Chapter 12
Vasculitis

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Introduction

The systemic vasculitides are a heterogeneous group of inflammatory diseases that share the pathogenic feature of inflammation focused in the wall of blood vessels. The vasculitides are categorized according to the caliber of the blood vessels involved, with large-vessel disease (such as Takayasu's) affecting the aorta and great vessels, while small-vessel disease (such as ANCA-associated vasculitis) mediates damage in the smallest capillaries of the lungs and kidneys. Because nearly every organ system in the body can be affected by vasculitic syndromes, the clinical approach to a case of suspected vasculitis involves recognition of typical patterns of organ involvement associated with each specific vasculitic entity and the assimilation of key laboratory, radiographic, and histologic findings to secure a diagnosis. In this chapter, we will summarize the clinical syndromes associated with each form of vasculitis, review diagnostic studies that assist in their identification, and summarize the current approaches to immunosuppressive treatment.

Diagnostic Approach

Vasculitis is often raised as a diagnostic consideration in patients with multi-organ disease and/or active inflammatory markers of unclear etiology. When considering a diagnosis of vasculitis, clinicians ought to consider several important questions [1]:

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1. Is this a true vasculitis, or a condition that mimics vasculitis?
2. If this is vasculitis, is it a primary vasculitis, or secondary to another underlying cause?
3. What is the extent of organ involvement present?
4. What specific type of vasculitis is this most likely to be?
5. How do I confirm the diagnosis of the suspected vasculitis?

The so-called vasculitis mimics include a variety of diagnoses capable of generating a clinical presentation similar to that of a systemic vasculitis, but whose pathogenesis is not due to primary inflammation within the walls of blood vessels. While the general elements of their presentation may appear quite similar to the vasculitides, careful assessment of the appropriate clinical data can help discriminate genuine vasculitides from these mimics. The vasculitis mimics include various types of infections (endocarditis, angioinvasive aspergillosis), thrombotic disorders (antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura, sickle cell disease), embolization (from atrial myxoma or cholesterol emboli from atheroma), noninflammatory vessel wall disorders (fibromuscular dysplasia, amyloidosis, scurvy), and vasospasm due to ergotism and other exposures. The list of vasculitis mimics with regards to more isolated or single-organ findings is even broader, such as is the case with malignancy or infections that cause cavitary lung lesions like those seen in granulomatosis with polyangiitis, or conditions such as reversible vasoconstriction syndrome that can mirror the findings of central nervous system vasculitis.

Histology

The diagnosis of vasculitis is made based on tissue histopathology in concert with the appropriate clinical presentation for the disease in question. While not necessarily available in the assessment of all suspected cases of vasculitis, tissue histopathology can be enormously helpful in accurately identifying the diagnosis of vasculitis. Thus, there are several key phrases that help to identify typical findings of vasculitis seen on histopathologic analysis of tissue. These include:

1. Infiltration of the vessel wall by immune cells
2. Fibrinoid necrosis of blood vessel walls
3. Leukocytoclasis

Since the mechanism of tissue and organ damage in vasculitis is due to sequential inflammation and necrosis of blood vessels leading to impairment of blood flow and perfusion, the nature of this vessel inflammation is of significant consequence. It is essential to identify what type of cellular infiltrate is present, such as with regards to the presence of neutrophils, lymphocytes, mononuclear cells, giant cells, or other leukocytes. The composition of the inflammatory cellular infiltrate in vasculitis is independent of the caliber of vessel involved, and mixed cellular infiltrates are common.

Fibrinoid necrosis describes the accumulation of proteinaceous material in the tissue matrix in a pattern that resembles fibrin. This finding can be seen with type III hypersensitivity immune reactions involving blood vessels in vasculitis, but can also be observed in cases of pre-eclampsia, malignant hypertension, and acute transplant rejection.

The breakup of nuclei of dying cells (also known as karyorrhexis) results in the pathologic finding known as nuclear dust. The presence of such nuclear debris, coupled with inflammatory infiltrate of blood vessels and deposition of fibrin within a vessel lumen or wall, can provide strong evidence for the presence of a vasculitis. Indeed, such findings in small vessels and with neutrophils as the cellular infiltrate are essentially the definition of leukocytoclastic vasculitis, and the presence of nuclear dust may in fact precede the accumulation of fibrin.

Taken together, the findings noted above can help to identify the presence of a vasculitic process and allow the physician to identify which specific vasculitis may be at play. For instance, polyarteritis nodosa, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis are all forms of necrotizing vasculitis that may demonstrate mixed cellular infiltrates, but granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis may also (as the names imply) demonstrate granulomatous inflammation and, in the case of the latter, involve prominent eosinophilic infiltrate.

Immunofluorescent staining for immune complex deposition (complement components and immunoglobulin isotypes) is an additional histologic technique that adds valuable information to the evaluation of suspected vasculitides, in particular the small-vessel vasculitides. This method permits the discrimination of pauci-immune vasculitis (e.g., ANCA), where minimal or no immune complex deposition is expected, from other causes of small-vessel vasculitis associated with positive immunofluorescent staining, such as HSP (characterized by IgA deposits) and cryoglobulinemia. Immunofluorescent staining should be obtained in the analysis of cutaneous vasculitis and glomerulonephritis, and may be valuable in other tissue sites in specific clinical scenarios as well.

Imaging

Specific imaging studies may be of help in the diagnosis of vasculitis and understanding the nature and degree of vessel and organ involvement. Imaging modalities that have traditionally been of significant use with respect to vasculitis include Doppler ultrasound, conventional angiography, computed tomography angiography, and magnetic resonance angiography. MRI/MRA is a noninvasive procedure of particular utility, as it can identify both vessel wall edema (as seen in aortitis) and luminal abnormalities (such as subclavian stenosis). This imaging modality can be valuable in a number of clinical scenarios, such as when there is a clinical history concerning for giant cell arteritis but negative temporal artery biopsy. However, it is important to note that artifactual findings, such as subclavian pseudostenosis, can

confound the picture and must be taken into account. PET/CT is an alternative technique that is now being used to identify large-vessel vasculitis by showing FDG avidity in blood vessels, thus indicating active disease. More recent research on PET/CT has indicated that this modality may have the potential to indicate signs of active disease in patients who otherwise appear to be in clinical remission based on history, exam, and laboratory studies [2].

Secondary Causes of Vasculitis

The term "secondary vasculitis" refers to a vasculitis syndrome that occurs in the context of an underlying disease or disorder. The causes of secondary vasculitis can be broken down into the categories of systemic rheumatic diseases, infections, drugs/medications, and cancer.

Among rheumatic diseases, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, and, to a lesser extent, scleroderma and inflammatory myopathies may be associated with secondary forms of vasculitis.

Rheumatoid vasculitis is fairly uncommon and, when it does occur, is more often seen in middle-aged male smokers with high-titer rheumatoid factor. Manifestations of the systemic vasculitis associated with rheumatoid arthritis may include nail fold infarcts, skin rash due to leukocytoclastic or lymphocytic vasculitis, and mononeuritis multiplex associated with neurovascular involvement. Small-vessel vasculitis may be complicated by microvascular thrombosis, and, rarely, leg ulcerations or gangrene can occur. The incidence of rheumatoid vasculitis has decreased with the advent of disease-specific drugs and immunotherapy with tumor necrosis factor inhibitors and anti-B cell therapy.

With regard to systemic lupus erythematosus (SLE), it is important to note that vasculopathy associated with inflammatory and noninflammatory occlusive disease can be seen and can precede the appearance of other clinical signs of SLE. Indeed, vasculopathy in SLE can further be broken down into the categories of vascular deposits of immune complexes, noninflammatory necrotic vasculopathy, thrombotic microangiopathy, and true lupus vasculitis. It is of great importance to evaluate for the presence of antiphospholipid antibodies in patients with SLE and vaso-occlusive disease. Cutaneous findings of SLE-associated vasculitis may include purpura, and small-vessel involvement of the kidneys, heart, brain, pulmonary alveoli, and gastrointestinal tract may occur. Leukocytoclastic vasculitis, cryoglobulinemic vasculitis, and systemic vasculitis following the pattern seen with polyarteritis nodosa are among the most common forms of lupus vasculitides.

In primary Sjogren's syndrome, vascular inflammation can result from hyperglobulinemia and immune complex deposition, or in the setting of cryoglobulinemia. With Sjogren's syndrome-associated cutaneous vasculitis, there is more often small- versus medium-vessel involvement, leukocytoclastic versus mononuclear vasculitis, and an association with a higher prevalence of extraglandular and other immunologic features of the disease. Small-vessel vasculitis may manifest as palpable purpura, urticarial lesions, or erythematosus maculopapules, while life-threatening

vasculitis is frequently associated with concurrent cryoglobulinemia. The presence of cutaneous vasculitis is an important marker of patients with more severe disease, including an increased risk of lymphoma.

In patients with systemic sclerosis, the distinction between occlusive and inflammatory vasculopathy can be clinically challenging and may require histopathologic analysis of tissue. These patients are often found to have decreased circulating levels of vasodilators (nitric oxide synthetase, prostacycline) and increased levels of vasoconstrictors (endothelin-1, vascular endothelial growth factor), thereby leading to intimal proliferation, luminal narrowing, and tissue hypoxia resulting in endothelial dysfunction and damage. Inflammatory vasculitis is less commonly encountered than noninflammatory vasculopathy in these patients, though a multitude of conditions that include ANCA-associated vasculitis, large-vessel vasculitis, Behçet's disease, and relapsing polychondritis have been reported to co-occur in a minority of patients with scleroderma.

Certain infections may play an interesting role in the development of vasculitis. Such is the case of polyarteritis nodosa associated with hepatitis B infection, when there is deposition of immune complexes formed from viral antigens and antibodies responsible for activation of the classic complement pathway and for neutrophil recruitment. Similarly, hepatitis C-associated cryoglobulinemia is a well-known phenomenon, and possible associations between hepatitis B and HIV with the development of cryoglobulinemia may exist as well. Tuberculous and syphilitic aortitis are well established conditions, and there is evidence that direct endothelial cell invasion may be the main pathogenic process accounting for vasculitis in infections caused by CMV, herpes simplex, rickettsiae, fungi, and bacteria. Additional work is needed to better understand the mechanisms underlying the development of primary vasculitides in the context of infection.

Drug-induced vasculitis is thought to be an immune complex-mediated process, and innumerable classes of drug have been reported as potential causes of vasculitis, most frequently with cutaneous manifestations. Among the most common culprits of drug-induced vasculitis are propylthiouracil, hydralazine, minocycline, allopurinol, D-penicillamine, sulfasalazine, penicillins, cephalosporins, and levamisole-contaminated cocaine. Drug-induced vasculitis cannot easily be differentiated from primary vasculitis, but this condition should be suspected when vasculitis manifests after a new drug exposure and when observing regression of the vasculitis after withdrawal of the potential offending agent. Urine drug screening should be considered in patients presenting with new vasculitic lesions of the face and ears.

A multitude of paraneoplastic vasculitides have been reported in the literature. Vasculitis due to myelodysplastic syndromes and other hematologic malignancies most frequently affects cutaneous vessels, but large-vessel vasculitis (in the form of giant cell arteritis and Takayasu's arteritis) and medium-vessel vasculitis (in the form of granulomatosis with polyangiitis and polyarteritis nodosa) have been described as well. Paraneoplastic vasculitis can be the initial manifestation of an occult malignancy. In addition to hematologic malignancies, tumors of the lung, gastrointestinal tract, and urinary tract can also be associated with the development of vasculitis, most frequently a leukocytoclastic vasculitis.

Primary Vasculitides

The primary vasculitides are a group of inflammatory diseases that mediate organ damage through primary inflammation within the walls of blood vessels. The primary vasculitides tend to affect blood vessels of specific size and are, therefore, organized according the caliber of involved blood vessels.

Large-Vessel Vasculitis

Giant Cell Arteritis (GCA)

Giant cell arteritis is a large-vessel vasculitis that occurs almost exclusively in adults over the age of 50, with a predominance among Caucasian women. Typical symptoms include headache, tongue and/or jaw claudication, scalp tenderness, fever, weight loss, vision change, and diplopia. There is also frequent co-occurrence with polymyalgia rheumatic, with up to 50% of patients with GCA manifesting signs of this condition. The systemic manifestations of GCA and PMR appear to result from production of pro-inflammatory cytokines derived from macrophages, such as tumor necrosis factor, interleukin (IL)-1, and IL6. Interferon-γ expression has also been shown in temporal artery biopsy samples from GCA patients. While nonspecific laboratory findings indicative of inflammation—elevated erythrocyte sedimentation rate and C-reactive protein, anemia, thrombocytopenia, hypoalbuminemia, elevated ferritin—support a diagnosis of GCA, it is the positive temporal artery biopsy, with vasculitis characterized by mononuclear predominant cellular infiltration or granulomatous inflammation usually with multinucleated cells, that serves as the gold standard for histopathologic diagnosis (Fig. 12.1). While corticosteroids have been the mainstay of treatment of GCA for many decades, methotrexate dosed at 7.5–15 mg weekly has been established in a series of randomized controlled trials as an effective steroid-sparing adjunct. More recently, randomized, placebo-controlled studies demonstrated that sustained steroid-free remission of GCA at 52 weeks could be achieved in patients treated with weekly or every other week tocilizumab, a humanized monoclonal antibody against IL6, and prednisone taper compared to those treated with placebo and prednisone taper; these patients also received significantly less total prednisone than patients in the placebo groups and the number of adverse events were similar across all groups [2, 3]. The findings are biologically plausible with respect to the role IL6 seems to play in the disease, and this study supported the Food and Drug Administration's approval of the medication in August 2017 for the treatment of GCA.

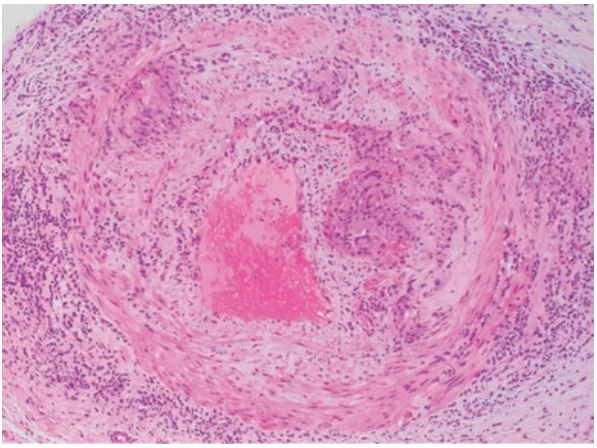

Fig. 12.1 Giant cell arteritis. The wall of this muscular artery is diffusely involved by granulomatous inflammation, including scattered multinucleated giant cells, with significant loss of the muscular media and internal elastic lamina due to the vasculitis. (Photo courtesy of Dr. Charles Eberhart, Johns Hopkins University School of Medicine, Department of Pathology)

Takayasu's Arteritis

Takayasu's arteritis is a large-vessel vasculitis that predominantly affects women under the age of 40, with an increased prevalence among individuals of Asian descent. There are two general phases to the condition: the systemic phase and the occlusive phase. The systemic phase may manifest with fever, fatigue, weight loss, and other nonspecific constitutional symptoms, while the occlusive phase reflects symptomatic ischemia due to arterial stenoses, such as with claudication pain in the limbs, vision loss, headache, or unequal or absent pulses in the upper extremities. Takayasu's arteritis is thought to start at the aortic annulus and progress from there, with autopsy studies rarely finding arteritis that is confined only to the aorta and its branches. Takayasu's arteritis appears to involve cell-mediated immunity, with Th1 CD4+ lymphocytes supporting granuloma formation via interferon-γ and HLA-DR+ circulating T lymphocytes that appear to be sensitized against aortal antigens [4]. The 1990 American College of Rheumatology (ACR) Classification Criteria for Takayasu's arteritis include disease onset before the age of 40, arteriographic narrowing of the entire aorta documented with CT angiography, decreased brachial pulse in at least one brachial artery, and a difference of >10 mm Hg in systolic blood pressure between both arms [5]; a minimum of three of six possible criteria are required for classification, and, though the diagnosis is supported by a history of elevated acute phase reactants at presentation, normal values do not exclude the diagnosis [6]. CT angiography and magnetic resonance angiography are the preferred imaging modalities for diagnosing Takayasu's arteritis. Reasonable initial treatment of the disease per EULAR treatment guidelines includes prednisone initially at 1 mg/kg/day up to 60 mg daily, maintained for at least 1 month, followed

by a gradual prolonged taper [7]. Immunosuppressive adjunctive therapy aside from glucocorticoids is also strongly recommended because of a propensity for Takayasu's arteritis to remain subclinically active even on glucocorticoids, with the possibility of relapse of the disease with steroid monotherapy; indeed, roughly 50% of patients with successfully induced remission suffer from relapse of disease [8]. Azathioprine 2 mg/kg daily or methotrexate 20–25 mg weekly can be used as steroid-sparing agents and, for refractory cases, alternative steroid-sparing adjuncts include anti-TNF agents or cyclophosphamide.

Cogan's Syndrome

Cogan's syndrome is a chronic inflammatory disease of unclear origin that manifests with ocular, vestibuloauditory, and vasculitic findings. These may include interstitial keratitis, episcleritis, uveitis, or other orbital inflammation; sensorineural hearing loss, tinnitus, or vertigo; and, in 10–30% of patients, aortitis or other similarly significant vasculitis. Atypical cases of Cogan's syndrome have been reported to involve the cardiovascular, neurologic, and gastrointestinal systems as well. Research has focused on the possible underlying autoimmune etiology of the condition, including the identification of an immunodominant peptide that shows similarity with autoantigens such as SSA/Ro and with the reovirus III major core protein lambda 1 and also shows similarity with the cell-density enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), which is expressed on the sensory epithelia of the inner ear and on endothelial cells [9]. Treatment of Cogan's syndrome depends on the type of organ involvement and the severity of disease. Keratitis, episcleritis, and anterior uveitis can typically be treated with topical prednisone acetate for several weeks. Deeper ocular inflammation and vestibuloauditory symptoms should be treated with at least prednisone 1 mg/kg daily and typically for at least 2–6 months. Some clinicians may also choose to add cyclophosphamide, methotrexate, cyclosporine, or infliximab for recalcitrant cases.

Behçet's Disease

Oral aphthosis, along with genital aphthosis, is a hallmark feature of Behçet's disease, though recurrent oral aphthosis in and of itself has a long differential that includes certain vitamin deficiencies, herpes simplex and other infectious etiologies, autoimmune blistering diseases such as IgA pemphigus or pemphigus vulgaris, drug-induced causes, or paraneoplastic phenomena. Celiac Disease and inflammatory bowel disease can also present with aphthous-like ulcerated lesions. The International Study Group for Behçet's Disease identified recurrent oral ulceration as the required criterion for diagnosis, with patients also needing at least two of the following minor criteria to indicate a diagnosis of Behçet's disease: recurrent

genital ulceration; characteristic inflammatory eye disease such as anterior or posterior uveitis, retinal vasculitis, or cells in the vitreous; characteristic skin lesions such as erythema nodosum; or positive pathergy test (hyper-reactivity of the skin to minor trauma) [10]. Research has identified a strong genetic underpinning in Behçet's disease of the MHC-related allele HLA-B51/B5, and carriage of this allele has been shown to predominate in men and be associated with a higher prevalence of genital, ocular, and skin manifestations and with a lower prevalence of gastrointestinal manifestations [11]. Behçet's disease is unusual among the vasculitides as it has been shown to affect small, medium, and large vessels and can also involve the central nervous system. Venous thromboembolism can also occur in Behçet's disease, and there is some discussion in the literature as to whether immunosuppression without anticoagulation is sufficient to prevent recurrence of this manifestation [12]. Colchicine, dapsone, azathioprine, apremilast, thalidomide, and interferon have all been used in the treatment of mucocutaneous manifestations of Behçet's disease, while azathioprine, methotrexate, and cyclosporine have been used for ocular manifestations. Cyclophosphamide, anti-TNF agents, and chlorambucil have been used for refractory, severe central nervous system disease or life-threatening complications of Behçet's disease.

Medium-Vessel Vasculitis

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. The disease is not associated with antineutrophil cytoplasmic antibodies (ANCA). Hepatitis B infection is commonly associated with PAN and is present in 20–30% of cases [13]. Clinical presentations are heterogeneous, with end-organ effects resulting from perfusion defects caused by the vasculitis. Common symptoms include constitutional symptoms, weight loss, myalgias, arthralgias, and skin abnormalities such as necrotizing purpura or subcutaneous nodules, while peripheral nerve involvement including mononeuritis multiplex is also common and is seen in roughly 80% of cases [14]. Involvement of the gastrointestinal, cardiac, genitourinary, and renal systems is seen as well. Mortality over a mean follow-up period of 6 years has been estimated at 25%, with one third of deaths being due to uncontrolled or relapsed vasculitis [15]. There are no specific biomarkers for PAN, and it is reasonable to screen for hepatitis B (HBV) and hepatitis C (HCV), human immunodeficiency virus (HIV), and parvovirus B19 to exclude the presence of these infections. Testing for ANCA, Proteinase 3 (PR3) antibodies, Myeloperoxidase (MPO) antibodies, cryoglobulins, and rheumatoid factor also should be obtained to exclude the differential diagnoses of ANCA-associated small-vessel vasculitis and cryoglobulinemic vasculitis. Serologic screening and

surveillance for end-organ involvement and damage with creatine kinase levels, troponin, liver function and renal function testing, spot urine protein:creatinine ratio, and urinalysis is important in disease management. Acute phase reactants should be followed to monitor disease activity and response to treatment. Conventional dye angiography can be used to assess for medium-vessel microaneurysms, stenoses, and luminal irregularities. In general, conventional angiography is the imaging gold standard for PAN since neither CT nor MRI angiography offer comparable sensitivity. Treatment selection should be based on HBV status, mortality risk as predicted by the Five-Factor Score, and the severity and degree of organ involvement [14]. For patients with HBV infection, lamivudine is the preferred antiviral agent of choice, with plasma exchange on a background of prednisone until HBeAb seroconversion occurs. For non-HBV cases with a Five-Factor Score > 0, which corresponds to a poorer prognosis and increased 5-year mortality, a combination of steroids and cyclophosphamide induction followed by azathioprine maintenance may be used. Plasma exchange has not been shown to be beneficial for non-HBV cases of PAN.

Kawasaki Disease

The most common systemic vasculitis among children worldwide is Kawasaki disease, a vasculitis that affects medium caliber vessels. Kawasaki disease occurs most frequently in children under the age of 5. While Kawasaki disease can affect children of all ethnicities, its highest prevalence is found in Asian populations, particularly Japanese children. Kawasaki disease typically presents with acute onset fevers and acute phase reactant elevation without an infectious source. Additional features may include cervical lymphadenopathy, generalized or palmoplantar rash, lesions of the mucus membranes (including strawberry tongue) and ocular disease including conjunctivitis and uveitis. The most feared complication of KD is cardiac disease: myocarditis in the early phase of the disease, and coronary artery aneurysms which develop in later stages. For this reason, echocardiography is a mandatory diagnostic study in the evaluation of suspected cases of Kawasaki disease and is performed serially to monitor for the development of aneurysms in confirmed cases. Ophthalmologic exam should also be obtained due to the high prevalence of uveitis. Additional studies should be undertaken to exclude infectious etiologies with similar presentations, including scarlet fever, parvovirus and herpesviruses, and other inflammatory conditions (JIA, periodic fever syndromes). Once the diagnosis of Kawasaki disease is made, therapy with IVIG is standardly implemented. The implementation of IVIG early in the disease course has demonstrated significant benefit in reducing the risk of coronary artery aneurysms [16] Additional therapies considered in refractory or severe Kawasaki disease include aspirin, glucocorticoids, and repeat courses of IVIG. With timely diagnosis and treatment, Kawasaki disease can be limited to a monophasic illness with minimal long-term sequelae in many patients.

Small-Vessel Vasculitis

Granulomatosis with Polyangiitis (GPA)

Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, is an ANCA-associated necrotizing vasculitis with granulomatous inflammation, predominantly affecting small to medium vessels and usually involving the upper and lower respiratory tracts. The varied clinical presentations of GPA are driven by the presence of granulomatous inflammation that can manifest as orbital pseudotumor, chronic sinusitis, Eustachian tube dysfunction, subglottic stenosis, and cavitary pulmonary lesions, or by the small- or medium-vessel vasculitis, which can result in pulmonary hemorrhage, glomerulonephritis, palpable purpura or mononeuritis multiplex. Abnormalities of the upper airway, including chronic rhinitis with or without nasal crusting, epistaxis, chronic sinusitis, and serous otitis, are typically the earliest presenting features and are estimated to be present in over 90% of cases [17]. Anti-PR3 antibody positivity with a C-ANCA pattern by indirect immunofluorescence microscopy has a high specificity and positive predictive value for GPA, but the absence of ANCA or PR3 does not exclude the diagnosis, and isolated granulomatous disease of the upper or lower respiratory tract in particular has a propensity to be associated with PR3 and C-ANCA negativity. PR3-ANCA is thought to be present in 80–95% of GPA cases, with the remaining 5–20% exhibiting atypical MPO-ANCA positivity or no ANCA [18]. GPA can be divided into the categories of limited disease, which tends to be characterized by predominance of necrotizing granulomatous manifestations, and severe disease, which is disease threatening the function of life or a vital organ, usually secondary to the vasculitis. The term "limited" may be misleading since patients with non-life-threatening forms of GPA often suffer from chronic morbidity and can require several years of continuous immunosuppression to adequately treat the mass lesions associated with this form of GPA. In general, patients with limited GPA are treated with an antimetabolite agent such as methotrexate, azathioprine, mycophenolate mofetil, or leflunomide. Rituximab may have a role for patients who have been refractory to this class of agents or are intolerant of these drugs. Patients with severe GPA should be treated with induction with pulse intravenous methylprednisolone 1000 mg daily for 3 days, thereafter converted to oral prednisone, used in conjunction with cyclophosphamide or rituximab. Concurrent cyclophosphamide as an induction agent can be given either orally at 2 mg/kg daily to a maximum dose of 200 mg daily for 6 months or as a series of IV pulses of 15 mg/kg to a maximum of 1.2 grams initially every 2 weeks for the first three pulses, followed by spacing to every 3 weeks for the next 3–6 pulses [19]. As an alternative to cyclophosphamide induction, rituximab is FDA-approved for induction in patients and should be administered according to the RAVE trial protocol at a dose of 375 mg/m^2 weekly for 4 weeks [20]. Among patients with the severe forms of ANCA-associated vasculitis, rituximab is commonly considered to be the treatment of choice for younger patients (who are concerned about preserving fertility), older patients (who may not be able to tolerate

traditional cytotoxic agents), or patients who have previously been treated with cyclophosphamide. Remission induction with cyclophosphamide should be followed by 18–24 months of immunosuppressive therapy in accordance with the 2008 EUVAS Management Guidelines [19]. Azathioprine 2 mg/kg daily is preferred, but options may also include methotrexate 20–25 mg per week if creatinine is <1.5 mg/dL, mycophenolate mofetil 1000 mg twice daily, or leflunomide 20–30 mg daily as second-line options. Rituximab can also be used as a long-term maintenance agent.

Microscopic Polyangiitis (MPA)

Microscopic polyangiitis is a necrotizing vasculitis with few or no immune deposits that predominantly affects small vessels, but without the presence of necrotizing granulomas that is characteristic of GPA. The initial presentation of MPA typically is characterized by a long prodromal phase dominated by marked constitutional symptoms followed by rapidly progressive necrotizing glomerulonephritis presenting as a nephritic syndrome. Glomerulonephritis is present in roughly 80% of cases at diagnosis, but pulmonary involvement is less common, occurring in about 10–30% of patients [21]. Another important distinguishing feature of MPA from GPA is that fever is the presenting feature in 80% of cases of MPA, but is an initial feature in only of 20–25% of cases of GPA. Anti-MPO antibody positivity with a P-ANCA pattern by indirect immunofluorescence microscopy has a high specificity and positive predictive value for MPA, but the absence of ANCA or MPO does not exclude the diagnosis. Although MPA and GPA can appear similar in many aspects of presentation, more detailed analyses of pathophysiology indicate key differences in these conditions. While both anti-MPO and anti-PR3 antibodies can activate neutrophils in vitro, the evidence for in vivo pathogenicity of anti-MPO is more robust than that for PR3-ANCA. A recent genome-wide association study of patients with ANCA-associated vasculitides demonstrated a significant association of PR3-ANCA and human leukocyte antigen-DP and the genes encoding α1-antitrypsin and PR3 while MPO-ANCA were significantly associated with human leukocyte antigen-DQ [22]. Nevertheless, similar to GPA, MPA can be categorized as limited or severe disease, and the treatment modalities are quite similar, including pulse methylprednisolone converted to oral prednisone and used in conjunction with cyclophosphamide or rituximab for induction for severe disease. Azathioprine, methotrexate, mycophenolate mofetil, leflunomide, rituximab, and, though with significant potential side effects form long-term use, cyclophosphamide can be used for maintenance therapy.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss syndrome, is an ANCA-associated, eosinophilic necrotizing vasculitis affecting

predominantly small to medium vessels that is associated with asthma and peripheral and tissue eosinophilia. Diagnosis of eosinophilic granulomatosis with polyangiitis is supported by a history asthma, peripheral eosinophilia with an absolute eosinophil count >1500/mm^2 and biopsy showing evidence of necrotizing granulomas and eosinophilic small-vessel vasculitis. Asthma is the defining clinical feature of EGPA, being present in >90% of patients at diagnosis and preceding the onset of vasculitis in roughly 80% of cases [23]. EGPA is typically divided into three phases of the disease: the allergic phase, with occurrence of asthma, allergic rhinitis, and sinusitis; the eosinophilic phase, in which eosinophilic organ infiltration (e.g., lungs, heart, and gastrointestinal system) occurs; and the vasculitic phase, with purpura, peripheral neuropathy, and constitutional symptoms. ANCA-positive patients are at increased risk for otolaryngologic involvement (usually sinusitis); neurologic complications including peripheral neuropathy and mononeuritis multiplex; renal involvement (typically an interstitial nephritis rather than glomerulonephritis). An unusual feature of neurologic involvement in EGPA is the occurrence of bilateral wrist or foot drop in patients, which is not typically seen in individuals with other small- or medium-vessel vasculitides. Similar to the approach for GPA and MPA described above, corticosteroids with cyclophosphamide or rituximab are classically used for remission induction, while azathioprine and methotrexate are some of the main therapeutic options for remission maintenance in EGPA. Interestingly, IL5 plays a central role in regulating eosinophil proliferation, maturation, and differentiation and is present at increased levels in patients with eosinophilic granulomatosis with polyangiitis, indicating that this cytokine may be important in disease pathogenesis [24]. In 2017, a multicenter, double-blind, parallel-group, randomized phase 3 clinical trial of 136 participants demonstrated that treatment with mepolizumab, an anti-IL5 monoclonal antibody that binds to IL5 and prevents its interaction with its receptor on the eosinophil surface, resulted in significantly more weeks in remission and a higher proportion of participants in remission than did placebo, thereby allowing for reduced glucocorticoid use [25]. On the strength of this and other trials, the FDA approved mepolizumab in December 2017 for the treatment of EGPA, though it is important to note that the dose of the medication used in the trial was 300 mg administered every 4 weeks, as opposed to the 100 mg dose every 4 weeks typically used in asthma without concurrent EGPA.

Henoch-Schonlein Purpura

Henoch-Schonlein purpura (HSP) is a small-vessel vasculitis that is more common in children than in adults, is typically self-limited, and is notable for histology demonstrating IgA deposition in the walls of involved blood vessels. While monophasic in children, it can be relapsing in adults and may result in renal failure and gut ischemia. Purpura not due to thrombocytopenia should raise suspicion for this condition, as should concomitant arthritis, abdominal pain, and glomerulonephritis. From the pediatric literature, there is little evidence that

immunosuppression is effective in the treatment of renal disease. For the cutaneous lesions of the condition, and possibly for the gastrointestinal symptoms as well, dapsone is often first-line therapy once glucose-6-phosphate dehydrogenase deficiency has been ruled out, given the possibility of significant hemolysis due to dapsone in such patients. Patients should be counseled that cutaneous vasculitis can be stimulated by activities that promote circulation to the lower extremities, including exercise, heat, and alcohol. Pressure stockings can be very effective for the treatment of the cutaneous manifestations of HSP and should be worn as much as possible, especially with regard to periods of activities such as those noted above. HSP is associated with a risk of renal insufficiency that remains even after initial recovery of renal function, thus routine monitoring of renal function should continue over a patient's lifetime.

Single Organ Vasculitis

The Chapel Hill Consensus Conference definition for single-organ vasculitis defines this entity as "vasculitis in arteries or veins of any size in a single-organ that has no features that indicate that it is a limited expression of a systemic vasculitis." Importantly, this definition is one that relies on vigorous exclusion of primary or secondary systemic rheumatic causes. When diagnosed, single-organ vasculitis by definition does not evolve into systemic vasculitis. Importantly, though, workup often reveals secondary non-rheumatic cause for the vasculitis such as cancer, environmental exposures, or infection.

Most available knowledge regarding single-organ vasculitis is based on small case series that have appeared in the literature over the last several decades [26]. Any organ system can be involved, but the most common targets are often skin, central and peripheral nervous system, muscle, gastrointestinal organs, the urogenital tract, breasts, and the eyes. In contrast, other visceral organs including the heart, liver, lungs, and the kidneys have never been established to be targets of single-organ vasculitis. The clinical presentation is a consequence of the specific end-organ that is involved. In general, however, constitutional symptoms are infrequently seen, acute phase reactants are usually normal to only slightly elevated, and the prognosis is often benign. The vasculitis itself is thought to follow a monophasic course in most cases. That being said, there is currently little evidence-based data to guide management of this group of vasculitides. Most experience with treatment has been based on retrospective series, and there are no randomized placebo-controlled trials of intervention for single-organ vasculitis to date.

High-Yield Review of Vasculitis

Key Points on Systemic Vasculitis

- Systemic vasculitides share the pathogenic feature of inflammation focused in the walls of blood vessels.
- Primary vasculitides are categorized according to the caliber of the blood vessels involved.
- Secondary vasculitis can be due to underlying connective tissue disease, infection, drug-induced, or paraneoplastic causes.
- Commonly used imaging modalities in suspected vasculitis include Doppler ultrasound, conventional angiography, computed tomography angiography, magnetic resonance angiography, and positron emission tomography.
- Diagnosis of vasculitis is made based on tissue histopathology in concert with the appropriate clinical presentation.
- Typical histologic findings of vasculitis include infiltration of the vessel wall by immune cells, fibrinoid necrosis of blood vessel walls, and leukocytoclasis.

Clinical Pearls on Primary Vasculitides

- Giant cell arteritis occurs almost exclusively in adults over the age of 50, with a predominance among Caucasian women.
- Takayasu's arteritis predominantly affects women under the age of 40, with an increased prevalence among individuals of Asian descent.
- Cogan's syndrome typically involves ocular, vestibuloauditory, and vasculitic findings.
- Hepatitis B infection is commonly associated with polyarteritis nodosa.
- The most feared complication of Kawasaki disease is cardiac disease, with myocarditis in the early phase of the disease and coronary artery aneurysms in later stages.
- Anti-PR3 antibody positivity with a C-ANCA pattern by indirect immunofluorescence microscopy has a high specificity and positive predictive value for granulomatosis with polyangiitis, but the absence of ANCA or PR3 does not exclude the diagnosis.
- Microscopic polyangiitis has a similar presentation as granulomatosis with polyangiitis but without the presence of necrotizing granulomas.
- An unusual feature of neurologic involvement in eosinophilic granulomatosis with polyangiitis is the occurrence of bilateral wrist or foot drop in patients, which is not typically seen in individuals with other small- or medium-vessel vasculitides.
- Henoch-Schonlein purpura is often monophasic in children but can be relapsing in adults and may result in renal failure and gut ischemia.

Questions

1. A 67-year-old Caucasian male presents with 5 weeks of headache lateralized to the right temporal region. He has also suffered recurrent fevers, myalgias, and an unintentional 10 lbs. weight loss. Two days ago, he suffered an episode of several hours of vision loss in the right eye.

   Examination is notable for tenderness to palpation and hair thinning over the right temporal region. There is also weakness of the proximal muscles of the shoulder girdle. Lab work is notable for ESR 78 mm/hour and CRP 3.4 mg/dL.

   Which of the following is a reasonable molecular target of therapy in this patient?

   A. TNF-α
   B. Il-4
   C. C5a
   D. IL-6

   Correct answer: D
   The patient has giant cell arteritis with polymyalgia rheumatica. IL-6 is a key T-cell cytokine mediator in this disease process. Tocilizumab, which targets the IL-6 axis, received the Food and Drug Administration's approval in August 2017 for the treatment of GCA.
2. A 28-year-old Puerto Rican male presents to the ER after tripping while descending stairs in his home. He endorses feeling unwell also for the past 2 weeks with subjective fever, chills, malaise, abdominal pain, and an unintentional five-pound weight loss. He has also noted right testicular pain.

   Examination is notable for mild diffuse tenderness to palpation of the abdomen. A right foot drop is present. 1+ bipedal edema is present. The lower extremities are also notable for livedo reticularis.

   A medium-vessel systemic vasculitis is suspected. Conventional angiography reveals multiple microaneurysms of the intrahepatic and intrarenal arteries. Fusiform aneurysms and occlusive lesions throughout the superior mesenteric arterial distribution including of the hepatic and splenic branches are also noted.

   Which of the following viral infections has NOT been associated with this systemic vasculitis?

   A. HIV
   B. Hepatitis B
   C. Zika virus
   D. Parvovirus B19

   Correct answer: C
   The patient has polyarteritis nodosa, a medium-vessel vasculitis. He presents with typical features including constitutional symptoms, livedo reticularis, and mononeuritis multiplex. The abdominal symptoms are from vasculitic involvement of the intra-abdominal medium vessels. HIV, parvovirus B19, and hepatitis B all have been reported in association with polyarteritis nodosa.

3. A 24-year-old Asian female presents to her primary care provider for a routine annual health physical. She has no significant prior medical history. Except for numbness and recurrent episodes of her left arm "falling asleep" several times in the last 2 months, she has no specific complaints. Interestingly, these episodes of numbness seem to occur after activity. She regularly participates in Zumba classes, but stopped going for the past 2 weeks to avoid provoking her left arm symptoms. She is left-handed.

   She has an unremarkable routine 10-system exam. CMP, CBC, ESR, CRP, urinalysis, and urine pregnancy screening are also unremarkable.

   Which diagnostic test is most likely to establish her diagnosis?

   A. EMG/NCS
   B. Chest CT angiography
   C. ANA screening
   D. Urine drug testing

   Correct answer: B
   The patient's presentation is most concerning for Takayasu arteritis. CT angiography and magnetic resonance angiography are the preferred imaging modalities for diagnosing Takayasu's arteritis.
4. A 22-year-old Caucasian female presents for evaluation of a recurrent nodular rash with burning pain on the bilateral lower extremities. She has not experienced any similar rash in the past, though she does have recurrent nodulocystic acne controlled with topical retinoids and minocycline. She does not smoke and denies any use of illicit drugs.

   Her examination revealed multiple violaceous, tender, subcutaneous nodular lesions ranging in diameter from 0.5 cm to 1 cm over the bilateral lower legs. The overlying skin was mildly warm but nontender.

   A short course of oral steroids led to remission for her lesions for roughly 1 week. However, the lesions recurred after stopping steroids. She also noticed new bilateral ankle pain, stiffness, and swelling. The rest of her exam was unremarkable.

   Lab work was significant for pANCA positive in 1:640 titer. Follow-up ELISA for MPO and PR3 was negative. Urine studies, chest X-ray, and sinus CT scans were unremarkable. A urine drug screen was negative.

   A skin biopsy of one of the nodules around the ankle revealed a necrotizing granulomatous vasculitis with neutrophil-predominant infiltration of medium- and small-sized arterial walls.

   Which of the following is most reasonable next step?

   A. Start rituximab.
   B. Discontinue her minocycline acne therapy.
   C. Start methotrexate.
   D. Maintain the patient on long-term low-dose prednisone (5 mg/d).

   Correct answer: B

The patient's presentation and her atypical (e.g., negative PR3 and MPO) high-titer pANCA in particular are highly suspicious for a drug-induced vasculitis. Minocycline is a known cause of drug-induced vasculitis.

5. A 54-year-old male presents for evaluation of fever, sinusitis with purulent crusting nasal discharge, and generalized malaise for the past 6 months. His symptoms have been refractory to multiple courses of oral antibiotics. He denies any shortness of breath, numbness or tingling, focal weakness, or skin lesions.

   Examination is notable for an anterior nasal septal perforation, nasal crusting with clots, and an early saddle nose deformity. Lungs are clear to auscultation. Skin and neurologic examinations are unremarkable.

   A cANCA is positive in 1:640 titer, and PR3 is positive. Renal parameters are unremarkable. A chest X-ray is clear. Sinus CT shows chronic pan-sinusitis.

   Aside from oral steroids, which of the following is the most appropriate therapy?

   A. Rituximab
   B. Hydroxychloroquine
   C. Colchicine
   D. Methotrexate

   Correct answer: D
   The patient has limited GPA. For limited GPA, Methotrexate is appropriate first-line therapy for both induction and remission maintenance. Rituximab is generally reserved for severe/generalized disease and as salvage therapy for treatment-refractory limited disease. Colchicine and hydroxychloroquine are immunomodulatory agents that have no established role in the treatment of GPA.

6. A 29-year-old female presents to the ER because of acute onset right-sided weakness and slurred speech. She is accompanied by her husband, who reports that the patient had been feeling unwell with subjective fevers, chills, malaise, and diffuse myalgias for the preceding week. She has no significant medical history otherwise and takes no medications or herbal supplements.

   Initial examination confirms a dense right-sided hemiparesis and prominent left facial droop. A bruit is auscultated over the left neck. A non-contrast head CT reveals an acute left MCA territory infarction. Reperfusion therapy with tPA is given, but with no improvement in her neurologic features over the next 48 hours.

   CBC is notable for a leukocytosis of 12.7 with neutrophil predominance. CMP reveals an elevated creatinine of 1.7. Acute phase reactants are elevated with ESR 89 mm/hour and CRP 3.7 mg/dL.

   CT angiographic is significant for focal stenotic lesions of the left subclavian, left common carotid and right renal arteries. There is also aortic root dilatation.

Echocardiography is negative for valvular vegetations, but shows diffuse global hypokinesis with a left-sided ejection fraction of 37%.

In addition to IV systemic steroids, induction with cyclophosphamide is discussed, but the patient and her husband adamantly refuse because of concerns about long-term fertility.

Aside from continuing systemic steroids, which of the following is a reasonable therapy?

A. IVIG
B. Azathioprine
C. Infliximab
D. Rituximab

Correct answer: C
The patient has suffered a stroke in the setting of newly diagnosed Takayasu arteritis. Because of severe life-threatening end-organ involvement, induction with cyclophosphamide or an anti-TNF agent is preferred. The patient, however, has declined cyclophosphamide because of concern about the impact of long-term fertility. Anti-TNF agents are not teratogenic, but the passive transfer of drug before delivery has consequences for the timing of newborn vaccinations that should be discussed in coordination with an obstetrician and pediatrician.

7. A 5-year-old boy is brought to the pediatric ER for evaluation of chest pain. His parents note that he also has been suffering from fevers to 102 degrees Fahrenheit and a painful tongue that has made eating difficult. He has no known sick contacts.

   Examination is notable for a maculopapular rash over the trunk and extremities, desquamation of the skin over the palms and fingertips, and bilateral conjunctivitis.

   ECG reveals ST elevations in leads II, III, and aVF. A stat echocardiogram reveals an ejection fraction of 39%.

   Which of the following should be initiated at this time?

   A. IV systemic steroids
   B. Rituximab
   C. Cyclophosphamide
   D. IVIG

   Correct answer: D
   The patient has Kawasaki disease with typical mucocutaneous features and evidence of a myocardial infarction due to coronary artery involvement. IVIG together with aspirin is first-line therapy.

8. A 37-year-old woman is referred for evaluation of abdominal pain and abnormal CTA findings. She describes postprandial epigastric pain ongoing for the past 3 months, but denies any associated constitutional symptoms.

   Examination is notable only for abdominal tenderness. Laboratory findings have included mild anemia with normal renal and hepatic function. ESR is 7 mm/hour and CRP 0.1 mg/dL.

CTA demonstrates serial stenotic and aneurysmal lesions of the celiac artery, creating a "beads on a string" appearance. All other vascular territories in the thorax and abdomen are normal.

What is the most likely diagnosis?

A. Polyarteritis nodosa
B. Segmental arterial mediolysis
C. Antiphospholipid syndrome
D. Thromboangiitis obliterans

Correct answer: B
Segmental arterial mediolysis is a noninflammatory vasculopathy that commonly affects the abdominal vasculature. The lack of acute phase reactant elevation and the isolated distribution in the celiac artery are keys to differentiating this diagnosis from polyarteritis nodosa. Antiphospholipid syndrome would be more likely to involve multiple vascular territories with occlusive rather than aneurysmal lesions. Thromboangiitis obliterans is not known to affect the visceral arterial system.

9. A 19-year-old male presents to the emergency department with purpuric skin lesions. He reports that the lesions developed over the past week and have been progressive.

Exam reveals retiform purpura involving the ears, cheeks, and nose. A nasal septal defect is also noted.

Chest X-ray and renal function parameters are normal.

Which of the following studies would you order next?

A. Urine drug screen
B. MRA of the abdomen
C. Anti-DNA antibodies
D. Paroxysmal nocturnal hemoglobinuria flow cytometry assay

Correct answer: A
This patient's presentation is suggestive of levamisole-induced vasculitis. Levamisole is an antihelminthic agent that is frequently identified as an adulterant in cocaine. The patient's nasal septal defect is a clue to the possibility of cocaine use. MRA of the abdomen would not add relevant information, and the patient's presentation is not suggestive of SLE. While PNH is associated with thrombosis, the finding of necrotic lesions on the face without any indication of visceral thrombosis would be unusual.

10. A 34-year-old woman presents for evaluation of purpuric skin lesions. For the past 6 months, she has noticed crops of coalescing purpuric lesions on the lower legs. She denies any sensory or motor deficits in the extremities. Review of systems is notable for prominent sicca symptoms. She has experienced painless swelling in the vicinity of her parotid glands for the past year, and the parotids are enlarged with palpable nodularity on exam.

Initial laboratory studies demonstrate high-titer anti-SSA, anti-SSB, and rheumatoid factor. Labial salivary gland biopsy demonstrates focal lymphocytic sialadenitis with a high focus score (5.4), and several germinal centers are noted.

Which of the following studies should be obtained next?

A. Salivary scintigraphy
B. Anti-CCP antibodies
C. EMG/NCS
D. Ultrasound guided parotid biopsy

Correct answer: D
This patient's presentation is consistent with primary Sjogren's syndrome, diagnosed on the basis of autoantibody positivity and labial salivary gland biopsy findings. The skin lesions are compatible with LCV, likely due to cryoglobulinemia. The reported major salivary gland enlargement is concerning for the presence of B cell (MALT) lymphoma. She should therefore be evaluated with major salivary gland imaging and biopsy. The other studies are of lesser priority in this patient's evaluation.

11. A 68-year-old woman with PMR returns for follow-up. 3 months ago, she presented with aching soreness of the upper arms, shoulders and back, and elevated acute phase reactants. Initial treatment with 15 mg prednisone daily led to rapid resolution of her symptoms. She has since tapered her dose to 5 mg daily.

She notes that for the past 2 weeks, she has had difficulty chewing food due to soreness in her jaw. She has also noticed tenderness of her scalp when laying her head on a pillow at night. Yesterday she experienced diplopia which lasted for several hours before spontaneously resolving.

Which is the most appropriate next step in this patient's management?

A. Referral to headache specialist.
B. Referral to ophthalmologist.
C. Addition of gabapentin 300 mg three times daily.
D. Increase prednisone to 60 mg daily.

Correct answer: D
This patient with recently diagnosed PMR is now presenting with signs of GCA, including jaw claudication, scalp tenderness, and visual disturbance. This is concerning for the risk of impending visual loss, and she should therefore be treated with high-dose glucocorticoid immediately, while being referred for temporal artery biopsy. Ophthalmology exam is indicated, but steroids should not be withheld while this referral is pending.

12. A 17-year-old male presents with 2 weeks of periumbilical pain and nausea. A purpuric rash has also appeared on the lower extremities. He describes aching and stiffness in the small joints of his hands as well as his knees.

Laboratory parameters are notable for mild anemia, ESR 85 mm/hour, and UA with 2 + RBC and 3 + protein.

A biopsy of a skin lesion is most likely to demonstrate what finding on immunofluorescent staining?

A. Intercellular IgG staining
B. Linear basement membrane zone staining of IgG and C3
C. IgA deposition
D. Minimal staining (pauci-immune)

Correct answer: C
This young male patient is presenting with typical findings of Henoch-Schonlein purpura, including abdominal pain, proteinuria, and purpuric skin lesions. HSP is mediated by IgA immune complex deposition, which can be visualized by immunofluorescent staining on skin biopsy.

13. A 27-year-old Turkish male with a history of recurrent oral and genital ulcers presents to the emergency department with hemoptysis. He gives additional history of recurrent uveitis treated with intermitted steroids and chronic pain in the knees, wrists, and hands. He has not received chronic immunomodulatory therapy and is not followed by a rheumatologist. For the past 24 hours he has been coughing up blood.

Which of the following is likely to be identified with additional studies?

A. Cavitary lung nodules
B. Pulmonary artery aneurysms
C. Mediastinal lymphadenopathy
D. Perforated gastric ulcer

Correct answer: B
This patient fits a diagnosis of Behcet's disease with oral and genital ulcers, uveitis, and arthritis. His presentation with hemoptysis is worrisome for a feared complication of Behcet's: pulmonary artery aneurysms.

14. A 72-year-old man presents for evaluation of aortitis. Over the past 3 months, he has experienced night sweats, fevers, and a 10-pound weight loss. Three days ago he presented to the emergency department where he was found to have highly elevated acute phase reactants. An MRI demonstrated thickening and enhancement of the wall of the thoracic aorta. A temporal artery biopsy was negative.

In addition to constitutional symptoms, he reports hearing loss as well as ringing in his ears over the past 3 months. For the past 2 weeks he has experienced pain and photophobia in his left eye. An ophthalmology exam performed today revealed signs of interstitial keratitis.

What is the most likely diagnosis?

A. Cogan's syndrome
B. Giant cell arteritis
C. Evans syndrome
D. Sweet's syndrome

Correct answer: A

Cogan's syndrome is a systemic vasculitis which characteristically affects the eyes and vestibuloauditory system. Cogan's syndrome can cause vasculitis in other vessels, including aortitis. Interstitial keratitis is the hallmark ocular finding and clue to this case. While GCA can manifest with symptoms involving the same organs, the negative temporal artery biopsy and specific finding of interstitial keratitis make Cogan's syndrome more likely than GCA. Evans and Sweet's are hematologic and dermatologic conditions, respectively.

15. A 43-year-old woman presents for evaluation of an orbital mass identified by her ophthalmologist. Over the past 2 months she has noticed diplopia and pain involving the left eye, leading to an MRI that showed a mass lesion in the left orbit. She has a history of recalcitrant sinusitis which has been increasingly problematic over the past year.

    Examination reveals proptosis of the left eye, crusting of the nasal mucosa, and a nasal septal perforation. Laboratory parameters include normal renal and hepatic function, ESR 52 mm/hour, and negative ANCA testing. Chest CT demonstrates several pulmonary nodules of moderate size, one of which shows signs of cavitation. Biopsy of the orbital mass demonstrates granumolatous inflammation and geographic necrosis. Microbial stains including AFB are negative.

    Which of the following is the most likely diagnosis?

    A. Sarcoidosis
    B. GPA
    C. Thyroid eye disease
    D. IgG4 related disease

    Correct answer: B
    This patient's presentation with sinusitis, orbital inflammatory disease, and pulmonary nodules is compatible with several diagnoses, including limited GPA. The histopathology confirms GPA as the etiology, despite negative ANCA testing which is more common in the limited form of GPA. While sarcoidosis, autoimmune thyroid disease, and IgG4RD can all cause orbital mass lesions, the histologic findings described here are not compatible with these diagnoses and instead implicate GPA as the diagnosis.

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