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The color of skin: purple diseases of the skin, nails, and mucosa

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Abstract The color purple can be seen in several types of eruptions including inflammatory dermatoses like lichen planus, infectious dermatoses like ecthyma gangrenosum, neoplasms like Kaposi sarcoma, and vasculitis and vasculopathy. The current review focuses on the clinical appearance, pathophysiology, and treatment of several vasculitides and vasculopathies including capillaritis, cutaneous small-vessel vasculitis, immunoglobulin A (IgA) vasculitis, cryoglobulinemia, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, polyarteritis nodosum, warfarin-induced skin necrosis, heparin-induced thrombocytopenia, purpura fulminans, antiphospholipid antibody syndrome, calciphylaxis, levamisole-induced vasculopathy, and thrombotic thrombocytopenic purpura. Dermatologists play a central role in treating patients with cutaneous vasculitis and vasculopathy and may have the opportunity to facilitate identification of systemic disease by diagnosing cutaneous vasculitis and vasculopathy.

Introduction

The morphology of skin lesions is of central importance in dermatologic diagnosis. One of the key components of morphology is color. The color of a skin lesion can aid the astute clinician in categorizing an eruption or even in arriving at the correct diagnosis. The color purple may present in the skin for various reasons including vascular pathology in the form of vasculitis and vasculopathy, inflammatory skin disease such as lichen planus, neoplasms such as Kaposi sarcoma, or infections such as ecthyma gangrenosum.[1–4]

The present review will focus on vasculitis and vasculopathy. Vasculitis is characterized by inflammation of the endothelium leading to damage and sometimes destruction of blood vessels. Vasculopathies are, in contrast, a more heterogeneous group of disorders in which there is vascular damage occurring by a mechanism other than direct immune system activity against endothelial cells. This may involve platelet pathology, factors related to endothelial cells, abnormalities in the clotting cascade, and several other mechanisms.[5]

Vasculitis

Capillaritis

Capillaritis, also known as pigmented purpuric dermatoses (PPDs), is a group of chronic and relapsing disorders characterized by petechial, erythematous, and hyperpigmented

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macules on the lower extremities.[6,7] The etiology is unknown, however, associations have been found with several medications, venous hypertension, exercise, chemical ingestion, and contact allergy to dyes.[6,8]

Histologic manifestations

Histologically, PPDs are characterized by extravasation of erythrocytes and hemosiderin deposition.[6] A perivascular infiltrate of lymphocytes and macrophages surrounding superficial small blood vessels with endothelial cell swelling and narrowing of lumina is commonly seen. Overt vasculitis is not usually present.[6]

Clinical manifestations

There are a number of clinical patterns of PPD: (1) progressive pigmented purpuric dermatosis (Schamberg disease); (2) purpura annularis telangiectodes (Majocchi disease); (3) lichen aureus; (4) pigmented purpuric lichenoid dermatosis (Gougerot-Blum syndrome); and (5) eczematid-like purpura of Doucas and Kapetanakis, along with more rare presentations such as linear or granulomatous, and familial forms.[6]

Schamberg disease is the most common form, occurring in both children and adults, and is characteristically described as 1- to 2-mm erythematous macules resembling grains of cayenne-pepper.[6,7] Majocchi disease initially may appear as bluish-red macules, however, the central part of the lesion fades and there is peripheral extension, creating an annular morphology.[6,7] Lichen aureus is a more localized, persistent, intensely pruritic eruption that classically presents as golden-brown lichenoid purpuric papules.[7] Gougerot-Blum syndrome typically presents as small lichenoid papules that coalesce into plaques.[6] Finally, eczematidlike purpura of Doucas and Kapetanakis has a more extensive clinical presentation of diffusely eczematous purpuric patches that are severely pruritic.

Differential diagnosis

The differential diagnosis for PPD includes venous stasis dermatitis, purpuric forms of allergic contact dermatitis, drug eruptions, or mycosis fungoides.[7] Laboratory investigations are commonly unremarkable; however, a laboratory workup may be done depending on the clinical scenario.

Treatment

Treatment is limited. The use of compression stockings and emollients may be beneficial, and when pruritus is present, topical corticosteroids and antihistamines may provide symptomatic relief. Psoralen with ultraviolet A phototherapy has also been effective in some cases of Schamberg disease.[9] Other therapies that have been reported with some success include narrow band ultraviolet B, rutocide 50 mg twice daily with ascorbic acid 1000 mg daily, colchicine 0.5 mg twice daily, and pentoxifylline 300 to 400 mg daily.[6,10–12]

Cutaneous small-vessel vasculitis

Cutaneous small-vessel vasculitis (CSVV) most classically and commonly presents as palpable purpura.[13] Several terms have been utilized to describe this clinical entity including cutaneous leukocytoclastic vasculitis, leukocytoclastic vasculitis, hypersensitivity vasculitis, and cutaneous leukocytoclastic angiitis.[13,14] There is marked variability in the clinical and histologic features of CSVV, making universal classification schema for this entity a challenge. Two commonly used schema are the American College of Rheumatology classification criteria and the Chapel Hill Consensus Conference (CHCC) nomenclature system (Table 1).[14] The CHCC was recently updated to include a focus on skin-limited or skin-dominant forms of vasculitis.[15] CSVV in this modified CHCC includes the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitidies, such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA); and non–ANCA-associated vasculitides, including Henoch-Schönlein purpura (HSP) and essential mixed cryoglobulinemia.[15] Waldenström hypergammaglobulinemic purpura, urticarial vasculitis, erythema elevatum diutinum, rheumatoid nodules, reactive leprosy, and septic vasculitis also fall under the CSVV category.[16]

Etiology and pathogenesis

Vasculitis is characterized by vessel wall injury, which may be mediated by the immune system, toxins, or infection.[17] The pathogenesis of the majority of CSVVs involves immune-complex deposition and a type III hypersensitivity reaction.[17] Antigens present in the setting of infections, medications, or connective tissue disease act as haptens and are bound by antibodies, forming immune complexes. These immune complexes become lodged and trapped within vessels and activate the classic and alternate complement cascades, leading to vessel destruction and extravasation of erythrocytes, which produce palpable nonblanching purpura.[13] Approximately 50% of the time, the etiology underlying this pathogenesis is idiopathic, with 30% to 40% of cases being postinfectious or medication-related, and 15% to 20% due to autoimmune connective tissue disease (systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, or dermatomyositis) or inflammatory conditions; 5% of cases are due to underlying malignancy.[13,16,18]

Insulin, penicillin, sulfonamides, and β-lactam antibiotics are some of the most frequent drugs associated with CSVV, and among infectious causes, upper respiratory infections (such as group A β-hemolytic streptococci) are commonly implicated.[13,16]

Clinical manifestations

CSVV affects individuals of all ages, but it is more common in adults than in children, who are more often (90%) affected by HSP.[19] The clinical hallmark of CSVV is palpable purpura (Figure 1); however, a multitude of possible

Table 1 CHCC and ACR definitions of disease entities *

Condition	ACR criteria	CHCC
IgA vasculitis	1. Palpable purpura 2. Age at onset < 20 y 3. Bowel angina 4. Granulocytes within blood vessel wall on histopathology Presence of two criteria: sensitivity 87% and specificity 88%	IgA1-dominant immune deposits in vasculitis of small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may be present.
Cryoglobulinemia		Cryoglobulin immune deposits in vasculitis of small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, kidney, and peripheral nerves are often involved.
Granulomatosis with polyangiitis	1. Nasal or oral inflammation 2. Chest X ray showing nodules, infiltrates (fixed) or cavities 3. Microscopic hematuria or red cell casts in urine 4. Granulomatous inflammation on histopathology (within vessel wall or perivascular) Presence of two criteria: sensitivity 88.2% and specificity 92%	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small-to-medium vessels (capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is commonly observed.
Eosinophilic granulomatosis with polyangiitis	1. Asthma 2. Eosinophilia > 10% on WBC count differential 3. Mononeuropathy (including multiplex) or polyneuropathy 4. Nonfixed pulmonary infiltrates 5. Sinusitis 6. Histopathology demonstrating a blood vessel with extravascular eosinophils Presence of four or more criteria: sensitivity 85% and specificity 99.7%	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent in the setting of glomerulonephritis.
Microscopic polyangiitis		Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be seen. Necrotizing glomerulonephritis is common. Pulmonary

Table 1
(*continued*)

Condition	ACR criteria	CHCC
		capillaritis often occurs. Granulomatous inflammation is absent.
Polyarteritis nodosa	1. Weight loss > 4 kg 2. Livedo reticularis 3. Testicular pain or tenderness 4. Myalgias 5. Mononeuropathy or polyneuropathy 6. Hypertension (diastolic blood pressure > 90 mm Hg) 7. Elevated blood urea nitrogen or serum creatinine levels 8. Hepatitis B 9. Arteriographic abnormality 10. Presence of granulocyte or mixed leukocyte infiltrate in an arterial wall on biopsy. Presence of three or more criteria: sensitivity of 82.2% and specificity of 86.6%	Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. ANCA-negative.

ACR, American College of Rheumatology; ANCA, antineutrophil cytoplasmic antibodies; CHCC, Chapel Hill Consensus Conference; IgA, immunoglobulin A; WBC, white blood cell.

* Definitions were obtained from primary published literature of the Chapel Hill Consensus Conference and American College of Rheumatology.[97–102]

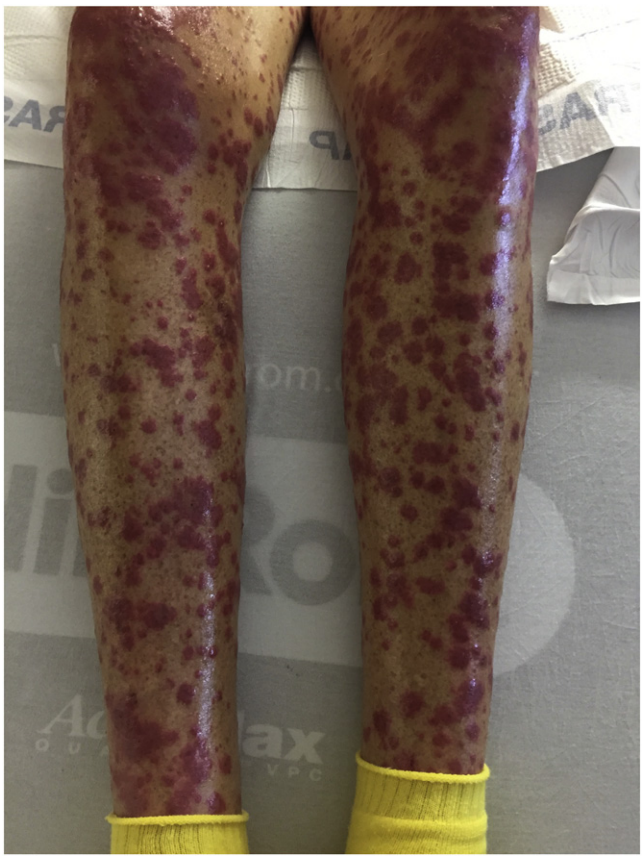

Fig. 1 Cutaneous small-vessel vasculitis. Purpuric macules and papules (palpable purpura) on the lower extremities. Courtesy of Dr Lawrence Charles Parish.

morphologies exist, including urticaria, purpura (Figure 2), hemorrhagic vesicles, nodules, ulcers, livedo reticularis or racemosa, cutaneous necrosis, and digital gangrene.[14,16,19] Patients may experience pruritus, pain, or burning.

Although it may not be palpable at the onset, all patients have purpura that may evolve, and even present with subcutaneous edema, as the process continues. Lesions appear first and predominate on the legs and ankles. Other dependent areas or areas under local pressure are also preferentially affected. The palms and soles, face, and mucous membranes are usually spared, and if involved, may suggest more severe disease or underlying systemic vasculitis.[16,19]

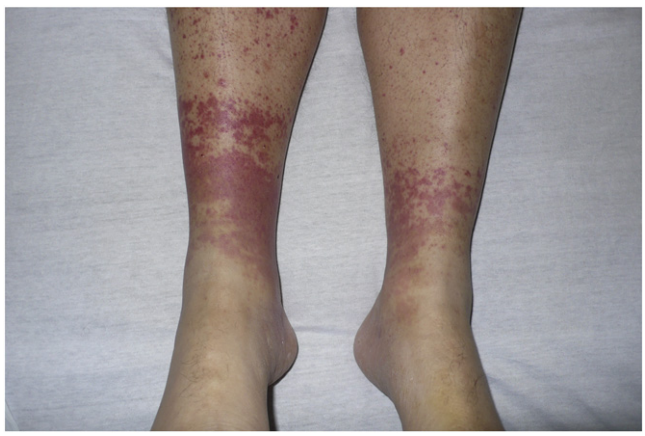

Fig. 2 Cutaneous small-vessel vasculitis. Erythematous macules and patches on the distal lower extremities. Courtesy of Dr Lawrence Charles Parish.

CSVV may be acute and self-limited, resolving in less than 6 months, which is often seen with drugs or an infectious trigger. It may also relapse and remit, as is seen in HSP and several connective tissue disease–associated CSVV. Finally, it can be chronic and unremitting, usually seen in cryoglobulinemia, hypergammaglobulinemia, and malignany.[19]

Histologic manifestations

Histologically, a neutrophilic infiltrate of superficial and middermal small blood vessels, accompanied by nuclear debris, extravasated red blood cells, and fibrinoid necrosis is commonly observed (Figure 3). Other features present on histology may narrow the differential diagnosis, such as eosinophilia, for example, which may suggest drug-induced CSVV.[13,16]

Differential diagnosis

Owing to the vast etiologies that may manifest as CSVV, the differential diagnosis is wide. All subtypes of CSVV or systemic vasculitides should be considered. Cryoglobulinemia, ANCA-associated vasculitis, arthropod bites, thrombocytopenia, platelet dysfunction, PPDs, erythema multiforme, and septic emboli are also part of the differential diagnosis for CSVV.[13]

Laboratory studies

A skin biopsy should always be performed to evaluate patients presenting with possible CSVV. The timing and location of the biopsy, as well as the type of biopsy, are critical for accurate diagnosis. A lesion that has been present for 18 to 48 hours is ideal, as this is the time of neutrophilic infiltration of the vessel wall and surrounding hemorrhage. After 24 hours, macrophages and lymphocytes will begin to replace neutrophils, and the histopathology may be nonspecific.[14,19] Biopsies should be obtained from nonulcerated sites or, if not possible, from the edge of a superficial ulcer.[19] The type of biopsy—shave, punch, or excisional—is generally determined by the depth of suspected involvement. Subcutaneous tissue may be required to rule out etiologies with deeper dermal involvement such as malignancies or connective tissue disease.[13,14,19] A second biopsy should be sent for direct immunofluorescence evaluation. The absence of immune complexes, termed pauci-immune vasculitis, is expected in GPA, EGPA, and MPA. Immunoreactant deposition, such as the presence of immunoglobulin A (IgA) deposits, can help to greatly narrow the differential diagnosis, and indicate the potential for systemic involvement.

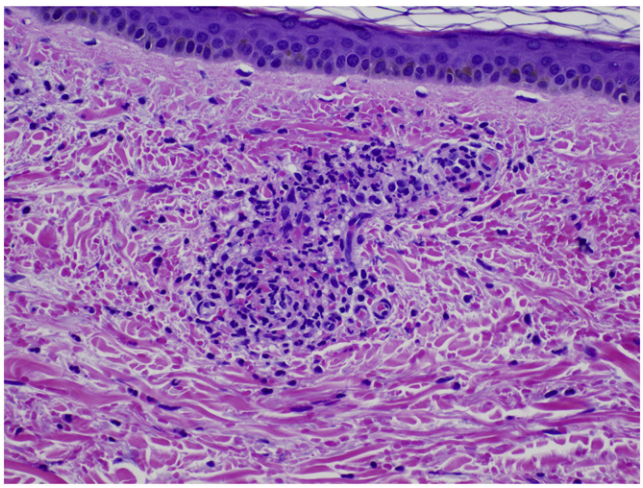

Fig. 3 Leukocytoclastic vasculitis. Superficial dermal blood vessels with neutrophilic infiltrate, neutrophilic debris, fibrin deposition, and extravasated red blood cells (hematoxylin and eosin, 40 x). Courtesy of Dr Lu Chen and Dr Nooshin K. Brinster.

Significant morbidity can result from systemic involvement of vasculitis; therefore, careful evaluation of the presence and severity of systemic disease is essential. There is no standard protocol for laboratory workup, however, the aim should be to elucidate the underlying cause and extent of organ involvement. A complete blood count, basic metabolic panel, urinalysis, liver function tests, hepatitis B and C serologies, along with infectious serologies, a rheumatologic workup (antinuclear antibody [ANA] and rheumatoid factor [RF]), and fecal occult blood testing are reasonable tests for an unclear clinical presentation.[13,20] Tests such as cytoplasmic-ANCA (c-ANCA) for GPA may also be helpful in patients with suspected systemic vasculitis.[16] A positive result, however, is not diagnostic of systemic vasculitis; 60% of patients with CSVV have a positive ANCA, and ANCAs can be positive in patients with other systemic inflammatory or pulmonary processes that mimic vasculitis.[19]

Treatment

For patients with a single self-limited episode, management involves removal of the inciting cause, and symptom alleviation with leg compression and elevation, topical corticosteroids, antihistamines, and nonsteroidal anti-inflammatory drugs (NSAIDs).[14] For patients with chronic and refractory vasculitis or severe cutaneous disease, systemic therapies may be required. Systemic corticosteroids, colchicine, and dapsone are among the first-line therapies.[14] Second-line therapies include immunosuppressive agents. Some algorithms recommend starting with mycophenolate mofetil, and then escalating to azathioprine. Furthermore, if the disease is recalcitrant, methotrexate can be considered.[14] Immunosuppressive therapies should be strongly considered in cases of CSVV that are rapidly progressive and uncontrolled with corticosteroids.[14,16] Other treatments that have been reported but are not routinely used are fibrinolytic agents, hydroxychloroquine, intravenous immunoglobulin, and rituximab.[14,16]

IgA vasculitis

IgA vasculitis, otherwise known as HSP, is an immune-complex small-vessel vasculitis with IgA-dominant immune deposits.[21] The diagnostic criteria have been somewhat controversial, but generally a mandatory criterion is purpura or

petechiae with lower extremity predominance in conjunction with a minimum of one out of four of the following criteria:

- diffuse abdominal pain with acute onset
- histopathology showing leukocytoclastic vasculitis or proliferative glomerulonephritis, with predominant IgA deposits
- arthritis or arthralgia of acute onset
- renal involvement in the form of proteinuria or hematuria.[22,23]

Etiology and pathogenesis

The etiology of the disease remains largely unknown, but it is often associated with preceding bacterial or viral infections (most frequently upper respiratory infections). Medications, tumors, hematologic malignancies, and vaccinations are among other potential underlying causes.[24] Like CSVV, the pathogenesis involves an abnormal immune response to one of these aforementioned factors that eventually leads to IgA, and later complement component 3 (C3), immune-complex deposition in small vessels of the skin, and sometimes joints, gastrointestinal tract, and kidneys.[22,24]

Clinical manifestations

Greater than 90% of patients with HSP are under 10 years of age.[22] It affects 10 to 20 per 100,000 children per year, whereas 0.8 to 1.8 of 100,000 adults are affected every year.[24] Adults, however, are more likely to have systemic involvement, whereas the disease is commonly self-limited in the pediatric population.[24] Approximately half of the time, HSP will be preceded by an upper respiratory infection.[22]

The eruption typically presents as petechiae and palpable purpura (Figure 4), mostly on the lower extremities and buttocks.[22] Arthralgias are very common, and occur in approximately two-thirds of cases.[25] Abdominal pain is also fairly common, and manifests as colicky pain that is the result of ischemia and edema.[25] Renal involvement initially presents as microscopic hematuria. Children with an abnormal urinalysis within the first 6 months of diagnosis require long-term follow-up, as they are more likely to develop renal failure 20 years after diagnosis compared with those with normal urinalysis.[19]

Although the diagnosis of HSP does not necessarily require a skin biopsy in children with a classic clinical presentation, a biopsy should be performed in adults, as well as in children for whom the clinical presentation is atypical. The histologic features of HSP are those of a leukocytoclastic vasculitis of small vessels. Direct immunofluorescence showing IgA and C3 deposited in vessel walls is diagnostic for IgA vasculitis (Figure 5).[22]

Differential diagnosis

The differential diagnosis for HSP includes other types of vasculitis (hypersensitivity vasculitis, urticarial vasculitis, mixed cryoglobulinemia, ANCA-associated vasculitis, CSVV, thrombocytopenic purpura, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, connective tissue diseases (systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disorder, dermatomyositis, antiphospholipid antibody syndrome), septicemia, papular-purpuric gloves-and-socks syndrome, and disseminated intravascular coagulation.[23]

Laboratory studies

Laboratory workup may involve confirmation of a normal platelet count and coagulation studies. Urinalysis and serum creatinine should be obtained, especially in adults with confirmed IgA vasculitis, due to the higher rates of renal involvement.[19]

Treatment

The mainstay of treatment is to alleviate clinical manifestations, as the disease course is usually benign. Rest, analgesia with acetaminophen or other non-NSAID pain relievers, topical corticosteroids, and compression may make patients

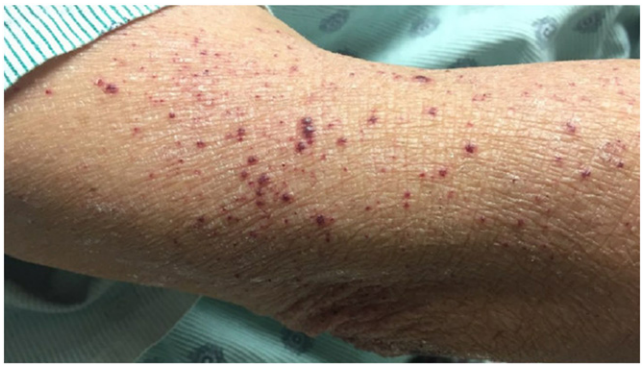

Fig. 4 IgA vasculitis. Purpuric papules and petechiae. IgA, immunoglobulin A. Courtesy of Dr Loren D. Krueger.

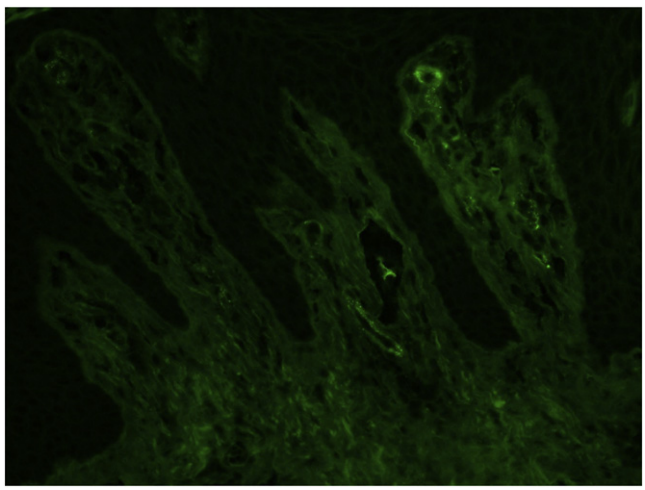

Fig. 5 IgA vasculitis. Direct immunofluorescence (40 x) demonstrating granular IgA deposition in blood vessel walls. IgA, immunoglobulin A. Courtesy of Dr Lu Chen and Dr Nooshin K. Brinster.

more comfortable. For more severe disease, corticosteroids or immunosuppressive medications may be necessary. Corticosteroids have been controversial, and several studies have found that although patients respond well initially, they do not significantly reduce the rates of renal complications on a population level.[26,27] However, they may still be used in severe cases with gastrointestinal involvement or proliferative glomerulonephritis.[24] Other treatments with variable response and response sustainability include immune modulating treatments such as colchicine, dapsone, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, and rituximab.[25]

Cryoglobulinemia

Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures less than 37°C and redissolve upon rewarming. The presence of cryoglobulins in serum is referred to as cryoglobulinemia, and cyroglobulinemic vasculitis refers to patients with clinical manifestations related to cryoglobulins.[28] There are three types of cryoglobulins:

- Type I consists of monoclonal immunoglobulin, mostly either immunoglobulin M (IgM) or immunoglobulin G (IgG).
- Type II are a mixture of monoclonal IgM and polyclonal IgG.
- Type III are a mixture of polyclonal IgM and IgG.

Types II and III are referred to as "mixed cryoglobulinemias" because they have IgG and IgM components.[28]

Etiology and pathogenesis

The pathogenesis of type I cryoglobulinemia differs from types II and III in that type I is truly a vasculopathy as a result of hyperviscosity from high concentrations of paraproteins, leading to sludging and vascular occlusion.[29] Type II and III rely on B-cell stimulation and expansion, the understanding of which has come mainly from hepatitis C virus (HCV) infection, because this is responsible in most cases. HCV viral particles bind to the protein CD81 on the surface B cells and enter the cell. Polyclonal expansion of marginal zone B cells occurs, resulting in the development of immunoglobulins with RF activity.

Subsequent loss of B-cell regulation results in a B-cell clone that produces monoclonal antibodies.[28,29] There are various etiologies in which these pathologic processes are present. Malignancy, particularly B-cell lymphoproliferative diseases, are associated with cryoglobulinemias. Type I is reported in patients with Waldenström macroglobulinemia, multiple myeloma, or chronic lymphocytic leukemia.[28] Infections are another common etiology, with HCV being especially associated with type II cryoglobulinemia.[28] Cryglobulinemia may also be caused by an underlying autoimmune disease such as Sjögren syndrome or systemic lupus erythematosus. Nearly 10% of cases of mixed cryoglobulinemia are regarded as idiopathic.[28]

Clinical manifestations

Clinically, the most common presentation is the triad reported in 80% of patients at disease onset[28]: (1) purpura, (2) arthralgia, and (3) weakness. Cutaneous manifestations are frequently observed in patients with cryoglobulinemia.[30] Small petechial to purpuric macules or papules on the lower extremities are common, and may also involve the abdomen. In some patients, lesions can be seen on the head or mucosal surfaces, which may suggest type I cryoglobulinemia.[31] Given the systemic nature of the disease, other organ systems may display signs of cryoglobulinemia, either secondary to hyperviscosity or vasculitis. Clinical manifestations may include headache, nonspecific clinical manifestations common to vasculitides such as fever, weakness, fatigue, myalgias, and arthralgias, and renal abnormalities, such as proteinuria, microscopic hematuria, red blood cell casts, and renal failure. Less commonly, patients may also experience pulmonary involvement or myocardial vasculitis.[28]

Histologic manifestations

Histologically, type I cryoglobulinemia is characterized by noninflammatory thrombosis on biopsy of skin, kidney, or nerves.[29] The mixed cryoglobulinemias tend to be associated with small- or medium-vessel vasculitis. Skin biopsy of palpable purpura demonstrates a leukocytoclastic vasculitis.[28,29]

Differential Diagnosis

The differential diagnosis includes vasculitides of small- and medium-sized vessels (IgA vasculitis, hypersensitivity, ANCA-associated, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis), vasculitides associated with infection or underlying connective tissue disease, thrombotic and embolic disorders (antiphospholipid syndrome, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome).

Laboratory studies

Cryoglobulin testing is essential to demonstrate cryoglobulins in serum. Blood should be collected in prewarmed syringes and tubes, transported, clotted, and centrifuged at 37°C to 40°C, ensuring that the temperature never falls below 37°C.[28] The serum should then be stored at 4°C for up to 7 days, as precipitation of type I cryoglobulins occurs within hours, whereas mixed can take days.[28] Quantification of the cryocrit (amount of cold precipitable protein in serum sample after centrifugation at 4°C, expressed as percentage) and immunofixation of the cryoprecipitate can correlate with the severity of clinical manifestations, and identify the type of cryoglobulin, respectively. Other laboratory tests appropriate to the clinical context should be obtained and may include C3, complement component 4 (C4), RF, and HCV testing.

Treatment

Treatment may involve conventional immunosuppression, antiviral treatments, and biologic therapies.[28] Systemic

corticosteroids can help to control the disease rapidly in patients with moderate to severe cryoglobulinemic vasculitis. Immunosuppressive medications, such as cyclophosphamide, azathioprine, and mycophenolate mofetil, can aid in rapid disease control but should ideally be tapered and discontinued after 2 to 3 months. Cryoglobulinemia associated with HCV benefits from antiviral therapies. B-cell depletion with rituximab is a promising approach to cryoglobulinemia.[28] In one study of patients with mixed cryoglobulinemia, rituximab treatment resulted in significant clinical improvement regardless of HCV status, with complete or partial remission in 74% of purpura, up to 87% of nonhealing vasculitic leg ulcers, and 44% of the peripheral neuropathy with two regimen: 1 g on 2 days every other week for 18 patients; intravenous infusions of 375 mg/m^2 of rituximab, once per week for 4 weeks for 59 patients; and six infusions of 375 mg/m^2 per week for 4 weeks, plus 375 mg/m^2 monthly for 2 months for 10 patients.[32]

Granulomatosis with polyangiitis

GPA, formerly known as Wegner granulomatosis, is a systemic, necrotizing vasculitis associated with the presence of ANCA directed against proteinase 3 (PR3).[33] Features that define this entity are evidence of a necrotizing granulomatous inflammation of the upper and lower respiratory tracts (sinuses and lungs) with necrotizing vasculitis of small-to-medium-sized vessels. Necrotizing glomerulonephritis is also common.[33]

Etiology and pathogenesis

The pathogenesis involves generation of ANCA against PR3 (c-ANCA) in 80% of patients with GPA, and against myeloperoxidase (MPO) and perinuclear ANCA (p-ANCA) 10% of the time.[34] The mechanism of neutrophil expression that leads to autoimmunity remains poorly understood.[35] It is thought to stem from environmental or infectious triggers that result in an inflammatory response and ANCA production in genetically susceptible individuals.[34] Patients also tend to have elevated B lymphocyte stimulating factors, leading self-reactive B lymphocytes to mature into durable plasma cells that secrete ANCAs. ANCAs cause neutrophils and monocytes to generate and release reactive oxygen species, proteases, and other cytokines that eventually activate the alternate complement cascade and further inflammation, leading to necrotizing systemic vasculitis and granulomatous inflammation.[34,36]

Clinical manifestations

Patients typically present with systemic findings, such as malaise, myalgias, arthralgias, anorexia, and weight loss.[34] Cutaneous manifestations may consist of palpable purpura, papules, ulcers, vesicles, necrotizing ulcers, subcutaneous nodules, papulonecrotic lesions, livedo reticularis, and petechiae.[37] Mucocutaneous manifestations may also present in the form of oral ulcers or oral granulomatous lesions.[34]

Histologic findings

The most common histopathologic finding is that of leukocytoclastic vasculitis, sometimes with a marked neutrophilic inflammatory infiltrate.[37,38] Cutaneous manifestations of GPA are generally accompanied by other common disease findings. Ear, nose and throat signs, particularly nasal sinus involvement (sinusitis, damage of the facial cartilage with deformities causing a saddle nose or perforation of the nasal septum, the palate, or the pinna of the ear) are present in 70% to 100% of cases at diagnosis.[33] Lung involvement typically includes pulmonary hemorrhage or parenchymal nodules.[33] Microhematuria and proteinuria may signify renal involvement, which is most commonly focal segmental necrotizing glomerulonephritis.[33] Involvement of the peripheral nervous system presents as mononeuritis multiplex, whereas ocular damage may include scleritis, corneal ulcerations, and retinal vasculitis.[33]

Differential diagnosis

The differential diagnosis for GPA includes EGPA and MPA, as they are pathologically indistinguishable. Asthma and eosinophilia may help to distinguish EGPA from GPA, and these two may be distinguished from MPA by granulomatous inflammation that usually affects the respiratory tract, which is absent in MPA. Other small- and medium-vessel vasculitides, including those mentioned previously should also be considered. Concurrent glomerular disease unrelated to a positive ANCA is also possible, including membranous nephropathy, lupus nephritis, or IgA nephropathy.

Laboratory studies

In addition to a skin biopsy, laboratory workup should include ANCA testing by immunofluorescence to identify c-ANCA, p-ANCA, and atypical ANCA, and by enzyme immunosorbent assays (ELISA) to measure PR3-ANCA and MPO-ANCA.[34,39] Serum creatinine and urinalysis should be obtained to assess for renal involvement. Other routine laboratory tests may be unremarkable, however, considerations include an ANA, antiglomerular basement membrane antibodies, C3 and C4, cryoglobulins, infectious serologies, or liver function tests to exclude other processes.

Treatment

Treatment includes cyclophosphamide and glucocorticoids; alternatives would be azathioprine, leflunomide, methotrexate, and mycophenolate mofetil.[40] In less severe cases, corticosteroids with methotrexate is preferred, versus more severe cases in which corticosteroids are used in conjunction with rituximab. When remission is achieved, patients should be maintained on a treatment regimen for 24 months.[40]

Eosinophilic granulomatosis with polyangiitis

EGPA, formerly known as Churg-Strauss syndrome, is dually categorized as a primary systemic ANCA vasculitis

and hypereosinophilic disorder.[41] According to the CHCC (2012) definition, EGPA is characterized by eosinophil-rich and necrotizing granulomatous inflammation that often involves the respiratory tract and necrotizing vasculitis predominantly affecting small-to-medium vessels of the skin and associated with asthma and eosinophilia.[42]

The American College of Rheumatology (1990) requires at least four out of six of the following for the diagnosis: (1) asthma; (2) eosinophilia > 10% of total white blood cell (WBC) count; (3) neuropathy; (4) pulmonary infiltrates; (5) sinus abnormalities; and (6) extravascular eosinophils.[42]

EGPA is divided into two main subsets of patients: (1) approximately 40% who have detectable ANCA (mostly p-ANCA) and (2) those who are ANCA-negative.[41,42]

Clinical differences exist between ANCA-positive and ANCA-negative EGPA. Positivity is associated with a predominantly vasculitic phenotype, and it is unclear whether the two also have distinct pathogenic mechanisms.[42]

Etiology and pathogenesis

The underlying pathogenesis is largely considered to be type 2 helper T lymphocyte (Th2)-mediated.[43] Other T cell responses, including those mediated by type 1 helper T lymphocyte (Th1) and helper T lymphocyte 17 (Th17) cells, are also present in addition to a reduced number of regulatory T cells during the active disease state.[44] Diverse cytokines such as interleukin (IL)-4, IL-5, IL-13, and IL-17 influence the inflammatory environment, and these may promote the eosinophilia (more than 1500 eosinophils/mm^3 or > 10% of the total WBC count) that is characteristic of EGPA.[44] Eosinophils promote inflammation, through substrates like eosinophil basic protein and eosinophil-derived neurotoxin, along with the aforementioned inflammatory cytokines that contribute to airway hyperresponsiveness and pulmonary eosinophilia.[44] Etiologic factors that underlie the pathogenesis include genetic predisposition, particularly the *HLADRB1*04* and *HLADRB1*07* alleles and the related *HLADRB4* gene, as well as environmental factors such as allergens, infections, vaccinations, and medications.[43]

Clinical manifestations

Clinically, EGPA characteristically develops in three sequential phases[42]:

- The allergic phase is a prodromal phase with asthma, allergic rhinitis, and sinusitis.
- This is followed by peripheral eosinophilia and eosinophilic tissue infiltration, organ involvement, such as lung, cardiac, and gastrointestinal involvement.[43] Lung involvement occurs in approximately two-thirds of patients.[43]
- Finally, the vasculitic phase presents as palpable purpura, peripheral neuropathy, and pauci-immune necrotizing glomerulonephritis with or without crescent formation.[42]

Histologic findings

Characteristic findings on histopathology are eosinophilic inflammatory infiltrates, extravascular granulomas, and necrotizing vasculitis.[42]

Differential diagnosis

The differential diagnosis includes other vasculitides. ANCA-associated vasculitides, such as MPA and GPA, share several features with EGPA. EGPA can be distinguished from these, as well as other vasculitides by the presence of asthma and eosinophilia.[43] Other eosinophilic disorders, such as parasitic or drug reactions should be excluded. The diagnosis of EGPA is mainly clinical.[43]

Laboratory studies

Given the appropriate clinical manifestations, laboratory findings will include marked peripheral eosinophilia, as well as ANCA positivity. Biopsy should be performed to confirm the presence of an eosinophilic inflammatory process, however, noncharacteristic histopathology does not exclude the diagnosis given an otherwise fitting clinical appearance.[43]

Treatment

Clinical trials regarding treatment of EGPA are limited.[41] Treatment typically involves corticosteroids and immunosuppressants. Corticosteroids alone are typically used in patients with less severe disease, whereas cyclophosphamide is often added for more severe presentations.[41,45] Medications targeting IL-5, such as mepolizumab, and monoclonal antibodies against immunoglobulin E, such as omalizumab, may become more widely used in the future.[45]

Microscopic polyangiitis

MPA is a systemic, pauci-immune vasculitis that was formerly considered to be a form of polyarteritis nodosa (PAN). It was segregated by the CHCC, with the main characteristic feature of MPA being small-vessel involvement, even in the presence of concurrent medium-vessel involvement.[46,47] MPA is among the family of ANCA-positive vasculitides. The etiologic factors underlying the formation of ANCAs are not entirely known; however, it is believed that a genetic propensity toward the development of an autoimmune response, compounded perhaps by molecular mimicry between microorganisms and human proteins, induces the formation of these autoantibodies.[48]

Etiology and pathogenesis

ANCAs activate neutrophils, causing them to release reactive oxygen species and enzymes that inflict endothelial damage. The ANCAs in MPA, which target MPO (p-ANCA), also induce the formation of neutrophil extracellular traps, which are further associated with the generation of anti-MPO antibodies and an autoimmune response.[48]

Clinical manifestations

Clinically, MPA manifests as a necrotizing vasculitis. Skin lesions may be the initial sign of disease in up to 30% of cases.[49] The most common cutaneous manifestation is palpable purpura, most commonly on the extremeties.[49,50] Livedo reticularis is another common manifestation along with nodular lesions.[50] Rarer presentations have included bullae, erythematous macules, erythema elevatum diutinum, oral ulcers, and a pyoderma gangrenosum-like lesions.[48,49] Outside of the cutaneous findings, renal abnormalities, most commonly a rapidly progressive glomerulonephritis, are present in almost all cases.[49] The lungs are also frequently involved, classically presenting as a diffuse alveolar hemorrhage due to pulmonary capillaritis.[49]

Histologic findings

The histologic pattern of MPA is relatively nonspecific, showing leukocytoclastic vasculitis with fibrinoid necrosis and neutrophilic infiltrates of small vessels in the dermis.[49]

Differential diagnosis

MPA must be distinguished from PAN. They can be differentiated on the basis of the vessels involved and the presence of ANCA; PAN is immune-complex mediated, and affects medium-sized vessels, whereas MPA has few or no immune deposits, features the presence of ANCAs, and affects small vessels.[46] In addition, CSVVs, such as HSP, may also be diagnostic considerations. MPA can be distinguished from these, as well, by the presence of p-ANCAs and the absence of immunoglobulin and complement localization in vessels.[51] GPA and EGPA are also on the differential for MPA; these can be ruled out by the lack of granulomatous inflammation on biopsy and involving the respiratory system, as well as the lack of eosinophilia (in the case of EGPA).[49,51]

Laboratory studies

The key to the diagnosis in MPA is biopsy.[51] Laboratory workup, however, should also include evaluation for serum ANCAs. The remainder of other testing exists to rule out other possibilities and may include a complete blood count, erythrocyte sedimentation rate and C-reactive protein, ANA, C3 and C4 levels, and hepatitis serologies. Urinalysis and serum creatinine should be obtained to assess the extent of renal involvement.

Treatment

Treatment is initially aimed at quelling disease progression and most commonly consists of systemic corticosteroids, in conjunction with either cyclophosphamide or rituximab.[46,49] For less severe disease, systemic corticosteroids can be combined with methotrexate or mycophenolate mofetil.[49] Corticosteroids and immunosuppressive drugs have improved the prognosis of patients with MPA, however, it is still associated with significant organ damage; for example, end-stage renal disease has been cited to occur in up to 30% of patients with MPA at 5 years from diagnosis.[48] It, therefore, requires prompt diagnosis and therapy.

Polyarteritis nodosa

PAN is a segmental necrotizing vasculitis of medium-sized arteries or arterioles.[52] It is divided into two major subtypes: (1) systemic PAN and (2) cutaneous PAN (CPAN).[52]

Etiology and pathogenesis

CPAN is rare and occurs more commonly in adults than children. When it develops in the pediatric population, the most common underlying etiology is group A β-hemolytic streptococcal infections. In adults, many other infections are associated with the disease, including hepatitis B and C, HIV, parvovirus B19, and *Mycobacterium tuberculosis*. Other etiologies include systemic diseases such as inflammatory bowel disease and rheumatoid arthritis, as well as certain drugs, such as minocycline.[52,53] The pathogenesis is believed to be immune-complex mediated. Etiologic factors induce production of IgM and C3, which deposit within affected arterial walls and trigger complement activation, leading to the clinical manifestations of CPAN.[54,55]

Clinical manifestations

The main cutaneous findings are: (1) nodules, (2) livedo reticularis, and (3) ulcers.[52]

The first disease manifestation is usually small nodules, more easily palpated than visualized, which are either preceded or followed by surrounding livedo reticularis.[55] Lesions are most often on the lower extremeties.[55] Approximately half of cases will be complicated by ulceration, and in such cases, a "burst" pattern of livedo reticularis around an ulcer is highly suggestive of CPAN.[55] Other less common skin findings include petechiae, purpura, cutaneous necrosis, and autoamputations.[52] Extracutaneous manifestations, such as constitutional clinical manifestations, myalgias, arthralgias, and neuropathies, may accompany skin lesions.[55] Although there is concern for CPAN progressing to systemic PAN, this has only been reported in one study, in which two out of 20 patients developed systemic PAN, and this occurred almost two decades after the initial presentation.[56]

Histologic findings

When CPAN is suspected, a deep incisional skin biopsy, including the subcutaneous tissue, should be obtained. On histopathology, CPAN shows a leukocytoclastic vasculitis in small- and medium-sized arteries of the deep dermis or hypodermis. A neutrophilic infiltrate predominates in the acute inflammatory phase. Increased lymphocytes and macrophages, with intimal proliferation and thrombosis of the artery leading to ulceration, are observed in later stages.[52,55]

Differential diagnosis

On the basis of similar clinical presentations, the differential diagnosis of CPAN includes erythema nodosum, as well as systemic PAN. These can be distinguished by histopathologic findings of septal panniculitis, and by the presence of other organ involvement (liver, kidney, heart), respectively.[55] Other vasculitides affecting small- or medium-sized vessels, such as MPA, GPA, and EGPA, must also be excluded. These can be distinguished by the fact that MPA affects the small vessels of the lungs and kidneys, and GPA and EGPA are both characterized by ANCA positivity and granulomatous inflammation.[55]

Laboratory studies

Laboratory studies largely aim to exclude systemic PAN. Complete blood count, erythrocyte sedimentation rate, liver and renal function tests, ANA, ANCA, RF, and complement levels may be helpful. In evaluation of causal factors, antistreptolysin O titers or throat swab culture, viral hepatitis serologies, tuberculosis testing, and an evaluation for other concomitant medical conditions such as inflammatory bowel disease, infection, and medication history may all be helpful in the workup.[55]

Treatment

Patients with mild CPAN often show improvement with NSAIDs alone. In patients who do not respond to NSAIDs, systemic corticosteroids are often helpful. Systemic immunosuppressants, dapsone, and colchicine, can be used in intractable cases. When CPAN is associated with streptococcal infection, treatment is primarily administration of penicillin.[57] The course of the disease tends to be chronic with spontaneous relapses, followed by remission. Overall, the disease carries a favorable prognosis with no known mortality from CPAN itself.[54]

Vasculopathy

Warfarin-induced skin necrosis

Warfarin-induced skin necrosis (WISN) is a rare, but known severe complication occurring in 0.01% of individuals who receive the drug.[58] Warfarin is an anticoagulant that inactivates vitamin K–dependent clotting factors II, VII, IX, X. It also inactivates protein C and S, which are themselves anticoagulant proteins that function primarily in the inactivation of factor Va and VIIa, rate limiting steps in the coagulation cascade.[58]

Etiology and pathogenesis

The pathogenic mechanism whereby initiation of an antithrombotic drug induces a paradoxic thrombotic phenomenon is not definitively known; nonetheless, it is believed that a rapid fall in protein C compared with the other vitamin K–dependent clotting factors with longer half-lives produces a hypercoagulable state that promotes the development of microthrombi in cutaneous and subcutaneous venules.[58,59] For this reason, congenital or acquired protein C deficiency is a risk factor for WISN. Other hypercoaguable states including obesity, perimenopausal age, hepatic disease, hyperhomocysteinemia, or congenital deficiency of protein S, antithrombin III, or factor V Leiden have also been associated with an increased risk of WISN, but to a lesser extent.[58]

Clinical manifestations

Clinically, skin lesions are preceded by parasthesias or sensations of pressure.[60] A poorly demarcated erythematous eruption then develops, followed by edema in the dermis and subcutaneous tissues, which demarcates the border of the lesions. There is progression to hemorrhagic bullae within 24 hours, signifying irreversible injury and full-thickness coagulative skin necrosis.[60,61] Most cases arise between 3 to 10 days after the initiation of warfarin therapy, with the majority occurring between the third and sixth day.[60,61] There is a predilection for lesions to occur over areas of high amounts of subcutaneous fat.[55]

Histologic findings

Diagnosis of WISN is made based on history, physical examination, and exclusion of clinical or laboratory mimickers of WISN. Although skin biopsy may not be necessary, histopathologic findings are diffuse microthrombi within dermal and subcutaneous capillaries, venules, and deep veins, with endothelial cell damage resulting in ischemic skin necrosis and marked red blood cell extravasation.[61]

Differential diagnosis

On the basis of similar clinical presentation of hemorrhagic or necrotic skin lesions, the differential diagnosis for WISN includes purpura fulminans, necrotizing fasciitis, calciphylaxis, cholesterol microemboli, and cryoglobulinemia.[61] Unlike purpura fulminans, WISN is not associated with disseminated intravascular coagulation (DIC), and is also nonpurulent, which differentiates it from necrotizing fasciitis. WISN can be distinguished from calciphylaxis and cholesterol microemboli by the histologic absence of perivascular or dermal calcifications and cholesterol deposits, respectively. In addition, vascular inflammation and arterial involvement are not known to be features of this disorder and differentiate it from primary vasculitic processes.[61] Heparin-induced thrombocytopenia (HIT) can induce skin necrosis that is histologically similar to WISN, but includes platelet thrombi, rather than fibrin thrombi seen in WISN.[61]

Laboratory studies

Given that the diagnosis of WISN is mainly clinical, basic laboratory workup, such as complete blood counts and coagulation studies, may be performed to exclude other potential causes. Notably, protein C and S concentration tests are neither sensitive nor specific and are not specifically recommended in evaluation of this condition.[58]

Treatment

The most important part of treatment relies on early diagnosis and drug withdrawal.[60] Treatment is also supportive, including fresh frozen plasma and vitamin K to restore levels of protein C and S, as well as an alternate anticoagulant, such as heparin.[61] Local therapies for necrotic skin lesions may include topical antimicrobials. Despite the best medical management, approximately half of patients with WISN will ultimately require surgical intervention with extensive debridement or amputation.[60,61]

Heparin-induced thrombocytopenia

HIT is a complication of heparin therapy characterized by thrombocytopenia and an increased risk of venous or arterial thrombosis.[62] Type I HIT, caused by the agglutinating effects of heparin on platelets, is less severe than type II, which is immune-mediated.[63]

Etiology and pathogenesis

The etiology of HIT involves antibodies that recognize complexes of platelet factor 4 (PF4) and heparin. PF4 is a positively charged platelet protein, released in high quantities at sites of platelet activation. Its physiologic function is to bind to negatively charged glycosaminoglycans on endothelial cells to promote thrombosis. PF4 has a higher affinity for negatively charged heparin than other glycosaminoglycans, therefore infusions of heparin allow for PF4-heparin complexes to form.[63] These complexes are highly immunogenic, inciting the formation of HIT antibodies (IgG antibodies to the heparin-PF4 complex).[64] It is for this reason that unfractionated heparin (UFH) has a higher propensity to induce HIT than low-molecular-weight heparin, given its larger molecular size and increased ability to cause generation of HIT antibodies.[64,65]

Once antibodies are generated, a subset of susceptible patients experience thrombocytopenia and thrombosis.[63] The pathophysiology of these complications involves binding of HIT antibodies to the FcγRIIa receptor on platelets, causing platelet activation.[65] This also generates thrombin and incites the release of procoagulant microparticles, which further activate platelets and promote formation of platelet-fibrin thrombi.[63,65]

Clinical manifestations

The clinical manifestation of HIT is typically described as a decrease in platelet count to <100,000 to 150,000 x 10^9/L or a 30% to 50% decrease in platelets from baseline, 5 to 10 days after initiating heparin therapy.[64] In a patient with previous heparin exposure, the onset of HIT may be earlier due to preexisting antibodies.[64] Patients with HIT rarely develop bleeding complications, rather various clinical presentations of thrombosis are more commonly observed. Both arterial and venous thromboses can result, including deep vein thromboses, pulmonary emboli, myocardial infarctions, thrombotic strokes, limb ischemia, and vein graft occlusions.[64] Skin involvement occurs in 10% to 20% of patients with HIT. These are the result of microvascular thromboses, beginning as erythematous patches or indurated plaques and generally developing a central black eschar surrounded by indurated erythema.[66]

Differential diagnosis

Although the differential diagnosis for thrombocytopenia is extensive, with regard to HIT, the main distinction to be made is from cutaneous delayed-type hypersensitivity responses to heparin.[66] Cutaneous delayed-type hypersensitivity reactions to heparin have a range of clinical presentations from erythema to infiltrated, sometimes scaling, blistering, or papulovesicular erythematous plaques. They may also generalize to morbilliform eruptions.[66] Early on in their course, HIT and cutaneous delayed-type hypersensitivity reactions can look very similar and have similar onset within 1 to 2 weeks.

Without the presence of clinically distinctive features (skin necrosis in HIT or pruritus in delayed-type hypersensitivity), the pretest probability of HIT should be determined.[65] The most common clinical assessment tool is the 4Ts score, taking into account thrombocytopenia, timing of the platelet fall, as previously described, the presence of thrombosis, and other potential causes of thrombocytopenia.[65] For patients with low risk of HIT (0-3), laboratory testing may not be required; however, for intermediate (4-5) or high (6-8) risk, laboratory workup is important.[65]

Laboratory studies

Laboratory workup for HIT is imperfect. Historically, HIT was diagnosed if the platelet count rebounded after heparin cessation.[64] The two main laboratory tests for HIT are antigen assays and functional assays. Antigen assays that detect the presence of HIT antibodies have a high sensitivity and are often preferred to functional assays, which detect HIT antibody immune complexes that cause platelet activation, and are more technically difficult and often not available.[65] Skin biopsy is not routinely performed, but it shows dermal microvascular thromboses, whereas cutaneous delayed-type hypersensitivity to heparin shows a perivascular mononuclear infiltrate of lymphocytes, accompanied by spongiosis and dermal edema.[66]

Treatment

Treatment includes discontinuation of all sources of heparin. Anticoagulation can be achieved subsequently with the heparinoid danaparoid or the direct thrombin inhibitors, such as lepirudin and argatroban.[66] There are several direct thrombin inhibitors available, and selection of a parenteral agent is generally based on drug availability or patient comorbities.[63] Overlap with a vitamin K antagonist, such as warfarin, should be considered only after platelet counts recover to a stable baseline or greater than 150,000 x 10^9/L, and if a patient is being treated with warfarin at the time of HIT diagnosis, reversal with vitamin K is recommended.[63]

Purpura fulminans

Purpura fulminans (PF) is a life-threatening disorder characterized by onset of progressive cutaneous hemorrhage and necrosis. There are three main settings in which PF occurs: (1) the neonatal period, commonly caused by an inherited, homozygous protein C or, rarely, protein S deficiency; (2) in conjunction with an acute infectious illness, most often with lipopolysaccharide-producing, gram-negative bacteria like *Neisseria meningitides*; and (3) postinfectious PF, occurring approximately 1 to 2 weeks after an antecedent infection involving the skin, such as varicella or scarlet fever.[67]

Etiology and pathogenesis

Although these underlying etiologies differ slightly in their presentations and pathogenesis, the mechanism whereby each of these produces PF is complex and poorly understood. Across all etiologies, there is an inciting factor that generates a shift from a state favoring anticoagulation toward procoagulation.[67] This may be a homozygous lack of protein C or S (vitamin K–dependent anticoagulants) or a "Shwartzman-like" reaction, in which endotoxin from Gram-negative bacteria provokes PF.[67,68]

Clinical manifestations

The clinical presentation of PF begins with erythematous macules that may be reversible with therapeutic intervention (Figure 6).[69,70] These lesions, however, progress rapidly to develop irregular central areas of blue-black hemorrhagic necrosis, surrounded by a thin border of erythema that fades into adjacent uninvolved skin.[70] The hemorrhage into necrotic dermis causes PF lesions to become painful, dark and raised, sometimes with vesicle or bulla formation.[70]

Each underlying cause is associated with a particular and slightly divergent clinical picture. In homozygous protein C deficiency, for example, neonates typically develop lesions in the first hours or days after birth. There is a predisposition of PF lesions to develop on the lower extremities, male genitalia, and at pressure points. Significant neurologic injuries, including cerebral venous thrombosis, periventricular hemorrhage, or blindness can present, secondary to brain or retinal hemorrhage or thrombosis.[70] PF in severe sepsis typically develops in the distal extremities and progresses proximally or becomes generalized.[70] As in neonatal purpura fulminans, acute infectious PF can be accompanied by microvascular thromboses and hemorrhagic infarction in other organs, especially the lungs, kidneys, central nervous system, and adrenal glands.[70] Postinfectious PF tends to favor the lower body and in males, the genitalia, and typically spares the distal extremities. The clinical manifestation of all forms includes a DIC-type picture with large- and small-vessel thrombosis, hemorrhagic necrosis of the skin and multiorgan failure.[70,71]

Differential diagnosis

With regard to the differential diagnosis, early lesions may be confused with traumatic purpura or with other purpuric eruptions, such as immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura (TTP), and HSP,[70] however, these conditions do not display prominent skin necrosis. Other forms of skin necrosis, including WISN, cryoglobulinemia, antiphospholipid syndrome, or paroxysmal nocturnal hemoglobinuria are on the differential, and can be distinguished from PF by the development of DIC, which is a defining feature of the disease.[67]

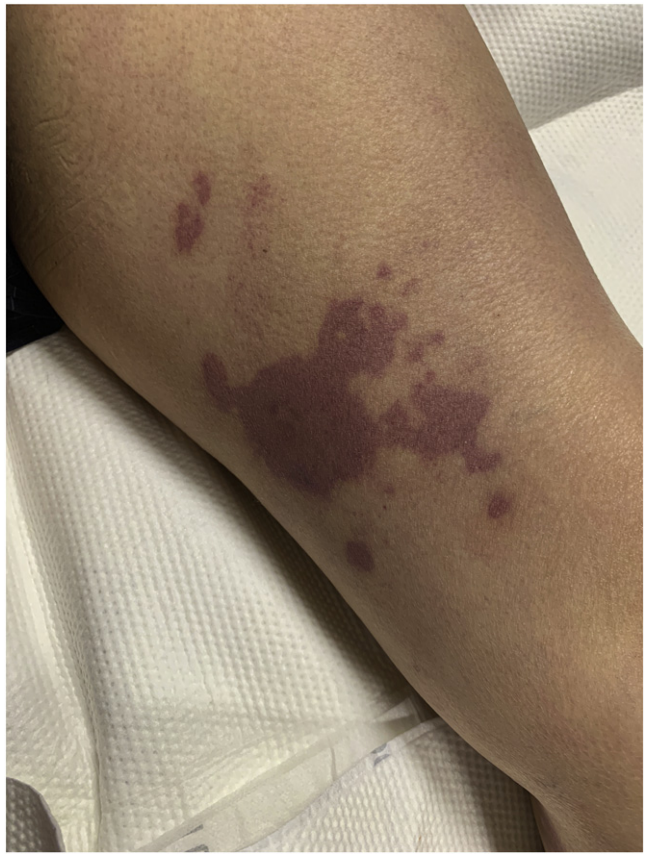

Fig. 6 Purpura fulminans. Purpuric patches on the lower extremity.

Histologic findings

Skin biopsy may not be necessary to make the diagnosis; nonetheless, histopathologic findings in PF include dermal vascular thrombosis and secondary hemorrhagic necrosis.[67] The cutaneous vessels most affected are the postcapillary venules in the subpapillary plexus of the papillary dermis, where blood flow velocity is slowest.[67] In acute infectious PF, a perivascular neutrophilic infiltrate can be seen along with the features of coagulative necrosis, which can distinguish it from other forms of PF.[67]

Laboratory studies

PF is a hematologic emergency. Surgical consultation should be sought early to monitor compartment pressures.[67] Initial laboratory evaluation that will help to guide therapeutic decisions includes a complete blood count, platelet count, prothrombin time, partial thromboplastin time, fibrinogen,

fibrin degradation products, protein C, free protein S, and antithrombin III.[70]

Treatment

Most patients are initially assumed to have underlying sepsis and are managed as such with broad spectrum antibiotics. All patients should also be emergently treated with vitamin K, fresh frozen plasma (FFP), antithrombin III, protein C, and protein S.[67,70] Although necessary, sustained protein C or S replacement by FFP can be complicated by fluid overload, allergy, and transfusion related lung injury.[70] This has led to the use of other experimental modalities. Activated protein C concentrate and antithrombin III concentrate are among the newer treatments that have shown effectiveness, though they lack prospective clinical data.[70] Anticoagulation may be necessary in cases of large vessel thrombosis, but should be used with caution. Weight-adjusted UFH, given concurrently with FFP replacement therapy to reduce bleeding risk and avoid heparin resistance caused by acquired antithrombin deficiency, is one way of achieving anticoagulation in these cases.[70] If long-term anticoagulation is required in the setting of widespread large-vessel thrombosis, vitamin K antagonists should be used with extreme caution, starting at low doses while UFH is continued for at least 48 hours after a therapeutic international normalized ratio is reached.[70]

Antiphospholipid antibody syndrome

Antiphospholipid antibody syndrome (APS) is an autoimmune disorder that leads to arterial thromboembolic events, venous thromboembolic events, obstetric complications, and thrombocytopenia due to antibodies against cell membrane phospholipids.[72,73] The most common antibodies include lupus anticoagulant, anticardiolipin antibodies, and antib2-glycoprotein I antibodies.[72] APS can be: (1) primary, occurring in the absence of other autoimmune disorders and (2) secondary, occurring with systemic lupus erythematosus, rheumatoid arthritis, or other autoimmune diseases.[73]

Etiology and pathogenesis

The etiology and pathogenesis are not fully understood. Environmental factors, such as infections, are hypothesized to induce the formation of antiphospholipid antibodies (aPL) in susceptible individuals.[74] The aPL interact with phospholipid binding proteins, the most important of which is phosphatidylserine, located on the inner surface of the cell membrane. Phosphatidylserine is exteriorized on activated or apoptotic cell membranes and has downstream effects such as cell activation, clearance of apoptotic cells, and coagulation,[74] furthermore, aPL interacting with endothelial cells may induce the expression of adhesion molecules and proinflammatory cytokines. They can also activate platelets and disrupt natural anticoagulant shields, such as annexin V.[74] All of these factors combined ultimately promote a prothrombotic state.

Clinical manifestations

In addition to the thrombotic and pregnancy complications, skin involvement is a prominent feature, occurring in 41% of patients as the initial presentation of APS.[73] Livedo reticularis (and sometimes racemosa) is the most frequently associated cutaneous manifestation.[75] Other manifestations include lower extremity ulcers, distal cutaneous ischemia, splinter hemorrhages, superficial thrombophlebitis, anetoderma, atrophie blanche, thrombocytopenic purpura, dermatographism, chronic urticaria, acrocyanosis, and alopecia.[73,76]

Differential diagnosis

The differential diagnosis of suspected APS includes other inherited or acquired thrombophilias, such as paroxysmal nocturnal hemoglobinuria and HIT. These conditions can usually be excluded on the basis of positive aPL; however, positive aPL may be present in some people who are otherwise healthy, have an autoimmune disease, or those who have been exposed to certain drugs or microorganisms. In systemic lupus erythematosus, for example, between 20% to 30% of individuals will be positive for one of the three main antibodies involved in APS.[77,78] Therefore, diagnosis requires both clinical and laboratory criteria.

Laboratory studies

The most important laboratory workup includes evaluation for aPL. Persistence for more than 12 weeks of lupus anticoagulant or medium-high titers of IgG or IgM autoantibodies to antib2-glycoprotein I or cardiolipin as detected by ELISA is required for the diagnosis of APS.[74] One of the laboratory criteria, in addition to at least one of the clinical criteria (vascular thrombosis and pregnancy complications) establishes the diagnosis of APS.[74]

Histologic findings

Skin biopsy is not always necessary, however, may be helpful in some clinical scenarios. Histologically, noninflammatory vascular thrombosis is the most frequent finding, which is nonspecific and may be seen in a variety of conditions including livedoid vasculitis, cryoglobulinemias, WISN, PF, emboli to the skin, thrombocythemia, and protein C deficiency.[75]

Treatment

The treatment of APS aims to reduce the formation of thrombi. UFH or low-molecular-weight heparin followed by long-term oral anticoagulation therapy is the most common regimen.[74] In patients with thrombosis, warfarin is used, with a recommended international normalized ratio of 3 to 4.[75]

Calciphylaxis

Calciphylaxis is a syndrome of arteriolar media calcification, leading to thrombotic ischemia, necrosis, and ulceration. Because it is common in individuals with end-stage

renal disease (ESRD), it is also sometimes referred to as calcific uremic arteriolopathy.[79]

Etiology and pathogenesis

The etiology is linked to dysfunction of the regulatory mechanisms for calcium and phosphate. The pathogenesis begins with the transformation of vascular smooth muscle cells into osteoblast-like phenotypes via hyperphosphatemia, uremic toxins, reactive oxygen species, and decrease of matrix Gla protein, a potent calcification inhibitor.[80] Vascular smooth muscle cells then promote calcification. In addition, bone morphogenetic protein 4 and osteopontin are also found in biopsies of patients with calciphylaxis, which act through reactive oxygen species and nuclear factor kappa B to contribute to calcification.[80]

Development of calciphylaxis lesions depends not only on medial calcification, but also intimal fibrosis of arterioles and thrombotic occlusion.[81] These processes occur after a period of sensitization induced by factors that favor calcification and a period of challenge such as trauma, surgery or any other event associated with an increase in inflammatory cytokines that then trigger endothelial injury in the setting of stasis and hypercoaguability.[81]

Clinical manifestations

Uremic calciphylaxis (in patients with ESRD) is differentiated from nonuremic calciphylaxis (in patients with normal kidney function or early renal disease).[82] Lesions appear similarly in both uremic and nonuremic calciphylaxis, with the exception of location. Seventy to 80% of lesions in patients with ESRD have a central distribution in adipose-rich areas of the abdomen or thighs, compared with nonuremic calciphylaxis which has a relative higher predominance of peripheral locations, such as the digits.[82] Initially, lesions may appear as mottled and netlike livedo reticularis, and then progress to livedo racemosa, and further to nonhealing stellate-shaped ulcers covered by black eschars (Figure 7).[80,81]

The diagnosis of calciphylaxis is predominantly clinical and histopathologic. In a patient with ESRD presenting with painful, erythematous, livedoid skin changes on adipose-rich areas, the diagnosis of calciphylaxis should be strongly considered.[80]

Histologic findings

For a definitive diagnosis, skin biopsy is necessary. Histology demonstrates calcification, intimal hyperplasia, and thrombosis in the subcutaneous adipose tissue and dermis.[82] This often leads to necrosis of epidermal and adipose tissue and separation between the dermis and epidermis, as well as panniculitis, proliferation of dermal endothelial cells, and extravascular calcifications.[82] Sampling error can be a problem in calciphylaxis, and many times the initial 3 to 5 mm punch biopsy that is performed may be nondiagnostic.[80,81] A von Kossa stain can be utilized to identify calcified vascular walls, which may help improve the sensitivity.[79] Excisional biopsies can be performed; however, there are risks of ulceration at the area of excision, infection, and poor healing.[81]

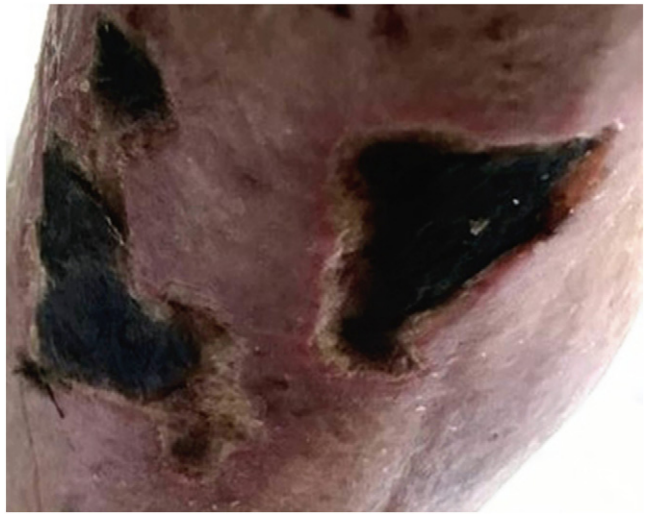

Fig. 7 Calciphylaxis. Stellate ulcers with overlying black eschars.

Differential diagnosis

The differential diagnosis primarily includes other conditions that present with livedo, including cholesterol embolism syndrome, APS, and WISN.[81] WISN is particularly difficult to differentiate clinically from calciphylaxis, because warfarin use is also associated with calciphylaxis. Timing from administration of warfarin is the key discriminator. WISN typically presents within the first 10 days of drug administration and responds quickly to warfarin cessation and heparin anticoagulation. Calciphylaxis potentially triggered by warfarin requires a prolonged period of use, 32 months on average, before lesion onset and involves persistent lesions, despite cessation of potential inciting factors.[80,83] Aside from WISN, warfarin can also induce calciphylaxis.[83] This can be differentiated from classic calciphylaxis in that warfarin-associated calciphylaxis affects the area below the knee, whereas ulcers in classic calciphylaxis are usually over adipose-rich, more proximal regions.[83] In addition, the mortality for warfarin-associated calciphylaxis is significantly less (17%) than that associated with classic calciphylaxis (50%-80%).[83] Medium- or small-vessel vasculitides, HIT, TTP, peripheral artery disease, and stasis, traumatic, or neuropathic ulcers are among other diagnoses to consider.[80]

Laboratory studies

In addition to skin biopsy, laboratory tests to evaluate for potential risk factors and to exclude other disorders that present similarly should be performed.[80] Urinalysis, glomerular filtration rate, serum blood urea nitrogen and creatinine, in addition to serum levels of parathyroid hormone, calcium, phosphorus, vitamin D, and alkaline phosphatase can be helpful in the assessment of risk factors. Appropriate laboratory tests to assess presence of infection, hypercoagulability,

inflammation, autoimmune disease and malignancy are also advised.[80] Noninvasive tests, such as plain x-rays, three phase nuclear bone scans, bone scintigraphy, and circulating fetuin-A levels may have some utility, but more data are needed to better understand their clinical utility.[81]

Treatment

Treatment of calciphylaxis should include pain control, in addition to pharmacotherapy to address causative factors. Pain control may require opioids, sometimes at high doses.[82] Wound management is also important. Whether or not surgical debridement of wounds should be pursued is controversial as the risks of exacerbating calciphylaxis and infectious complications of cutaneous ulcers must be weighed.[79]

Other options to promote wound healing include negative pressure wound therapy, hyperbaric oxygen, and skin grafting.[81] There are several options for medical pharmacotherapy, one of which is sodium thiosulfate, an antioxidant with vasodilatory properties that inhibits adipocyte calcification and blocks adipocyte-induced calcification of vascular smooth muscle cells.[82] Sodium thiosulfate administered intravenously (25 mg three times per week with hemodialysis) or intralesionally (generally diluted 250 mg/mL) and has been associated with marked clinical improvement in skin lesions, even for patients with typically poor wound healing on hemodialysis.[82,84,85]

Pharmacotherapy also aims to reduce hypercalcemia and hyperphosphatemia. This may include the use of noncalcium/nonaluminum-containing phosphate binders (sevelamer hydrochloride), bisphosphonates, calcimimetic antagonist of parathyroid hormone (cinacalcet), and selective activators of vitamin D receptors (paricalcitol).[79] Given the association between warfarin and calciphylaxis, emerging evidence suggests that apixiban is safe and potentially preferred for individuals with ESRD and calciphylaxis requiring anticoagulation.

Levamisole-induced vasculopathy

Cocaine is a local anesthetic with potent stimulant and vasoconstrictor properties, which after oral, intravenous, or inhaled administration, increases central nervous system dopamine concentrations in the synaptic cleft by inhibiting its reuptake.[86] Levamisole, initially used as an antiparasitic and immunomodulatory drug, is a nicotinic antagonist that releases glutamate and potentiates the dopaminergic effect of cocaine.[86]

In 2011, it was estimated that approximately 70% of the cocaine in the United States was adulterated with levamisole.[87] This is hypothesized to be due not only to its psychotropic properties, but also to its resemblance to cocaine, stability at high temperatures, undetectability on impurities tests, and short half-life.[86] Levamisole is responsible for the development of a constellation of clinical manifestations including agranulocytosis, neutropenia, and a tender, vasculitis-like purpuric skin eruption.[87]

Etiology and pathogenesis

The mechanism whereby cocaine adulterated with levamisole causes a vasculopathy is tied to the generation of unusually high titers of p-ANCAs directed against atypical antigens within the neutrophil granules, such as human neutrophilic enolase and not against MPO.[86] How the antibodies develop is unknown.[88] Both cocaine and levamisole induce the formation of neutrophil extracellular traps, a potential source of self-antigens, which can activate the immune system.[86,88] Priming of neutrophils leads to translocation of ANCA antigens to the cell surface, further activating neutrophils and causing increased adherence and migration. Reactive oxygen species generation and neutrophil degranulation cause small-vessel destruction.[88] Drug-mediated agranulocytosis may potentially be due to levamisole acting as a hapten, reacting with a self-peptide to cause T cell activation and a delayed hypersensitivity reaction, which has also been described for other drugs that cause agranulocytosis, such as propylthiouracil.[88]

Clinical manifestations

The characteristic skin manifestations are retiform purpuric plaques with a bright erythematous edge and necrotic center, that may progress to bullae, and are generally followed by necrosis (Figure 8).[86,87] The lesions occur suddenly and have a predilection for ears and cheeks.[87]

Histologic findings

Histologically, these lesions show a small-vessel vasculitis in the form of leukocytoclastic vasculitis.[88] Intravascular thrombi are common, along with angiocentric mixed inflammatory cell infiltrates in superficial and deep dermal vessels.[88] Direct immunofluorescence in some cases highlights antibodies and complement deposition in vessel walls, supporting an immune-complex mediated process.[87]

Differential diagnosis

The differential diagnosis includes other ANCA-associated vasculitides, from which it can be distinguished by its characteristic clinical distribution and the fact that p-ANCA levels are so high, whereas other systemic ANCA vasculitides have lower ANCA titers that are directed against a single neutrophil antigen, rather than several.[86] Secondary causes of CSVV, including medications, infections, neoplasms, and autoimmune connective tissue disorders should be considered.[87,89] Finally, cryoglobulinemias, WISN, skin necrosis secondary to HIT, immune thrombocytopenic purpura, and APS can all present similarly and maybe diagnostic considerations in cases of levamisole-induced vasculopathy.[89]

Laboratory studies

Skin biopsy is relatively nonspecific. Laboratory evaluation should include a routine urinalysis and urine toxicology screen to detect cocaine, liver and renal function tests, a complete blood count, ANCAs, aPL, and coagulation studies.[87]

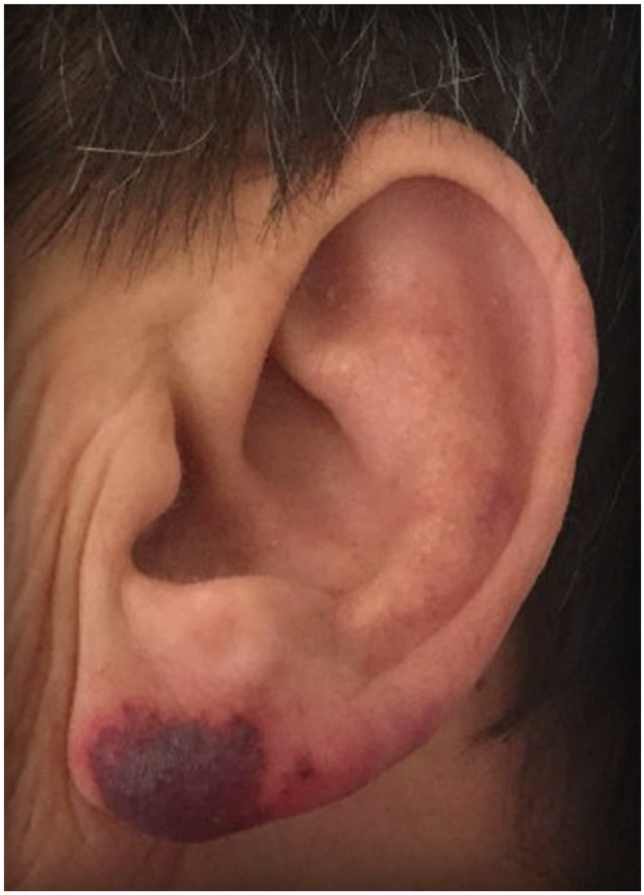

Fig. 8 Levamisole-induced vasculopathy. Ear lobe with purpuric patch with irregular border and surrounding edema and erythema. Courtesy of Dr Kristen I. Lo Sicco.

Treatment

The first-line treatment is discontinuation of cocaine use and supportive measures like wound care and antibiotics for infected lesions. Corticosteroids are reserved for individuals who do not improve with supportive measures or those with debilitating joint disease, very high C-reactive protein values or histopathology-proven vasculitis.[86] With cessation of cocaine use, lesions begin to improve within 2 to 3 weeks and neutropenia improves in 5 to 10 days, but the serological profile may persist for up to 14 months.[86]

Thrombotic thrombocytopenic purpura

TTP is characterized by thrombocytopenia in addition to platelet aggregation, widespread platelet thrombi, and microangiopathic hemolytic anemia (MAHA).[90]

Etiology and pathogenesis

The underlying cause of TTP is a deficiency of ADAMTS13, a metalloprotease involved in the cleavage of polymers of von Willebrand factor. Deficiency of this enzyme causes platelet accumulation and consumption into formation of microthrombi. The disease may be congenital or may be caused by an acquired deficiency in ADAMTS13 secondary to IgG antibody formation. Idiopathic TTP also exists.[72,90]

Clinical manifestations

The classic pentad of TTP includes: (1) fever, (2) hemolytic anemia, (3) thrombocytopenia, (4) renal impairment, and (5) neurologic manifestations.[90] This is not universal, and presentation may also include weakness, confusion, headache, nausea, vomiting and diarrhea.[91] Cutaneous manifestations of TTP are nonspecific and include petechiae and purpura. TTP has been reported to occur in concordance with several other conditions, including adult-onset Still disease, mixed connective tissue disease, dermatomyositis, and systemic lupus erythematosus.[92–95]

Differential diagnosis

The main differential diagnosis for TTP includes hemolytic uremic syndrome, a MAHA associated with Shiga toxin-producing *Escherichia coli*. Hemolytic uremic syndrome can usually be distinguished by the presence of a diarrheal illness preceding MAHA, predominant renal involvement, and plasma ADAMTS13 levels > 10 IU/dL.[91] Other thrombotic microangiopathies are also on the differential diagnosis for TTP; however, most are associated with another disease such as malignancy, organ transplantation, sepsis, or pregnancy in the case of preeclampsia and the hemolysis elevated liver enzymes low platelet count syndrome. Hematologic abnormalities, such as isolated thrombocytopenia, and ischemic manifestations of autoimmune diseases (immune thrombocytopenia, systemic lupus erythematosus, or APS) should also be considered.[96]

Laboratory studies

Laboratory screening for ADAMTS13 activity should be performed.[96] If ADAMTS13 activity is less than 10% in a fitting clinical scenario, the diagnosis of TTP is confirmed.[96] There are a variety of available methods for ADAMTS13 investigation, including ELISA, mass spectrometry, and coagulation analyzer-based assays.[91] Due to their varying availability, accuracy, and time requirements, reliable results of ADAMTS13 investigation usually cannot be made acutely in the setting of an emergency. Other laboratory results can support a clinical diagnosis.[96]

Standard laboratory analysis includes a complete blood count, notable for signs of MAHA and consumption thrombocytopenia. A high reticulocyte count, low serum haptoglobin, and elevated lactate dehydrogenase level are typical. Blood smear showing schistocytes is also characteristic.[96] Coagulation studies may be performed, however, these are usually normal. Finally, assessment for end organ damage, including renal or cardiac abnormalities, should be pursued.

Treatment

TTP is a medical emergency and treatment should be urgently initiated, usually in intensive care units. Primary

treatment is plasma exchange therapy to replace ADAMTS13 and remove the antibody. Plasma infusion therapy can be used if plasma exchange therapy is unavailable, however, the antibody persists.[90] Although there is evidence for the efficacy of rituximab, data on its use in the emergent setting is limited and, therefore, it is not typically utilized in the acute phase.[96]

Despite the presence of severe thrombocytopenia, platelet transfusion is contraindicated and will worsen the disease by facilitating the formation of thrombi.[90] Other immunosuppressive therapies for sustained remission and elimination of antibody formation may include corticosteroids, vincristine, cyclophosphamide, or cyclosporine.[91]

Conclusions

Purple lesions in the skin may represent a variety of pathologic processes, including inflammation, infection, or neoplasm. Cutaneous vasculitis and vasculopathy can both present with purple skin lesions. This review discusses the clinical presentation, pathophysiology, and treatment several of the most common and most important vasculitides including capillaritis, CSVV, IgA vasculitis, cryoglobulinemia, GPA, EGPA, MPA, and PAN and vasculopathies including WISN, HIT, PF, APS, calciphylaxis levamisole-induced vasculopathy, and TTP.

Dermatologists play a central role in treating patients with cutaneous vasculitis and vasculopathy. They have the opportunity to facilitate identification of systemic disease by diagnosing cutaneous vasculitis and vasculopathy.

Conflict of interest

The authors have no conflicts of interest to report.

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