardiovascular (58%), cutaneous (56%), neurologic (54%), pulmonary (49%), hepatic (30%), and gastrointestinal manifestations (14%), although frequencies of organ involvement differ considerably among series.[74,75] Both EGPA and HES can present with myocarditis, cardiomyopathy, pulmonary infiltrates, peripheral neuropathy, or erythematous skin lesions. Clinical characteristics that can help distinguish EGPA from HES include the presence of asthma and sinonasal disease such as sinusitis, allergic rhinitis, and nasal polyposis, which are present infrequently in HES.[75] In contrast, angioedema and splenomegaly are more common in HES. An important distinguishing feature between the two conditions is the presence of vasculitis, which is seen principally in EGPA. Therefore, skin lesions such as palpable purpura or vasculitic nodules suggest EGPA, although vasculitic lesions and ischemic lesions from arterial microthrombi have rarely been reported in HES.[76,77] Mononeuritis multiplex, which is most commonly caused by a vasculitic process, similarly suggests a diagnosis of EGPA, although mononeuritis multiplex has been reported in several patients with HES.[78]

Laboratory examinations can further aid in the diagnosis. Serologic testing for ANCA strongly suggests EGPA when positive, but ANCA are absent in approximately 50% of patients with EGPA. If HES is suspected, further testing to confirm the diagnosis and determine the subtype of HES is indicated. The myeloproliferative form of HES can be detected with examination of the bone marrow in addition to blood or bone marrow aspirate testing for FIP1L1/PDGFRA fusion, which is present in a subset of such patients.[79] In addition, flow cytometry may be able to detect lymphocytic variants of HES, which are driven by an overproduction of cytokines that coordinate eosinophil production.[80] Tissue biopsy is an important diagnostic modality when attempting to differentiate EGPA and HES. Because vasculitis is seen infrequently in HES, the presence of vasculitis on pathology, particularly in a patient with a history of asthma or sinonasal disease, strongly suggests the diagnosis of EGPA.

The treatment of HES varies by disease subtype. First-line therapy for patients with the FIP1L1/PDGFRA mutation is a tyrosine kinase inhibitor (such as imatinib).[79] Glucocorticoids are the mainstay of treatment of the lymphocytic variants of HES, with the addition of glucocorticoid sparing agents such as hydroxyurea, interferon alfa, or other chemotherapeutic agents as necessary.[75] Because treatment options differ considerably between HES and EGPA, distinguishing HES from EGPA and other eosinophilic disorders is of the utmost importance.

LYMPHOMATOID GRANULOMATOSIS

LMPG is a rare syndrome most commonly affecting the lungs that was described originally by Liebow and colleagues[81] in 1972. Most experts think that LMPG is a

myeloproliferative B-cell disorder associated with Epstein-Barr virus (EBV) infection.[82,83] Men are affected preferentially (approximately 2:1) and although the condition can be seen at any age, onset is most commonly in the fourth to sixth decade of life.[81] Occurrences of the disease among individuals receiving immunosuppressant therapy[84,85] or in patients with other known underlying immunodeficiencies have been reported, but such cases comprise a minority of LMPG diagnoses.[86]

Pulmonary manifestations are the most common form of involvement, affecting approximately 60% to 90% of patients.[83] LMPG appears radiologically as bilateral infiltrates and nodules that can mimic several rheumatologic conditions, including granulomatosis with polyangiitis (GPA), EGPA, and sarcoidosis. Constitutional symptoms are often present. The skin or the nervous system is also involved in approximately one-third of patients.[87] Cutaneous manifestations are most typically nodules or nonspecific erythematous lesions. Neurologic manifestations include symptoms resulting from cerebral or cerebellar involvement, as well as cranial or peripheral neuropathies. Hepatomegaly or splenomegaly has been reported in a minority of patients.[84]

The diagnosis of LMPG is made histologically. Because LMPG is characterized by a polymorphic infiltrate that can affect arteries and veins in addition to parenchymal tissues, it is often difficult to distinguish from certain forms of primary vasculitis (eg, GPA). Although areas of necrosis are commonly seen within the parenchymal infiltrate, necrosis of the blood vessel wall (the sine qua non of a true vasculitis) is absent in LMPG.[88] Another differentiating feature of LMPG is the presence of large, atypical-appearing lymphoid cells thought to be a clonal B-cell population.[89] These cells typically express CD-20 and staining for the presence of EBV is positive in most cases. In some cases, differentiation from lymphoma can be challenging. Although macrophages and spindle-shaped histiocytes are present, palisading and well-formed granulomas are typically absent.[85] Thus, the granulomatosis portion of the LMPG name exaggerates the granulomatous features that are present in this condition.

LMPG carries significant mortality, ranging from 38% to 71%, and is generally thought to be a form of lymphoma.[83] Optimal treatment relies on the accurate differentiation of LMPG from vasculitis.

MALIGNANT ATROPHIC PAPULOSIS

Malignant atrophic papulosis (MAP), also known as Kohlmeier-Degos disease, is a vasculopathy that can mimic vasculitis affecting the brain, skin, and gastrointestinal tract. Described in 1941 by Kohlmeier[90] and a year later by Degos and colleagues,[91] it is a rare entity with fewer than 200 cases reported in the literature to date.[90–92] Although its cause remains unknown, the condition has been described as a familial autosomal dominant disorder as well as in association with autoimmune conditions such as dermatomyositis.[93,94] The hallmark of the disease are characteristic skin lesions that appear as papules (0.5–1 cm) with a white, atrophic center and an erythematous rim, most commonly on the trunk and extremities (**Fig. 5**). The skin lesions typically appear weeks to years before clinically apparent involvement of other organs.[94] In some cases the condition remains limited to the skin, leading some experts to suggest the term benign cutaneous Degos disease for this patient subset.[95] When internal organs are involved, the gastrointestinal tract (approximately 50% of patients) and the brain (approximately 20% of patients) are affected most commonly.[96] The lesions in these organs are similar in appearance to those in the skin and lead to ischemic complications such as stroke, bowel infarction, and hemorrhage. Mortality from ischemic complications is high: 50% of patients succumb to the disease within 2 to 3 years.[92]

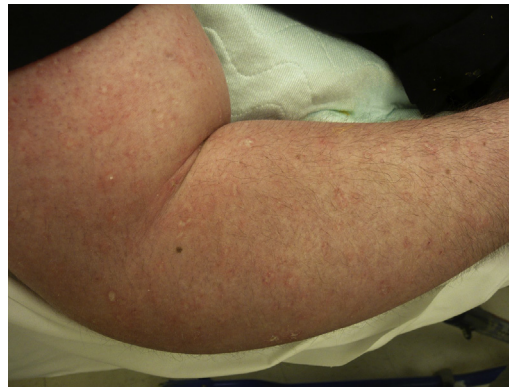

Fig. 5. Malignant atrophic papulosis. Skin lesions in a patient with malignant atrophic papulosis (Degos disease). Note the characteristic discreet porcelain papules with erythematous rim. These lesions are small and regular in appearance, differentiating them from atrophie blanche.

Because there are no diagnostic laboratory findings, the diagnosis is typically confirmed with skin biopsy. There are no diagnostic serologic or other laboratory findings. The pathology of MAP, regardless of the organ affected, consists of a thrombotic vasculopathy with intimal hyperplasia and thrombosis of small arteries. A lymphocytic vascular infiltrate can sometimes be seen, particularly early in the disease course.[97] Recently, C5b-9 deposition in the lesions, implicating complement in the pathogenesis, has been described.[98] Dysfunction of endothelial cells and fibrinolysis has also been implicated in MAP.[92]

Several therapies have been attempted in MAP but none has been widely successful to date, except in anecdotal cases. Success with antithrombotic agents and anticoagulants such as aspirin, dipyridamole, and heparin has been described in case reports.[96] Immunosuppression with glucocorticoids and cytotoxic agents have generally been ineffective.[96] Recent efforts have centered on inhibition of complement activation with eculizumab, a C5 inhibitor, but sustained remission remains elusive and most patients treated with eculizumab have succumbed to their illness.[99] New insights into disease pathophysiology are required for the development of more effective therapies.

REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME

Reversible cerebral vasoconstriction syndrome (RCVS) is a heterogeneous group of conditions leading to vasoconstriction of arteries within the central nervous system (CNS). RCVS is one of the most common mimickers of primary and secondary CNS vasculitis. The condition is most commonly seen in clinical settings that serve as a trigger for vasospasm, such as the exposure to certain medications (pseudoephedrine, selective serotonin reuptake inhibitors, ergots, and many others) or during the postpartum period.[100] Women are affected more often than men and the average age at onset is in the third to fifth decade of life.[100,101]

The hallmark of RCVS is the sudden onset of severe headache, often described as thunderclap in nature. These types of headaches usually achieve their peak severity within a minute, raising concern about the possibility of subarachnoid hemorrhage, and can last for hours. Such headaches can recur over periods of days to weeks

and are accompanied by neurologic deficits in approximately 40% of cases. Seizures have been reported in nearly 20% of patients. Vascular imaging shows diffuse vasoconstriction that cannot be distinguished from CNS vasculitis. The intensity of vasoconstriction in some RCVS cases is such that infarction (reported in up to 40% of cases), subarachnoid hemorrhage, and lobar intracerebral bleeding can occur.[101]

The combination of clinical features, cerebrospinal fluid (CSF) analysis, and imaging tests can help make the important distinction between RCVS and CNS vasculitis. Although the most common symptom of CNS vasculitis is headache, the quality is typically subacute to chronic and is less severe than the headache of RCVS. Lumbar puncture is normal in approximately 80% of patients with RCVS, in contrast with CNS vasculitis in which CSF pleocytosis or increased protein levels are seen in most patients.[102] Strokes can be observed in both conditions, but in RCVS the areas of infarction typically occur in the watershed regions. In contrast, ischemic lesions from CNS vasculitis can occur in both the cortex and the subcortex without a distinct vascular pattern.[102]

When medication-induced RCVS is suspected, the inciting agent should be removed immediately. There are no universally accepted treatment protocols for RCVS. However, several case series show good outcomes with nimodipine[103] or other calcium channel blockers.[101] A large retrospective series showed a trend toward worse outcomes with glucocorticoids, therefore currently there is no clear role for the use of steroids in RCVS, which underscores the importance of distinguishing between RCVS and CNS vasculitis.[101]

LIVEDOID VASCULOPATHY

Livedoid vasculopathy is a thrombotic condition affecting the small blood vessels of the skin; chiefly those of the lower extremities. Livedoid vasculopathy, sometimes also termed segmental hyalinizing vasculopathy, can be a primary condition or be associated with disorders such as inherited coagulopathies, the APS, Sneddon syndrome, venous insufficiency, varicosities, deep vein thrombosis, systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, Sjögren syndrome, mixed connective tissue disease, or cancer.

The classic clinical lesion of livedoid vasculopathy is atrophie blanche: porcelain-colored scars sometimes dappled with small red points, occurring at the sites of ulcers (Fig. 6). Livedoid vasculopathy, which has a predilection for the tops of the feet, the perimalleolar areas, and the distal legs, often mimics medium vessel vasculitides such as polyarteritis nodosa, cutaneous polyarteritis nodosa, rheumatoid vasculitis, and the vasculitis associated with Sjögren syndrome. The typical skin lesions begin

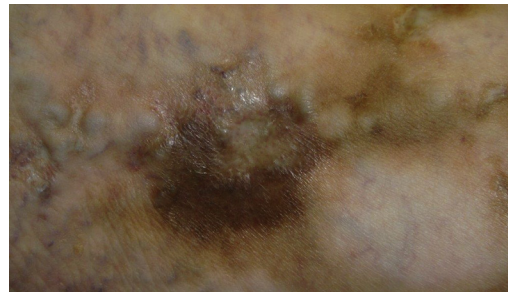

Fig. 6. Atrophie blanche. Porcelain-colored scarring on a background of hyperpigmentation (hemosiderin) in a patient with livedoid vasculopathy.

as tender erythematous nodules that then rapidly ulcerate and scar with atrophie blanche. The ulcers have an irregular shape and are extremely painful.

An adequate skin biopsy is required to make the diagnosis but multiple, repeated biopsies are discouraged because the biopsy sites can be slow to heal. Histopathologic examination of the lesions shows a thin and flattened epidermis. The superficial dermis shows segmental hyalinization of small vessels, endothelial swelling, and dilated capillaries with tortuous loops. Hemosiderin or extravasated red blood cells can be observed. Microthrombi are present in most cases. Although a perivascular lymphocytic infiltrate is a part of the morphologic picture, there is no damage to the blood vessel wall. Fibrinoid necrosis of the vessel wall, leukocytoclasis, and frank vasculitis are all absent in livedoid vasculopathy.

The pathophysiology of livedoid vasculopathy is not fully understood and the condition is likely not a single pathophysiologic entity but rather a final common pathway resulting from a variety of issues (often more than 1) that facilitate a hypercoagulable state. aPL are often present in this condition, as are other hypercoagulable risk factors including heritable factors (eg, the factor V Leiden mutation), functional or de facto protein C or S deficiency, the use of oral contraceptives, and smoking. A thorough review and evaluation for hypercoagulable risk factors should be undertaken when assessing patients for the possibility of livedoid vasculopathy.

A host of therapies, all generally designed to interrupt the tendency to coagulation, have been used in this condition. Therapies include baby aspirin, dipyridamole, low-molecular-weight heparin, Coumadin, and hydroxychloroquine.[104] Combinations of these agents are often used, and empiric approaches are typically required.

IMMUNOGLOBULIN G4–RELATED DISEASE

IgG4-RD, a fibroinflammatory condition that has emerged in recognition only in the past 10 years, is a subtle mimicker of multiple rheumatologic and malignant conditions, including the vasculitides.[105] In 2 important respects, IgG4-RD may even be not only a vasculitis mimic but a form of vasculitis. First, on a microscopic level, vasculotropism is a cardinal pathology feature of this disease. Obliterative phlebitis and (less often) obliterative arteritis are hallmark pathology manifestations of IgG4-RD. Second, IgG4-RD can also affect the aorta with a true aortitis, creating confusion with giant cell aortitis and other forms of inflammatory aortitis.[106,107] Thus, IgG4-RD is a common mimicker of small and medium vessel vasculitides, particularly GPA, but it can also cause a true vasculitis of large vessels, requiring distinction from GCA, among other vasculitides.

IgG4-RD was identified first in the pancreas among patients with sclerosing pancreatitis,[108] now termed type 1 IgG4-related autoimmune pancreatitis,[109] but in the past decade the disease has been described in almost every organ system (striated muscle and the brain being the 2 main exceptions). The organs affected most frequently by IgG4-RD include the pancreas, the major salivary glands, orbital tissue (particularly the lacrimal glands), the biliary tree, lymph nodes, and the retroperitoneum (ie, retroperitoneal fibrosis).

IgG4-RD is defined pathologically by several features that are remarkably consistent from organ to organ.[110] These features include a lymphoplasmacytic infiltrate with a disproportionate percentage of plasma cells staining for IgG4 (**Fig. 7**), a highly characteristic form of fibrosis known as storiform fibrosis, mild to moderate tissue eosinophilia, and the aforementioned obliterative phlebitis. Neither increased serum IgG4 concentrations nor increased numbers of IgG4+ plasma cells in tissue are sufficient to establish the diagnosis of IgG4-RD. Clinical correlation between the classic

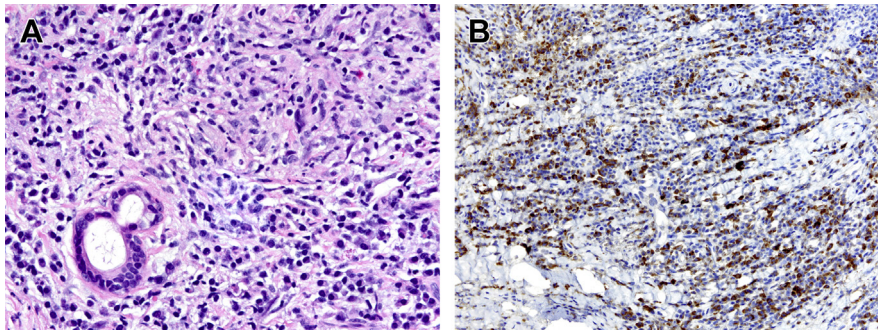

Fig. 7. IgG4-related disease: histopathology and immunopathology. Biopsy of a subglottic lesion affecting a 70-year-old woman who also had large vessel imaging that was diagnostic of aortitis. The subglottic lesion mimicked GPA. The patient's antineutrophil cytoplasmic antibody assay was negative, but her serum IgG4 concentration was increased to 3 times the upper limit of normal. (*A*) Histopathology. Subglottic lesion showing a lymphoplasmacytic infiltrate and a swirling, storiform pattern of fibrosis (hematoxylin-eosin stain, magnification 400×). (*B*) Immunopathology. Immunostain for IgG4, showing more than 50 IgG4+ plasma cells (brown-staining cells) per high-power field (magnification 400×).

histopathologic findings (lymphoplasmacytic tissue infiltrate, storiform fibrosis, obliterative phlebitis) and rigorous clinicopathologic correlation are required.

The propensity of IgG4-RD to affect multiple organs and its ability to affect the orbits, lungs, kidneys, and pachymeninges also make it a particularly effective mimicker of GPA. IgG4-RD can cause proptosis through involvement of several orbital structures, including the lacrimal gland, extraocular muscles, and retrobulbar mass lesions that are independent of these structures. Scleritis and involvement of the nasolacrimal duct, both common features of GPA, have also been reported in IgG4-RD.[111]

The lung is the site of the most protean involvement of IgG4-RD. The disease has a tendency to affect the bronchovascular bundle, leading to thickening of the airways on cross-sectional imaging. Mass pulmonary lesions can also be observed in IgG4-RD, imitating malignant lesions or the nodules of GPA. Ground-glass infiltrates and interstitial fibrosis are also seen, mimicking either alveolar hemorrhage or the interstitial lung disease sometimes associated with ANCA-associated vasculitis, particularly cases associated with antimyeloperoxidase ANCA. Subglottic stenosis, other types of large airway involvement, and extensive pleural disease are also known to occur in IgG4-RD.

The typical renal manifestation of IgG4-RD is tubulointerstitial nephritis, presenting chiefly with renal dysfunction and white blood cells in the urine. A membranous glomerulonephropathy (GN) has also been reported to occur in this disease. The IgG4-related membranous GN is clearly a condition distinct from idiopathic membranous GN, which is associated with autoantibodies (usually IgG4) directed against the PLA2 receptor. In addition, IgG4-RD is an important cause of idiopathic hypertrophic pachymeningitis and rivals GPA as a cause of that condition.[112]

The first line of therapy for IgG4-RD is generally glucocorticoids. Most patients with IgG4-RD respond to glucocorticoids and in many patients the response is striking, reminiscent of the types of response observed in GCA and polymyalgia rheumatica following the institution of steroids. However, most patients, particularly those with multiorgan disease at baseline, relapse during or after glucocorticoid tapers. Moreover, because IgG4-RD tends to target middle-aged to elderly patients and to affect

the pancreas, lengthy courses of glucocorticoids are generally tolerated poorly. Among patients whose disease is refractory to glucocorticoids or to glucocorticoid tapers or whose comorbidities suggest that glucocorticoids will be tolerated poorly, B-cell depletion with rituximab seems to be an excellent therapy (Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Submitted for publication).[113]

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