An Approach to Vasculitis and Vasculopathy

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Vasculitis and vasculopathy may arise from a primary or secondary cause, which often makes the workup and diagnosis challenging. Vasculitis occurs when inflammation in the blood vessel wall leads to its destruction and vasculopathy when a thrombus forms in the arterial lumen and compromises blood flow. The difference is subtle but important to distinguish since there are divergent diagnoses and treatments for vasculitis and vasculopathy. The hallmark clinical feature of vasculitis is palpable purpura, which also can be a manifestation of vasculopathy. Similarly the emergence of livedo reticularis is more consistent with vasculopathy but also may be seen with either entity. This overlap is important to keep in mind. Herein I will give a brief overview of how I approach vasculitis and vasculopathy. For starting residents, having an uncomplicated methodology will allow you to work quickly and thoroughly through the possible causes of vasculitis and vasculopathy.

The Workup

When vasculitis or vasculopathy is suspected, I perform a skin biopsy to confirm the diagnosis and immediately pursue an evaluation to survey for other organ involvement. A thorough review of the organ systems with the patient can be useful. Even when the exact cause may be unknown, severity can be quickly evaluated with a nonspecific workup including a complete blood cell count, comprehensive metabolic panel, urinalysis, erythrocyte sedimentation rate assay, and chest radiograph. I can then make an incisive decision about care escalation and how to proceed (ie, hospitalization if not already addressed). Ideally the workup should be tailored to the clinical situation and the diagnosis. Generally I order several specific tests at the initial visit to look for diagnoses such as connective-tissue disease or infection. Frequently taking a good patient history will guide you on what to order. However, when I am uncertain, gauging the severity and level of care needed should be the first step. Organ involvement usually results in morbidity and mortality and requires aggressive intervention and treatment. After assessing the patient's level of illness, determining whether the outbreak is vasculitis or vasculopathy is crucial. Unless there is compelling evidence for vasculopathy, I tend to assume patients have a vasculitis and consider adding in the workup for vasculopathy as appropriate.

Vasculitis Versus Vasculopathy

Laboratories to evaluate inherited vasculopathies are expensive. Nevertheless, as already stated, when suspecting vasculitis, vasculopathy is always in the differential diagnosis and vice versa. If livedo reticularis is present, I usually consider performing a workup for vasculopathy. Retiform purpura is the netlike pattern of livedo reticularis with purpura and is rather specific for vessel occlusion. If retiform purpura is present, I favor vasculopathy over vasculitis. A skin biopsy usually can differentiate between vasculitis and vasculopathy; if the patient shows no symptoms of illness, it can be helpful to wait for the results of the skin biopsy. The vasculopathy differential diagnoses can be divided into sick patients and nonsick patients. If the patient is sick, diagnoses such as disseminated intravascular coagulation, purpura fulminans, thrombotic thrombocytopenic purpura, heparin-induced skin necrosis, and cholesterol emboli should be considered. If the patient is not acutely sick, I consider type 1 cryoglobulinemia or myeloproliferative disease, cryofibrinogenemia, antiphospholipid antibody syndrome, and the inherited mutations causing

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hypercoagulability (eg, proteins C and S, antithrombin III, and factor V Leiden mutation).

Classifying Vasculitis

There is no formal classification system for vasculitis. Historically, vasculitides have been classified by the size of the vessel involvement. As a rule of thumb, the risk for organ involvement beyond the skin increases with the size of the involved blood vessels. Palpable purpura emerges when there is vasculitis in the postcapillary venules and skin ulceration occurs when the arterioles or small arteries become involved. Gangrene as well as gastrointestinal, renal, pulmonary, or neurologic symptoms can occur with capillary to medium-sized artery involvement. Involvement of the kidneys or lungs is common with purely capillary involvement.

When evaluating vasculitis, I rule out secondary causes first because management can differ and the conditions often are self-limited. Infection can be a secondary cause of vasculitis and administration of immunosuppressive therapy can have catastrophic consequences. Considerations would include group A streptococci, mycoplasma, tuberculosis, hepatitis C or B, and others. Other secondary causes of vasculitis include drug reactions; malignancy; and connective-tissue disorders, most commonly systemic lupus erythematosus and rheumatoid arthritis. The term *hypersensitivity vasculitis* is often used to refer to secondary causes of vasculitis. A hypersensitivity vasculitis primarily affects the postcapillary venules of the skin. However, if hypersensitivity vasculitis is serious, it also may affect the joints, gastrointestinal tract, and kidneys. After ruling out the secondary causes of vasculitis, I will consider the size of the involved vessels based on the patient's history, present symptoms, physical examination, and simple laboratory evaluation. However, receiving the test results of some laboratory evaluations may take time. Skin ulceration and organ involvement speaks to larger vessel pathology. The patient's age also should be considered as well as the organ systems that have been affected.

Small Vessel Vasculitis—Henoch-Schönlein purpura (HSP), cryoglobulinemia, and urticarial vasculitis are small artery vasculitides. Henoch-Schönlein purpura generally is seen in the pediatric population following an upper respiratory tract infection. Classically, HSP presents with palpable purpura on the buttocks and lower extremities. Generally it is self-limited and requires no treatment. However, the risk for arthritis, glomerulonephritis, and gastrointestinal ischemia from intussusception can be a concern. Cryoglobulins are immunoglobulins that reversibly precipitate with exposure to the cold. Cryoglobulinemia is divided into 3 types and usually is caused by an underlying disorder but can be idiopathic. Type 1 is always associated with a lymphoproliferative disorder, such as Waldenström macroglobulinemia, which is a vasculopathy and not a vasculitis. Types 2 and 3 are associated with connective-tissue disorders or infections (ie, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus). The difference between type 2 and type 3 cryoglobulinemia is the causative immunoglobulin: monoclonal (type 2) or polyclonal (type 3). Similar to HSP, skin involvement is common and can be associated with arthritis, Raynaud phenomenon, or glomerulonephritis. Urticarial vasculitis usually is caused by underlying disorders, such as connective-tissue disorders. I consider urticarial vasculitis to be a diagnosis of exclusion that takes into account the clinical presentation.

Medium Vessel Vasculitis—Vasculitides involving medium-sized vessels include polyarteritis nodosa, Wegener granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis. Contained within this group are antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides. Because medium-sized vessels are involved, several organ systems can be affected. If a patient presents with lung involvement, I generally jump to this group of vasculitides. Palpable purpura with livedo reticularis also is a common presentation in medium vessel vasculitis. Polyarteritis nodosa can appear similar to erythema nodosum but with ulcerations; erythema nodosum never ulcerates. Polyarteritis nodosa can involve any organ system but generally not the lungs. The development of the mononeuritis multiplex is unique to polyarteritis nodosa. Mononeuritis multiplex occurs when at least 2 separate peripheral nerves (sensory or motor) exhibit damage. Polyarteritis nodosa is not cytoplasmic or perinuclear ANCA positive. Granulomatous involvement of the upper respiratory tract (ie, sinusitis) is unique to Wegener granulomatosis. Wegener granulomatosis is nearly always cytoplasmic ANCA positive with antibody to proteinase 3. Churg-Strauss syndrome–associated vasculitis can be related to allergic rhinitis, asthma, and eosinophilia. Both Churg-Strauss syndrome–associated vasculitis and microscopic polyangiitis can have perinuclear ANCA positivity with antibody to antimyeloperoxidase. Microscopic polyangiitis may present with both lung and kidney involvement.

Large Vessel Vasculitis—Large vessel vasculitis includes temporal arteritis and Takayasu arteritis. Neither one typically presents with skin findings such as palpable purpura; therefore, they are not discussed here.

Summary

My approach to vasculitis and vasculopathy includes: (1) Determine the level of care the patient needs. If I am not sure, I will order a basic laboratory evaluation while I decide on the more specific laboratory tests to order and of course do a skin biopsy. (2) Determine if the eruption represents vasculitis or vasculopathy. The presence of livedo reticularis or retiform purpura points toward vasculopathy, but keep in mind the overlap, especially with the ANCA-associated vasculitides. (3) If vasculitis, rule out the secondary causes (ie, infection, drug reactions, malignancy, connective-tissue disorders) first. (4) Determine the size of the vessel involvement and the organ systems involved, which will narrow down the differential diagnosis. Although no one approach works for everyone, I find this method to be simple and keeps you organized when tackling the workup of vasculitis and vasculopathy.