Vasculitis

8

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Key Points

- The vasculitides are a group of diseases characterized by inflammatory destruction of blood vessels.
- While skin-limited disease is commonly encountered by the dermatologist, serious organ- and life-threatening complications can occur.
- A systematic approach to diagnosis and evaluation is required to ensure diagnostic accuracy and identify those with systemic disease who are at risk for poor outcomes.
- Inappropriate use and interpretation of laboratory tests may result in confusion and delay and should be avoided.
- Effective coordination of care with other medical providers is an essential part of successful diagnosis and management.

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Interdisciplinary Introduction

"Vasculitis" refers to inflammation and destruction of blood vessels, which results in tissue damage. The vasculitides are a rare and heterogeneous group of diseases. Diagnosis of any particular type of vasculitis can be made based on characteristic clinical findings and histology, with careful clinicopathologic correlation. Cutaneous eruptions are frequently encountered in many types of vasculitis. The cutaneous eruption, which is highly visible and accessible for biopsy, may be the presenting sign of systemic disease and as such represents an important opportunity for diagnosis and treatment. The eruption itself is also a significant source of morbidity.

This chapter will achieve the following: (i) review the classification of vasculitis; (ii) outline the cardinal features of the major vasculitides; (iii) focus on the diagnosis and management of small-vessel vasculitis, which is encountered frequently by dermatologists, rheumatologists, and other physicians; and (iv) discuss the diagnostic approach and systemic evaluation in cases in which vasculitis is a consideration, all with the goal of improving diagnosis and management for this complex group of diseases.

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Nomenclature and Classification of Vasculitis

The 2012 revised International Chapel Hill Consensus Conference nomenclature (Table 8.1) names a limited set of vasculitides described according to size of the affected blood vessels affected, which often correlates with clinical morphology [1]. Importantly, however, the Chapel Hill nomenclature is not the same as classification schema, as it does not contain diagnostic criteria. The 1990 American College of Rheumatology Classification Criteria, by contrast, include sets of clinical features (criteria) that are sensitive and specific for the most common forms of vasculitis; it remains the standard system used in research [2]. However, this schema was created before antineutrophil cytoplasmic antibody (ANCA) testing and some forms of diagnostic imaging were in widespread use, and it is currently undergoing revision [3].

While nomenclature and classification schemes have limitations, it is indeed helpful to correlate clinical manifestations of vasculitis with size of the vessels affected. It is also important to recognize that "leukocytoclastic vasculitis" is not a specific disease or diagnosis but rather one of the possible pathologic findings in vasculitis.

Pathophysiology and Clinical Features

Small-Vessel Vasculitis

Small-vessel vasculitis of the skin is commonly mediated by immune complex deposition. Circulating antigens (whether triggered by medications, infections, connective tissue disease, or neoplasia) are bound by antibodies, forming immune complexes [4]. These complexes become lodged within small vessels of the superficial dermis (which are analogous to the small branches at the top of a tree), often in dependent areas, such as the legs, or in areas of pressure. These complexes activate complement, inducing an inflammatory response that leads to vessel destruction and extravasation of red blood cells.

The lesions in small-vessel vasculitis are small, superficial, and localized to the area fed by the affected vessels. Classically, they present as crops of purpuric, round, 1-to-5 mm papules (so-called "palpable purpura"). The complement cascade and inflammation account for the palpability as well as associated symptoms, such as burn or itch. Red blood cell extravasation, meanwhile, results in purpura.

Additionally, urticarial papules, pustules, vesicles, petechiae, and erythema multiforme-like lesions may appear. When several small lesions

Table 8.1 Classification of vasculitis by vessel size

Affected vessels	Classification	Subclassification
Small	Cutaneous small vessel (leukocytoclastic) vasculitis	Idiopathic Infectious Medication exposure Inflammatory (CTD)
	Small vessel vasculitis—special types	IgA Vasculitis (Henoch-Schönlein purpura) Urticarial vasculitis Acute hemorrhagic edema of infancy Erythema elevatum diutinum
Small and medium	Cryoglobulinemic	Types II and III
	ANCA-associated	EGPA (Churg-Strauss), Microscopic Polyangiitis, GPA (Wegener)
Medium	Polyarteritis nodosa (PAN)	Benign cutaneous form Systemic form
Large	Temporal arteritis Takayasu arteritis (TAK)	

ANCA antineutrophilic cytoplasmic antibodies, *CTD* connective tissue disease, *EGPA* eosinophilic granulomatosis with polyangiitis, *GPA* granulomatosis with polyangiitis

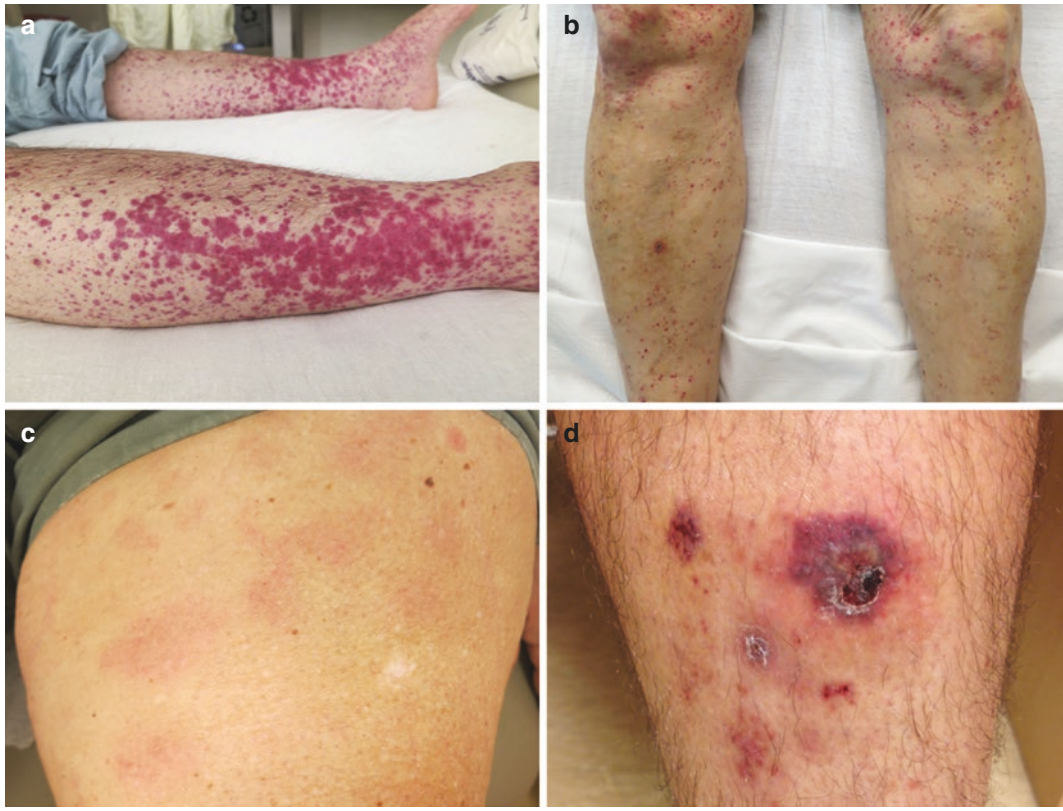

Fig. 8.1 Clinical manifestations of vasculitis involving small vessels. (**a**) Coalescing purpuric macules and papules; (**b**) Scattered purpuric macules and petechiae; (**c**) Urticarial papules; and (**d**) Rounded ulceration formed by coalescing purpuric papules

coalesce, rounded purpuric patches, plaques, or ulcers may form (Fig. 8.1). If such lesions are seen in isolation, the differential diagnosis includes cutaneous small-vessel vasculitis, IgA vasculitis (Henoch-Schönlein purpura), and urticarial vasculitis.

Medium-Vessel Vasculitis

The affected vessels in medium-vessel vasculitis are located in the deep dermis or subcutis and are analogous to the trunk of a tree. The resulting affected area includes all downstream vessels (analogous to overlying tree branches) and the tissue they supply. Cases of medium-vessel vasculitis usually involve both small- and medium-sized arteries.

Medium-vessel vasculitis of the skin manifests with lesions of larger size and more destructive potential than those seen in small-vessel vasculitis. Characteristic findings include livedo reticularis, subcutaneous nodules, retiform (or "stellate") purpura, hemorrhagic bullae, ulceration and necrosis (Fig. 8.2). Livedo reticularis is a net-like, mottled or reticulated, pink or red-blue discoloration of the skin, resulting from reduced blood flow and oxygen tension in the venous plexus of the skin. Hemorrhagic bullae, ulceration and necrosis occur due to devitalization of tissue; if necrosis or purpura occur in the livedoid areas, the terms retiform or stellate purpura may apply.

The morphologies of both livedo reticularis and retiform purpura derive from the size of the vessel involved; a single involved "trunk" may

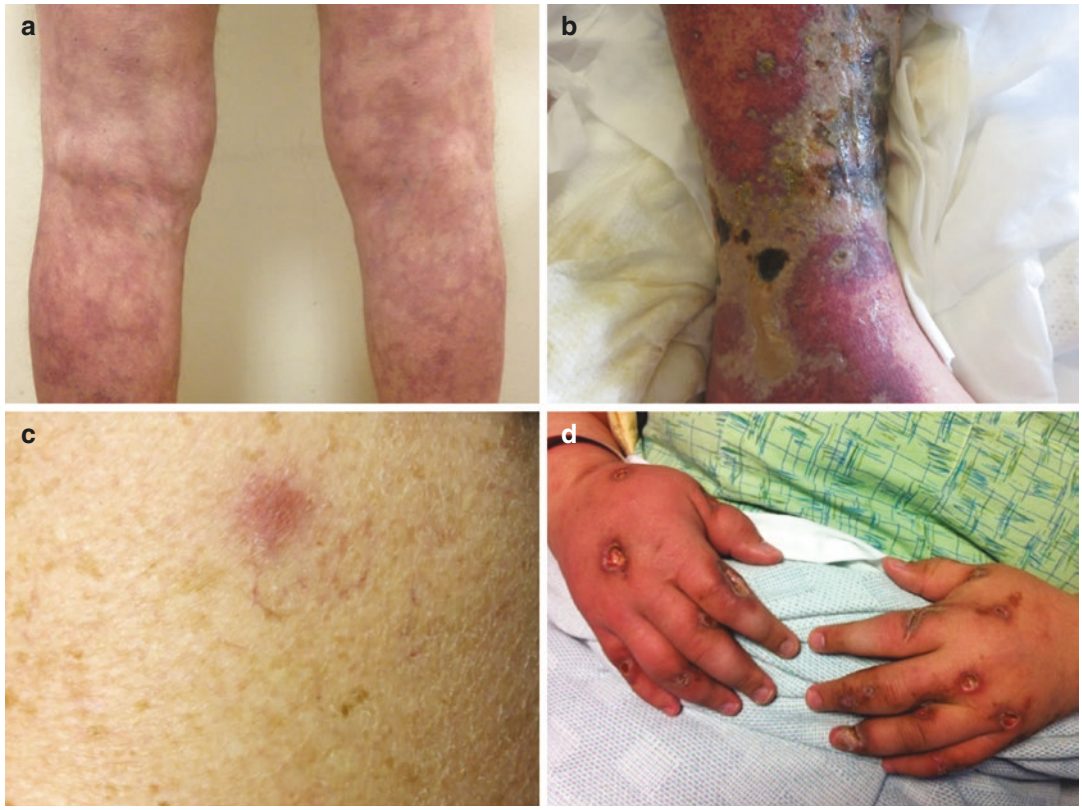

Fig. 8.2 Clinical manifestations of vasculitis involving medium-sized vessels. (**a**) Extensive livedo reticularis in a patient with eosinophilic granulomatosis with polyangiitis (Churg-Strauss); (**b**) Retiform purpura and ulceration in a patient with cryoglobulinemic vasculitis; (**c**) A tender nodule on the leg of a patient with polyarteritis nodosa (PAN); and (**d**) Digital ulceration and infarct in a patient with PAN. (*Photo courtesy of Antoine Sreih, MD*)

affect a large number of overlying branches, while the presence of nearby "trees" with branches feeding adjacent and intervening areas of skin accounts for the uneven, netlike, jagged, or retiform appearance of the lesions. The jagged or netlike shape seen in livedo reticularis and retiform purpura is an important diagnostic clue that can help distinguish medium-vessel vasculitis from small-vessel vasculitis, which has a more rounded shape, as discussed above.

When findings of medium-vessel vasculitis are seen in the skin, the differential diagnosis includes cutaneous or systemic polyarteritis nodosa (PAN). If these findings are seen together with an eruption suggestive of small-vessel vasculitis (e.g., palpable purpura), the differential diagnosis broadens to include ANCA-associated vasculitis or cryoglobulinemic vasculitis, each of which may have overlapping small- and medium-vessel manifestations.

Extracutaneous Manifestations

Just as the size and morphology of cutaneous lesions are predictive of the type of underlying vasculitis, extracutaneous manifestations can offer important clues to the size of vessel affected. Both small- and medium-vessel vasculitis can affect the kidney, for example, but with different manifestations. Small-vessel vasculitis affects the glomerulus, disrupting the kidney's filtering function and leading to hematuria and proteinuria. Medium-vessel vasculitis, by contrast,

results in characteristic aneurysmal dilation and narrowing of renal arteries, manifesting as renovascular hypertension or renal infarction.

Another important distinction can be made based on the presence or absence of neurologic manifestations. Small-vessel vasculitis does not typically affect the nerves. Medium-vessel vasculitis, by contrast, can result in a motor neuropathy ("mononeuritis multiplex").

Types of Vasculitis with Skin Involvement

Cutaneous Small-Vessel Vasculitis/ Small-Vessel Vasculitis of the Skin

Small-vessel vasculitis of the skin is most commonly immune complex-mediated, self-limited, and confined to the skin. It may be idiopathic or triggered by infection, drug, connective tissue disease, or neoplasia. Care should be taken to differentiate single-organ vasculitis of the skin from other types of vasculitis or systemic disease.

Cutaneous Manifestations

Palpable purpura is the classic presentation of small-vessel vasculitis of the skin, but purpuric macules, petechiae, urticarial papules, and erythema multiforme-like lesions may be seen. Rounded small ulcers may occur from coalescing palpable purpura. The eruption favors dependent areas, such as the lower extremities, as well as areas of pressure.

Systemic Findings

Arthralgias are fairly common during flares. The presence of frank arthritis, constitutional symptoms, abdominal pain, melena, hematuria, or cough suggests the presence of systemic disease [5].

IgA Vasculitis

IgA vasculitis (Henoch-Schönlein purpura) is a small-vessel vasculitis mediated by IgA immune complexes. The initial presentation is often indistinguishable from that of other forms of cutaneous small-vessel vasculitis.

Cutaneous Manifestations

Patients present with palpable purpura and other small-vessel lesions. There is a preference for dependent areas, as lesions result from immune complex deposition.

Systemic Findings

Abdominal pain or gastrointestinal bleeding occur in 65% of patients, arthralgias or arthritis in 63%, and glomerulonephritis in 40% [6]. Symptoms of an antecedent infectious trigger may be present or recently resolved.

Urticarial Vasculitis

As many as 5–10% of patients with chronic urticarial eruptions actually have urticarial vasculitis [7]. This type of small-vessel vasculitis may be skin-limited or, particularly when associated with low complement levels, involve internal organs, with patients sometimes meeting criteria for systemic lupus erythematosus.

Cutaneous Manifestations

Patients present with hive-like eruptions. Unlike in true urticaria, individual lesions last greater than 24 hours, classically burn instead of itch, may evolve into ecchymoses, and typically do not respond to antihistamines. Other manifestations of small-vessel vasculitis, such as palpable purpura, may be present.

Systemic Findings

Clues to a diagnosis of urticarial vasculitis include the presence of fever or other constitutional symptoms as well as arthralgias.

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis is an immune-complex mediated vasculitis that results from B-cell stimulation, most commonly by chronic

infection with hepatitis C virus. Cryoglobulinemic vasculitis not associated with hepatitis C virus infection is rare but can occur in association with lupus, Sjögren syndrome, hepatitis B virus or human immunodeficiency virus, or as an idiopathic disorder. A monoclonal gammopathy (Type I cryoglobulins) with cryoglobulinemic characteristics can occur with some B cell lymphomas or plasma cell disorders.

Cutaneous Manifestations

The eruption includes manifestations of both small- and medium- vessel disease, including palpable purpura but also livedo reticularis, retiform purpura, and ulceration. There is a predilection for the lower extremities as well as cold-exposed sites, such as the feet, hands, and ears.

Systemic Findings

Arthralgias and peripheral neuropathy are the most common extracutaneous manifestations. Disease follows a benign course in about half of patients, but one-third develop severe glomerulonephritis or other visceral complications. Patients with cryoglobulinemic vasculitis associated with the systemic disorders reviewed above may also present with the usual signs and symptoms of those diseases.

Granulomatosis with Polyangiitis (Wegner's)

Granulomatosis with polyangiitis (GPA) is an ANCA-associated vasculitis characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tract, necrotizing glomerulonephritis, and small and medium vessel vasculitis of other organs. GPA is frequently an organ- and life-threatening disease.

Cutaneous Manifestations

Cutaneous manifestations of GPA occur in about 50% of patients [8]. Morphologically, these include a mix of small- and medium-vessel manifestations, including palpable purpura but also subcutaneous nodules and ulcers (also called "malignant pyoderma") [9]. Flesh-colored papules with central necrosis on the extensor surfaces of the elbows are typical of GPA and represent palisaded and neutrophilic granulomatous dermatitis histologically.

Systemic Findings

Upper airway symptoms such as rhinorrhea, severe sinusitis, nasal ulcerations, epistaxis, and upper airway nodules are ubiquitous in patients with GPA, present in 90%. Renal (85%), pulmonary (70%), and ophthalmic (60%) manifestations are also common [10].

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is an ANCA-associated vasculitis that, unlike GPA, lacks upper respiratory tract involvement and granulomatous inflammation.

Cutaneous Manifestations

The skin is involved in 44% of patients with MPA, showing a mix of small- and medium-vessel involvement. Purpuric papules and macules are most common. Livedo reticularis, retiform purpura, cutaneous ulcers, and digital infarcts are also seen [11].

Systemic Findings

Constitutional symptoms, including fever and flu-like symptoms, are common. Glomerulonephritis occurs in 80–90% and pulmonary capillaritis in 25–65%. Peripheral neuropathy, including mononeuritis multiplex, is a prominent and characteristic feature (58%) [12].

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

EGPA is an ANCA-associated vasculitis that presents with eosinophilia, asthma, and eosinophil-associated disease manifestations.

Cutaneous Manifestations

A cutaneous eruption is seen in two-thirds of patients with EGPA. These include non-specific,

allergic-type lesions such as urticarial, pruritus, and non-specific rash, as well as manifestations of vasculitis such as palpable purpura (50%) and livedo reticularis. Nodules on the extensor elbows are also common (30%) [13].

Systemic Findings

Most patients have asthma, sometimes long-standing and sometimes adult-onset, before the onset of vasculitis. Atopy, nasal polyps, and eosinophilic pulmonary infiltrates are common, unlike in GPA. Peripheral neuropathy is frequent, and, unlike in GPA, cardiomyopathy is relatively common.

Polyarteritis Nodosa

PAN is characterized by necrotizing vasculitis of medium-sized vessels. PAN may be either skin-limited (so-called cutaneous PAN, 10% of patients) or systemic (90%). Patients with cutaneous PAN must be followed closely due to the potential for systemic complications to develop over time [14].

Cutaneous Manifestations

An eruption is seen in 60% of patients with systemic PAN. They consist of medium-vessel manifestations, such as retiform purpura, ulcers, digital necrosis, livedo reticularis, and subcutaneous nodules distributed along blood vessels [15]. The legs are most commonly affected, followed by the arms and trunk. Skin-limited PAN presents with similar cutaneous findings.

Systemic Findings

Systemic symptoms of PAN include fever and weight loss (90%), arthralgia or arthritis (75%), and peripheral neuritis (75%). Approximately 50% of patients have renal involvement, which may present with hypertension. Some 40% have gastrointestinal involvement, presenting with abdominal pain and gastrointestinal bleeding. Other manifestations may include stroke, myocardial infarction, and bowel infarction. The lungs are spared [16]. Regardless of organ system, the characteristic abnormality in PAN is stenosis or aneurysm of medium-sized arteries.

Giant Cell Arteritis and Takayasu Arteritis

Giant cell arteritis (temporal arteritis, GCA) and Takayasu arteritis (TAK) are vasculitides affecting large arteries (the aorta and its primary branches). Cutaneous manifestations of these diseases are rare.

GCA commonly involves branches of the carotid artery and exclusively affects adults over age 50 years. Headache, jaw claudication, and constitutional symptoms are common. Blindness can occur if untreated. GCA is frequently associated with polymyalgia rheumatica, and diagnosis is made on the basis of temporal artery biopsy. Ultrasound of the temporal artery and other imaging techniques (3-Tesla MRI and positron emission tomography) are gaining acceptance as a diagnostic approach to GCA.

In GCA, the temporal arteries can be nodular and tender. The overlying scalp may appear red or cyanotic. Frank necrosis of the scalp or tongue are extremely rare signs of GCA.

TAK affects the aorta and its major branches. Most patients are young women. TAK may present with limb claudication, pulselessness, and abnormal blood pressure readings; constitutional symptoms; and dizziness, angina, or bowel ischemia. Characteristic angiographic changes are diagnostic.

Rare cutaneous eruptions of TAK may resemble erythema nodosum or pyoderma gangrenosum. Histologically, a necrotizing vasculitis may be present [17].

Initial Evaluation of Patients with Possible Vasculitis

The eruption of vasculitis should initially be considered a symptom of disease rather than a distinct entity, for two reasons. First, identical lesions may be produced in a variety of other disease states, including infection and coagulopathy/vasculopathy, which must be ruled out. Second, when cutaneous vasculitis is confirmed, it is crucially important to establish whether systemic manifestations of vasculitis (e.g., renal, joint, gastrointestinal) or underlying causes or

disease associations (e.g., infection, medication reaction, connective tissue disease) are present, as such associations affect management and prognosis. Patients with evidence of systemic vasculitis need urgent medical treatment and referral to colleagues in rheumatology, nephrology, and other specialties.

When a patient presents with an eruption suspicious for vasculitis, initial evaluation should attempt to answer three basic questions:

1. Is the eruption due to vasculitis?
2. Are other organ systems involved?
3. Are there findings that help establish a particular diagnosis or etiology?

Table 8.2 Partial differential diagnosis of purpuric macules and papules

Skin-limited, small-vessel vasculitis
IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulinemic vasculitis
ANCA-associated vasculitis
Polyarteritis nodosa (PAN)
Bacteremia
Arthropod bites
Macular purpura due to trauma, skin fragility, or anticoagulation
Platelet dysfunction or deficiency
Pigmented purpuric dermatosis
Cholesterol emboli
Septic emboli
Livedoid vasculopathy

The answer to the first question can often be established via a skin biopsy, which should be performed in nearly all circumstances. To answer the second question, a thorough review of systems, physical exam, and basic set of laboratory tests should be performed in a timely fashion. Answering the third question may necessitate a more targeted and specialized "second-level" set of testing. Here we review the available modalities for evaluation of patients with vasculitis, followed by a suggested workup by specific type of vasculitis.

Skin Biopsy

Biopsy Selection and Performance

A skin biopsy should be performed whenever possible to confirm the diagnosis of vasculitis and guide further management. Even the most experienced clinician can be fooled by conditions that mimic vasculitis (Table 8.2).

The type of biopsy performed is dictated by lesion morphology, which suggests where the pathology may be located. For cutaneous manifestations of small-vessel vasculitis, such as palpable purpura, a 4 mm punch biopsy should be sufficient to sample the entire dermis. For "deeper" manifestations of medium- or small-to-medium vessel vasculitis, such as subcutaneous nodules or retiform purpura, sampling of the deep dermis and subcutis is required. This may be accomplished using an incisional biopsy or deep or "telescoping" punch biopsy (e.g., 6 mm punch followed by 4 mm punch) to ensure an adequate amount of fat is sampled.

Because of the natural progression of vasculitis lesions, the timing and selection of the biopsy site is critical. A biopsy performed too early or too late in the development of a lesion may be nondiagnostic. Ideally, a representative, well-established, but not old, lesion (1–2 days old) should be biopsied. For this reason, if new lesions are present, every effort should be made to perform a biopsy the same day the patient is seen.

Whenever relevant and possible, a second biopsy should be performed for direct immunofluorescence studies, as detection of immune complex deposition may have diagnostic and prognostic significance [18]. Proper selection of the biopsy site is even more critical for immunofluorescence studies than for routine biopsy, as immune complexes are most likely to be seen in "fresh" lesions, or those that are between 8 and 24 hours old. Because the subsequent inflammatory cascade destroys deposited immune complexes, older lesions may be falsely negative. Biopsies for direct immunofluorescence should be taken from lesional skin, and the specimen

should be placed in Michel's medium or normal saline (not formalin) for processing. Alternatively, a single biopsy can be obtained and cut in half to be sent for both standard processing and direct immunofluorescence.

Histologic Findings in Cutaneous Vasculitis

Characteristic histologic features of leukocytoclastic vasculitis include a neutrophilic inflammatory infiltrate involving dermal blood vessels, granulocytic debris and nuclear dust (leukocytoclasis), fibrinoid necrosis and disruption of vessel walls, and extravasation of red blood cells into the surrounding skin (Fig. 8.3) [19]. Differentiation between small- and medium-sized blood vessels can be somewhat subjective, but small vessels are typically located in the superficial and mid dermis, while medium-sized vessels are located in the deep dermis and subcutaneous fat. The severity of the histologic changes and the depth of the inflammatory infiltrate may predict disease severity or even underlying malignancy [20].

Several other histopathological findings are suggestive of specific etiologies. The presence of tissue eosinophilia may suggest drug-induced vasculitis [21]. The presence of extravascular granulomas with vasculitis is suggestive of GPA or EGPA, especially if eosinophils are also present. The presence of IgA deposits in vessel walls on direct immunofluorescence studies suggests a diagnosis of IgA vasculitis [1] and increases the likelihood of the renal, joint, and gastrointestinal symptoms seen commonly in that syndrome. The presence of IgM may correlate with renal involvement [22] or cryoglobulinemia [23]. A continuous band of C3 or IgG at the dermoepidermal junction (sometimes called a positive lupus band test, though this name has been applied to different findings), may suggest hypocomplementemic urticarial vasculitis and underlying systemic lupus erythematosus.

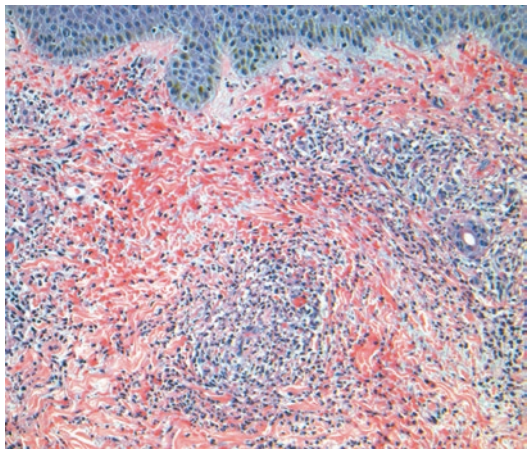

Fig. 8.3 Small vessel vasculitis of the skin showing neutrophilic infiltration of superficial and mid dermal blood vessels, leukocytoclasis, fibrinoid necrosis of vessel walls, and extravasation of red blood cells

Common Pitfalls in Using Skin Pathology to Evaluate Possible Vasculitis

The term "leukocytoclastic vasculitis" is sometimes used improperly on histology reports to describe isolated perivascular neutrophilic inflammation or leukocytoclasis without true fibrinoid necrosis of vessel walls. Although such findings are suggestive and may represent early vasculitis, they are not diagnostic of the condition and may lead to confusion. It is, therefore, important to read the pathology report in its entirety, including direct immunofluorescence, if done, and not rely solely on the summary text.

Similarly, the simple presence of leukocytoclastic vasculitis in a biopsy specimen does nothing to establish its etiology. It is important to understand that "leukocytoclastic vasculitis" is *not* a specific disease entity but a pathologic term and a common finding in the skin in patients with vasculitis. It is important to consider mimickers, such as arthropod bites, ulcers, and neutrophilic dermatoses, in which a secondary vasculitis can be seen, but no clinical syndrome of idiopathic vasculitis is present (Fig. 8.4). Careful clinicopathologic correlation is required.

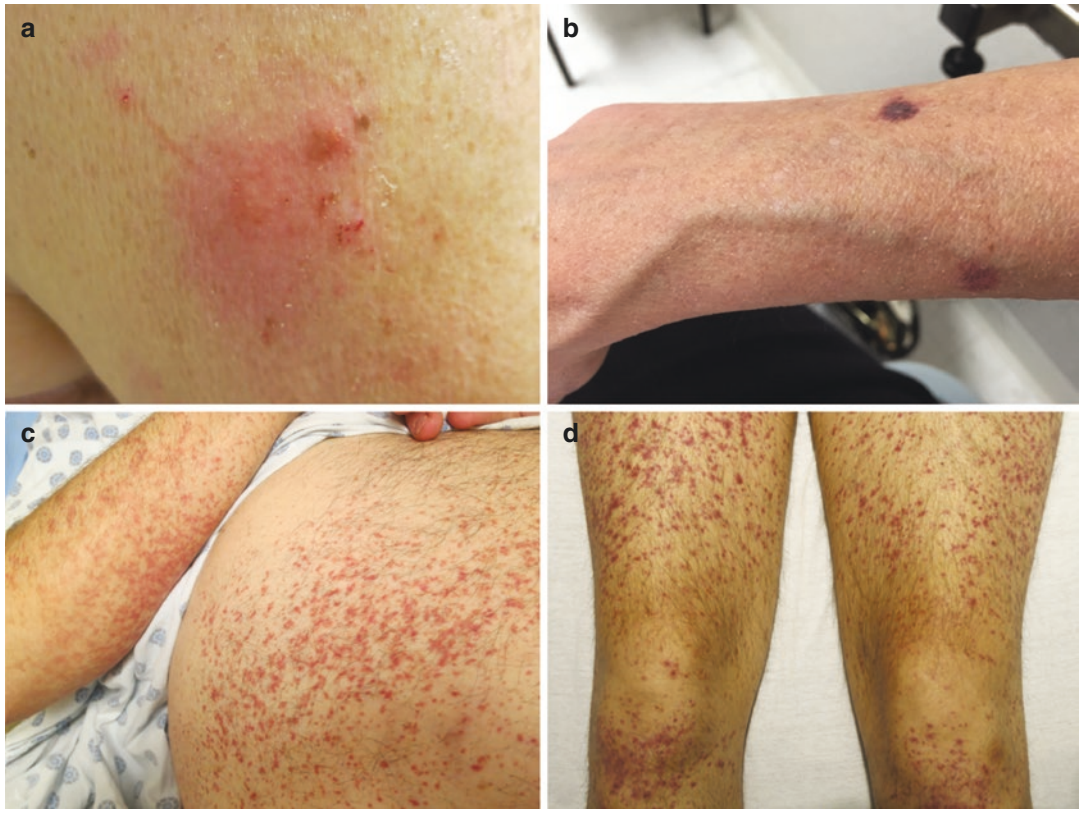

Fig. 8.4 Various "mimickers" that may be mistaken for vasculitis clinically or histologically. (**a**) Arthropod bites and (**b**) Actinic purpura that showed leukocytoclastic vasculitis on biopsy; (**c**) Extensive pigmented purpuric dermatosis clinically mimicking small vessel vasculitis; and (**d**) Viral eruption mimicking palpable purpura but with no histologic evidence of vasculitis

Review of Systems and Medical History

A thorough history and review of systems is essential for separating patients with skin-limited vasculitis from those with systemic involvement or underlying disease. In skin-limited vasculitis, extracutaneous organ manifestations are lacking, although fever and fatigue may occur [5].Review of systems should include fever, weight loss, or other constitutional symptoms; arthralgias or arthritis; myalgias; abdominal pain, melena, or hematochezia; cough, hemoptysis, or dyspnea; hematuria; sinusitis or rhinitis; paresthesias, weakness, or foot drop (Table 8.3); and any other symptom suggestive of additional organ-system involvement with vasculitis. Pertinent positives can direct further targeted workup. Additionally, because disease processes may develop over time, and patients with or without extra-cutaneous manifestations of vasculitis may have identical skin findings on initial presentation, the review of systems should be repeated at subsequent visits.

In addition, a thorough history of the timing and onset of the eruption and other symptoms should be obtained. Questions should review potential triggers, including preceding infectious symptoms, ingestion of prescribed and non-prescribed drugs, and comorbid medical conditions.

Table 8.3 Possible signs and symptoms of systemic vasculitis with corresponding laboratory evaluation

Organ System	Symptoms	Signs	Work-up
Constitutional	Fever, chills, sweats, weight loss, fatigue	Fever	CBC, ESR, CRP, ANA
HEENT	Hair loss, dry eyes/mouth, eye pain, oral/nasal ulcers, sinusitis, epistaxis	Iritis, sinus tenderness, otitis, lymphadenopathy	ANCA, ophthalmologic exam, laryngoscopy
Cardiovascular	CP, orthopnea, dyspnea	Gallop, rub, edema	ECG, echocardiogram
Pulmonary	SOB, cough, hemoptysis, wheeze	Crackles, wheeze, rhonchi	Chest x-ray
Gastrointestinal	Abdominal pain, melena nausea/vomting	Abd tenderness, hepatosplenomegaly	Fecal occult blood, liver function tests
Musculoskeletal	Joint pains, muscle aches	Joint swelling	X-ray, ultrasound
Renal	Hematuria, frothy urine	Hypertension,lower extremity edema	BMP, urinalysis, urine sediment, UProt/Cr
Neuro	Paresthesias, numbness, weakness	Foot/wrist drop, reflexes, sensation, proprioception	Nerve conduction studies

*Signs, symptoms, and laboratory evaluation **highlighted in red** are suggested essential elements of initial basic screening

ANA antinuclear antibodies, *ANCA* antineutrophilic cytoplasmic antibodies, *BMP* basic metabolic panel, *CBC* complete blood count, *CP* chest pain, *CRP* C-reactive protein, *ECG* electrocardiogram, *ESR* erythrocyte sedimentation rate, *SOB* shortness of breath, *UProt/Cr* urine protein to creatinine ratio

Laboratory Studies

No standard protocol for laboratory studies exists in cutaneous vasculitis. Rather, laboratory evaluation should be guided by clinical signs and symptoms, with the goal of identifying the underlying cause and extent of systemic organ involvement. Not every test needs to be ordered in every patient. False positive or irrelevant results can be confusing. Here we review the utility of certain laboratory tests in vasculitis to help guide clinicians in ordering.

Basic Tests That Should Be Ordered in All Patients

Initial tests that should be ordered in all patients include urinalysis with microscopic examination, serum creatinine, and complete blood count (CBC). When the presentation is straightforward and typical of cutaneous small-vessel vasculitis, there is a recent medication or infectious trigger, and the review of systems is unremarkable, no further laboratory testing may be required.

Urinalysis with Microscopic Examination

Urinalysis is the single most important laboratory test for evaluating a patient with suspected vasculitis, because renal disease is seen in many vasculitides, and its presence is likely to change management. Though common and potentially devastating, renal vasculitis rarely results in signs or symptoms until end-stage renal failure occurs. Therefore, urinalysis (including microscopic examination) should be performed in all patients with suspected vasculitis, and it should be repeated periodically as long as active vasculitis is present in another organ system, such as the skin.

If any blood is present on routine urinalysis, the urine should be evaluated for the presence of red blood cell casts and dysmorphic red blood cells by someone trained to do so (usually a nephrologist). Note that this is not a routine test performed by laboratory technicians.

The presence of protein on urinalysis can be more fully evaluated using a spot urine protein / creatinine ratio or a 24-hour urine protein study. Any significant amount of protein should prompt referral to a nephrologist and initiation of steroids or other systemic therapy.

While small-vessel vasculitis affecting the glomeruli produces hematuria and proteinuria, urinalysis may be normal in patients with vasculitis of medium-sized renal vessels (PAN). Instead, they may present with hypertension, creatinine elevation, and abnormal angiographic findings (see below).

Basic Metabolic Panel

Serum creatinine and estimated glomerular filtration rate (GFR), both measured in the basic metabolic panel (BMP), are other important measures of renal function. Serum creatinine must always be interpreted in relation to the patient's baseline creatinine, if known, as well as in the context of patient age, sex, ethnicity, and habitus. Creatinine may fall within the normal range yet be abnormal for the patient in question. A small change in creatinine may in fact represent a large decrease in GFR; for example, a change from 0.4 mg/dL to 0.8 mg/dL is a 50% decrease in GFR.

Complete Blood Count

A CBC should be ordered in all patients. Anemia or thrombocytosis consistent with systemic inflammation may suggest vasculitis not limited to the skin. Significant anemia can result from gastrointestinal vasculitis with bleeding. An elevated eosinophil count may suggest untreated EGPA (Churg-Strauss).

Other Laboratory Tests Useful in Select Cases

Liver Function Tests

Vasculitis can involve the liver, but significant hepatic dysfunction is rare. Baseline values are useful in preparation for administration of treatments that may be hepatotoxic.

Acute Phase Reactants

Measurement of acute phase reactants are of limited value in the evaluation and management of vasculitis affecting the skin. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are elevated in most patients with vasculitis, but these tests are neither sensitive nor specific for the diagnosis of vasculitis. Inflammatory markers are frequently elevated in conditions which mimic vasculitis, and elevation (or absence thereof) is not necessarily predictive of systemic involvement or disease activity. There is variable correlation between the levels of acute phase reactants and disease activity.

Serologic Tests of Autoimmunity

"Autoimmune serologies" can play an important role in the diagnosis of vasculitis, but they require interpretation and by themselves are not diagnostic. All positive and negative results should be interpreted in the context of clinical signs and symptoms as well as biopsy results. Inappropriate ordering of these tests can be a source of confusion and misdiagnosis.

Antineutrophilic Cytoplasmic Antibodies (ANCAs)

ANCA testing is an essential component of evaluating patients for ANCA-associated vasculitides. However, it can also be a source of confusion. ANCA testing involves two laboratory methods: i) immunofluorescence testing, which results in staining patterns interpreted by a technician as cytoplasmic (C-ANCA), perinuclear (P-ANCA), or atypical; and ii) ELISA testing for two specific autoantigens, proteinase-3 (PR3) or myeloperoxidase (MPO). To interpret ANCA testing properly, clinicians must understand the test characteristics of both the immunofluorescence and ELISA testing.

Immunofluorescence testing is less specific than ELISA testing for ANCA-associated vasculitis, and the combination of the two tests provides the highest diagnostic utility. Although the C-ANCA pattern is fairly specific for granulomatosis with polyangiitis (Wegener's, GPA) and MPA, it can be seen in patients without vasculitis. The P-ANCA immunofluorescence pattern is much less specific, and positive tests can be seen in all forms of ANCA-associated vasculitis, as well as in a series of other autoimmune diseases or drug exposures. Atypical ANCA patterns have no specific diagnostic significance.

ELISA testing for ANCA, by contrast, provides a considerably higher degree of diagnostic specificity for vasculitis. Anti-PR3 ANCA, especially in combination with C-ANCA positivity by immunofluorescence, is extremely specific for ANCA-associated vasculitis. The combination of positive tests for P-ANCA and anti-MPO antibodies is also fairly specific for ANCA-associated vasculitis. Importantly, positive tests for ANCA, including by ELISA, can be seen in situations not involving vasculitis, such as bacteremia (anti-PR3) and certain drug exposures (anti-MPO). Patients presenting with dual positivity (both C-ANCA and P-ANCA positive) should be suspected of having a drug-induced vasculitis (e.g., levamisole-induced vasculitis / vasculopathy with cocaine use).

The current standard of care when ANCA testing is desired in the evaluation of vasculitis is to test for ANCA by both immunofluorescence and ELISA; the combination of C-ANCA with anti-PR3 or P-ANCA with anti-MPO is considered a positive result. Ultimately, ANCA testing confirmed with ELISA is most useful in the appropriate clinical context, where signs and symptoms are suggestive and histology shows vasculitis. It is reasonable to order such testing in patients presenting with skin vasculitis, especially in those with chronic or recurrent lesions or concerning systemic symptoms with no obvious cause.

Anti-Nuclear Antibodies

Testing for anti-nuclear antibodies (ANA) and related antibodies is warranted in evaluation of vasculitis if there is suspicion for systemic lupus or Sjögren syndrome as an underlying cause. In both conditions, the vasculitis typically affects small vessels. As in the case of ANCA, ANA testing has its limitations; while extremely sensitive, it is not specific for lupus, and a positive result must be interpreted in the context of relevant signs and symptoms. A low-titer test for ANA (e.g., 1:80 or 1:160) is often a false positive or clinically irrelevant. Other than testing for ANA and anti-SSA, testing for antibodies to additional nuclear antigens such as double-stranded DNA and Smith/RNP should only be performed if the ANA is positive and systemic lupus remains a consideration.

Rheumatoid Factor

In nations with access to modern therapies for rheumatoid arthritis, rheumatoid vasculitis has become an extremely rare manifestation of this disease, as it is usually associated with long-standing, severe rheumatoid arthritis. Such patients may have small-medium vessel manifestations, such as digital infarcts, ulcers, and mononeuritis multiplex. Since rheumatoid factor (RF) is positive in >95% of patients with rheumatoid

vasculitis [24], the absence of a positive RF is useful to exclude this form of vasculitis in patients with arthritis. However, the presence of RF is not specific for any form of vasculitis.

RF testing is sometimes useful as a screening tool for mixed cryoglobulins and cryoglobulinemic vasculitis. Routine testing for RF measures the IgM version of RF, which is one of the types of cryoglobulins present in most cases of Type II and III, mixed cryoglobulinemia [25]. Because testing for cryoglobulins can be difficult and unreliable (see below) and typically takes a few days to complete, testing for RF may be a useful first step in patients in whom cryoglobulinemic vasculitis is suspected.

Complement Levels

C3 and C4 serum complement levels measured during a flare may be low in certain types of vasculitis, such as urticarial vasculitis, cryoglobulinemic vasculitis, or rheumatoid vasculitis, and may signal more significant systemic involvement. Complement levels are also commonly low in the setting of systemic lupus erythematosus.

Complement testing is particularly important in the setting of suspected urticarial vasculitis, to differentiate hypocomplementemic from normocomplementemic urticarial vasculitis. Low complement levels in patients with urticarial vasculitis increase the likelihood of systemic lupus and extra-cutaneous manifestations of disease.

Cryoglobulins

Cryoglobulins are cold-precipitable circulating immunoglobulins that form immune complexes that can deposit in vessels and damage end organs, resulting in cutaneous and systemic manifestations of vasculitis. Testing for cryoglobulins is best performed during vasculitis flares. The blood sample should be kept warm (37 °C) and transported to the lab immediately after being drawn. The test is limited by a high false-negative rate due to improper collection and processing techniques; therefore, repeated testing should be performed (along with RF testing) when suspicion for cryoglobulinemic vasculitis is high. Patients with suspected cryoglobulinemic vasculitis should also be tested for hepatitis C virus, hepatitis B virus, and human immunodeficiency virus, and for the presence of paraproteins by serum and urine protein electrophoresis and/or immunofixation.

Serum Protein Electrophoresis (SPEP) and Immunofixation

A monoclonal gammopathy or lymphoproliferative disorder can rarely cause small-vessel vasculitis, including IgA vasculitis, cryoglobulinemic vasculitis, or non-specific small-vessel vasculitis. In such cases, identification of a clinically significant monoclonal disease is crucial to establish the correct diagnosis and treatment plan. SPEP can be used to look for evidence of a paraprotein. Immunofixation is a more comprehensive screen for clonal immunoglobulins that may be performed if suspicion is high. Other abnormalities may be noted on CBC or blood smear.

Serologic Tests for Infections

Hepatitis C virus is strongly associated with cryoglobulinemic vasculitis, as are, to a lesser extent, other persistent viral infections, such as HIV and hepatitis B. Prior to widespread introduction of vaccination against hepatitis B virus, this infection was cause of the majority of cases of PAN and still must be considered in patients who live in or have emigrated from countries without comprehensive vaccination programs. It is also reasonable to test for hepatitis B and C infection in patients presenting with skin vasculitis of otherwise unclear etiology as well as prior to starting many immunosuppressive agents.

Cases of small-vessel vasculitis and IgA vasculitis may be secondary to infection with *Streptococcus* and a host of other bacterial and viral infections. When there is history of an expo-

sure or symptoms of current or past infection, targeted testing (e.g., ASO titer) may be indicated.

Urine Drug Screen

Exposure to certain illegal recreational drugs may cause vasculitis, presenting with isolated palpable purpura, retiform purpura, necrosis, and ulceration. Levamisole, an additive currently found in much of the "street" cocaine sold in the United States and some other countries, may cause a fairly unique vasculitis and vasculopathy leading to necrotic lesions on the extremities (often non-distal areas), ears, cheeks, and nose. Levamisole-associated vasculopathy is also frequently associated with positive tests for both anti-PR3 and anti-MPO ANCA (dual positivity in the same patient), as well as cytopenias. Because its half-life is only 5.6 hours, confirming the presence of levamisole in urine samples can be difficult, but its use is currently so widespread that its presence in cocaine can be assumed in most cases [26].

Cocaine itself is not clearly associated with vasculitis but can lead to severe midline nasal destructive lesions (due to inhalation) as well as positive tests for ANCA, thereby mimicking granulomatosis with polyangiitis (Wegener's). Methamphetamines are also a well-established, but rare, cause of vasculitis.

Diagnostic Imaging Studies in the Evaluation of Possible Vasculitis

Chest Imaging

Data are lacking to guide imaging in the evaluation of vasculitis. However, in our experience, chest x-ray is not typically a useful screening test in patients with vasculitis who do not have pulmonary symptoms. If a patient has cough, dyspnea, or other pulmonary symptoms, however, a computed tomography (CT) scan is indicated to detect subtle but important changes, such as nodules or cavities, which may be evidence of pulmonary vasculitis. Patients with suspected or known GPA, MPA, or EGPA, should undergo baseline screening CT scan even if asymptomatic. Intravenous iodinated contrast is usually not needed for chest CT imaging in case of suspected vasculitis and is sometimes contraindicated (e.g., in vasculitis with renal involvement). The exception is when evaluating for pulmonary embolus, a potential complication of ANCA-associated vasculitis.

Sinus and Upper Airway Imaging

Sinus and upper airway involvement are common complications of GPA and EGPA. CT of the sinuses and neck are valuable in these conditions and can complement direct examination by an otolaryngologist. Head CT or MRI can be used to study not only the sinuses but also the mastoid air spaces and the orbits, both areas of involvement in ANCA-associated vasculitis.

Catheter-Based Angiography, MR Angiography, and CT Angiography

Angiography is an important diagnostic tool in cases of suspected medium- or large-vessel vasculitis. In the proper setting, angiography demonstrating aneurysmal dilation and stenosis of abdominal or renal vessels is pathognomonic of systemic polyarteritis. Angiography of extremities may also reveal the presence of stenosis associated with gangrenous lesions. The choice of modality for angiography may depend on the availability and expertise at a given medical center. However, the use of catheter-based studies is becoming increasingly uncommon, as the resolution of CT or MR angiography continues to increase, including for distal extremity vessels. MR angiography has the advantage of avoiding radiation exposure and use of iodinated contrast. These advantages may compound when serial imaging is needed.

Nerve Conduction Studies and Electromyography

These studies may provide objective evidence of neuropathy and are appropriate in patients with

neurological signs and symptoms consistent with a vasculitis affecting medium-sized vessels, such as wrist or foot drop (i.e., mononeuritis multiplex).

Workup and Treatment of Specific Vasculitides with Skin Involvement

Cutaneous Small-Vessel Vasculitis/ Small-Vessel Vasculitis of the Skin

Diagnostic Evaluation

Punch biopsies of lesional skin should be performed for H&E and direct immunofluorescence to confirm the diagnosis. In most cases, the vasculitis is skin-limited, but systemic vasculitis and important underlying disease states should be ruled out. A thorough review of systems and physical exam should be performed. Basic labs are indicated, including CBC, BMP, and (most importantly) urinalysis with microscopic examination. Ordering of additional studies should be guided by signs or symptoms of systemic disease or when vasculitis is recurrent or refractory with unknown cause.

Treatment

Skin-limited small-vessel vasculitis is typically self-limited. Systemic therapy is indicated for severe, intractable, or recurrent disease (8–10% of such cases become chronic and recurrent [27]). There is a dearth of high-quality data to direct management. Colchicine, dapsone, and azathioprine are commonly used. Additional medications, including methotrexate, leflunomide, biologics, and other agents can be considered for refractory disease. Use of these drugs for this indication is supported only by case series and expert opinion [28].

IgA Vasculitis

Diagnostic Evaluation

The approach to diagnosis and evaluation is initially the same as in any other patient presenting with palpable purpura. Biopsies for H&E and direct immunofluorescence should be performed to help confirm the diagnosis. A thorough review of systems and exam are paramount given the high rate of systemic involvement, with particular attention to the gastrointestinal and renal systems. Urinalysis and blood pressure should be monitored weekly while the rash is present, then monthly for up to 6 months, as late glomerulonephritis can occur [29]. Serum creatinine should also be monitored over time. Most patients with nephritis will develop urinary abnormalities within 4 weeks [30].

Treatment

The treatment of IgA vasculitis remains challenging, with no drug, including systemic glucocorticoids, found to change the course of disease or prevent organ damage. Many cases of IgA vasculitis can be treated with observation alone, especially for skin-limited disease. A Cochrane review did not find evidence of benefit from prophylactic use of glucocorticoids to prevent systemic complications, but some experts advise the use of glucocorticoids when severe skin, gastrointestinal, or renal disease occurs [31]. Glucocorticoid-sparing forms of immunosuppression have been attempted, but there is no evidence that these agents are effective. Fortunately, most cases of IgA vasculitis are self-limited, and long-term renal complications are uncommon. However, some (mostly adult) patients develop recurrent bouts of skin disease over months to years, associated with progressive decline in renal function.

Urticarial Vasculitis

Diagnostic Evaluation

Patients with a hive-like eruption that follows an atypical course, as above, or patients with "red flag" symptoms such as fever or arthralgias, should undergo skin biopsy [32]. In urticarial vasculitis, skin biopsy reveals vasculitis involving small vessels. Evaluation should include a thorough review of systems and physical exam,

as well as basic labs, urinalysis with microscopy, and other studies dictated by the findings on presentation.

C3 and C4 levels (ordered during a flare) are critical. Patients with normal complement levels usually have an idiopathic small-vessel vasculitis that is skin-limited and self-resolving, best considered a subset of cutaneous small-vessel vasculitis. Those with low C3 and C4 (hypocomplementemic urticarial vasculitis syndrome) are more likely to have systemic lupus (50%), arthritis, obstructive pulmonary disease, gastrointestinal symptoms, and glomerulonephritis [33].

Treatment

Treatment depends on severity and symptoms. Colchicine, dapsone, pentoxifylline, hydroxychloroquine, and immunosuppressive agents such as prednisone, mycophenolate, azathioprine, and rituximab have all been used, but data from controlled clinical trials are not available [34, 35].

Cryoglobulinemic Vasculitis

Diagnostic Evaluation

RF is a good surrogate marker for the presence of cryoglobulins, positive in the vast majority of those with cryoglobulinemic vasculitis, often at extremely high levels. Cryoglobulins should be drawn during a flare and kept at 37 ° C from the time of collection through delivery to the testing lab. The test should be repeated if negative when clinical suspicion is high. Complement levels are usually low. Tests for hepatitis C virus, hepatitis B virus, human immunodeficiency virus, and SPEP should be checked to look for possible triggers. Testing and evaluation for lupus, Sjögren syndrome, or lymphoma should be pursued, as appropriate.

Treatment

It is important to address underlying hepatitis C infection or another disease process, if identified. Idiopathic, refractory, or severe disease should be treated with systemic agents such as high-dose glucocorticoids and rituximab [36, 37]. Acute, severe disease may be treated with glucocorticoids and plasma exchange.

Granulomatosis with Polyangiitis (Wegener's)

Diagnostic Evaluation

GPA is associated with a positive test for ANCA in 90% of cases, typically C-ANCA/anti-PR3 but sometimes P-ANCA/anti-MPO. ANCA-negative GPA is relatively uncommon but does occur and can be quite severe [38]. Diagnosis of GPA requires careful clinicopathologic correlation. A biopsy showing leukocytoclastic vasculitis with extravascular granulomas is classic but not always present. In the right clinical context, skin vasculitis in combination with a positive test for ANCA may be diagnostic for GPA.

Treatment

Most cases of GPA are treated by inducing remission with a combination of high-dose glucocorticoids and either cyclophosphamide or rituximab [38], followed by maintenance therapy with methotrexate, azathioprine, or rituximab. Less severe disease can be treated with glucocorticoids and methotrexate. Disease relapse is common. Targeted agents, including the oral C5a receptor inhibitor avacopan, as well as lower dose glucocorticoid regimens, are under investigation [39].

Microscopic Polyangiitis

Diagnostic Evaluation

MPA is most frequently associated with positive tests for P-ANCA/anti-MPO, but patients may be positive for C-ANCA/anti-PR3. Lesional skin biopsy reveals necrotizing leukocytoclastic vasculitis in the reticular dermis. MPA lacks the granulomatous inflammation and upper respiratory tract involvement of GPA and the eosinophilia of EGPA. However, it is important to understand that cases that appear to be MPA may

progress to include additional manifestations that lead to reclassifying patients with GPA.

Treatment

Treatment of MPA is similar to that of GPA. Relapses are common, though less so than in GPA.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Diagnostic Evaluation

Peripheral eosinophilia is characteristic. Approximately 40% of EGPA patients are ANCA positive, most frequently (75%) P-ANCA / MPO. Necrotizing granulomatous vasculitis with eosinophils may be seen on biopsy.

Treatment

Treatment of non-severe EGPA may include glucocorticoids alone. However, cyclophosphamide is usually added in the setting of neuropathy, refractory glomerulonephritis, myocardial disease, severe gastrointestinal disease, or CNS involvement—the manifestations that make up the "five-factor score" that signify poor prognosis. A case series indicated that rituximab may be a useful agent for EGPA, particularly for patients who test positive for ANCA [40]. Mepolizumab, an anti-IL-5 antibody, showed efficacy in a randomized trial and is now approved by the US Food and Drug Administration for treatment of EGPA [41].

Polyarteritis Nodosa

Diagnostic Evaluation

Biopsies are crucial for diagnosis and reveal fibrinoid necrosis of medium-sized vessels, as well as surrounding small vessels, with thrombosis and neutrophilic inflammation. Skin biopsies must be deep enough to sample the subcutaneous tissue where medium-sized vessels reside. Computed tomography (CT) or conventional angiography can reveal characteristic microaneurysms along the renal, gastrointestinal, and other vessels of the viscera [42]. Patients with PAN are ANCA-negative. Until recently, most cases of PAN were considered secondary to infection with hepatitis B virus. With the widespread adoption of vaccination for hepatitis B virus, the prevalence of PAN has been markedly reduced. Testing for hepatitis B and C virus infection should be done in all suspected cases of PAN.

Treatment

Hepatitis B or C infection should be treated, if present. Early diagnosis and treatment are important to avoid mortality. High-dose glucocorticoids are the mainstay of therapy of PAN. Cyclophosphamide may be added for patients with serious systemic involvement. Maintenance therapy or treatment of less severe disease may be accomplished with methotrexate or azathioprine. Skin-limited disease (cutaneous PAN) may respond to alternative therapies such as dapsone or colchicine.

Referral and Coordination of Care

Given the wide variety of potential systemic manifestations, appropriately partnering with colleagues in multiple specialties is an essential part of the diagnosis and management of vasculitis. Biopsy of an affected organ can provide diagnostic confirmation in the right clinical context. Because the skin often is the most easily accessible affected organ, dermatologists should make every effort to accommodate referrals for possible vasculitis while active skin disease is present.

Conversely, if evidence of serious systemic disease is present, patients should be referred to a clinician (usually a rheumatologist) experienced in the management of vasculitis with systemic immunosuppressive therapies. Additional expert care of individual organ systems by nephrologists, pulmonologists, and other providers can be essential. Effective communication among members of the care team is vital to ensure timely diagnosis and treatment.

Summary

The cutaneous eruption may be the first and most visible manifestations of vasculitis. The size and morphology of lesions help predict the clinical syndrome, but a suspected diagnosis of vasculitis should always be confirmed with biopsy and close clinicopathologic correlation. Once the diagnosis of vasculitis is confirmed, important systemic manifestations or underlying associated disease states must be identified quickly to limit morbidity and mortality. Inappropriate use and interpretation of laboratory tests may result in confusion and delay. A systematic and sensible approach to evaluation begins with a thorough review of systems and physical exam, followed by important basic labs (CBC, BMP, UA with microscopic examination) and other selected testing dictated by the review of systems and exam. A familiarity with disease presentations and test characteristics may improve diagnostic accuracy and enable timely initiation of appropriate therapy. Coordination of care between dermatology, rheumatology, nephrology, and other experts is an essential component of successful diagnosis and management of vasculitis.

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