Chapter 6
Vasculitis and Thrombotic Disorders

Keywords Leukocytoclastic vasculitis • Henoch–Schönlein purpura • Urticarial vasculitis • Wegener's granulomatosis • Churg–Strauss syndrome • Polyarteritis nodosa • Cryoglobulinemia • Coumadin necrosis • Atrophie blanche • Antiphospholipid antibody syndrome • Cholesterol emboli

This chapter will focus on different forms of leukocytoclastic vasculitis and cutaneous diseases that are the result of vascular occlusion. There are a group of entities that some consider lymphocytic vasculitides (e.g., pigmented purpuric dermatosis and perniosis), but histologic evidence of vascular damage is often subtle in entities considered lymphocytic vasculitides and some dermatopathologists do not consider them a true vasculitis. Therefore, that group of entities will not be discussed in this chapter, but some entities considered to represent lymphocytic vasculitis are discussed in the chapter on perivascular dermatitis. This first part of the chapter will focus on entities that are the result of different forms of leukocytoclastic vasculitis. Leukocytoclastic vasculitis in many respects is a reaction pattern with a perivascular infiltrate of neutrophils and evidence of vascular damage (Fig. 6.1). The second part of the chapter will discuss disease processes that occlude vessels resulting in ischemic damage, but are not associated with significant inflammation (Fig. 6.2).

Leukocytoclastic Vasculitis (Cutaneous Leukocytoclastic Angiitis)

Clinical Features

Leukocytoclastic vasculitis most commonly affects middle-aged adults, but a broad age range may be seen. The lesions present as palpable purpura usually on the lower extremities. This entity is also referred to as hypersensitivity or allergic vasculitis. The most common triggering agents are drugs or infections.

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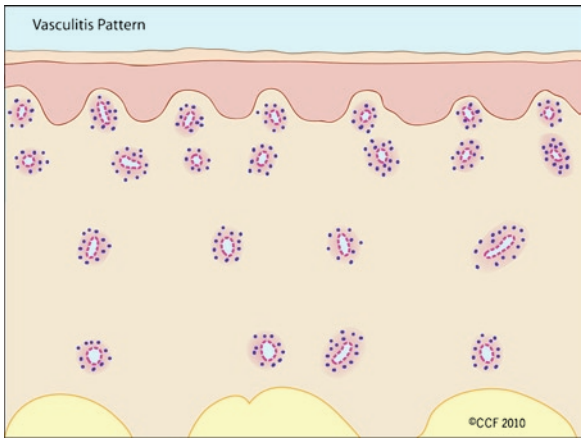

Fig. 6.1 *Schematic representation of leukocytoclastic vasculitis*. Leukocytoclastic vasculitis is characterized by a perivascular infiltrate of neutrophils with evidence of vascular damage

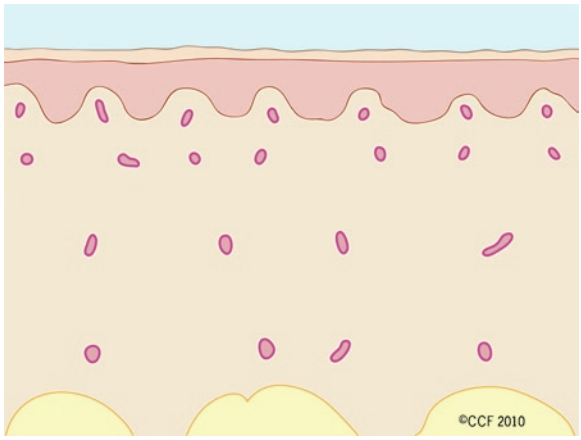

Fig. 6.2 *Schematic representation of vaso-occlusive disease*. There is thrombosis of blood vessels with little to no inflammation

Microscopic Features

The superficial vascular plexus has a perivascular infiltrate of neutrophils with fragmentation of the neutrophils resulting in nuclear dust (leukocytoclasis), extravasation of erythrocytes, and fibrin deposition in the vessel wall with or without overt fibrinoid necrosis of the blood vessels (Fig. 6.3). In reality, all of these features are not necessarily present. The histologic features are dependent on the timing of the biopsy. Early in the course, there may be a perivascular neutrophilic infiltrate with extravasation of erythrocytes, but no evident fibrin deposition or fibrinoid necrosis. Ideally, the biopsy will be from a lesion that is 24 h old. Lesions at this stage will typically demonstrate diagnostic features. After 48 h, the infiltrate is largely composed of lymphocytes. In such cases, the vessels need to be scruti-

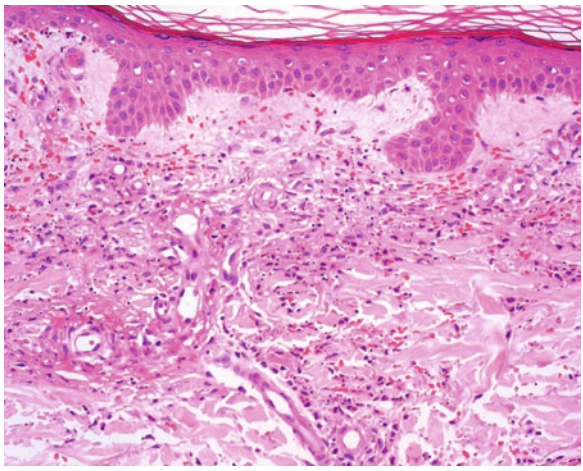

Fig. 6.3 *Leukocytoclastic vasculitis*. There is a perivascular infiltrate of neutrophils with associated leukocytoclasis, hemorrhage and fibrin deposition in the vascular walls

Table 6.1 Key microscopic features: leukocytoclastic vasculitis

- Perivascular infiltrate of neutrophils
- Fragmented nuclear debris (leukocytoclasis)
- Extravasation of erythrocytes
- Fibrin deposition in vessel walls
- Variable fibrinoid necrosis of blood vessels

nized closely for evidence of injury. Direct immunofluorescence (DIF) is often performed in the evaluation of leukocytoclastic vasculitis, mostly in the setting of possible Henoch–Schönlein purpura (HSP) (see below). In hypersensitivity type leukocytoclastic vasculitis, DIF usually demonstrates perivascular deposits of complement C3 and fibrinogen without IgA deposition. Microscopic features of leukocytoclastic vasculitis are summarized in Table 6.1.

Differential Diagnosis

The primary differential diagnosis is other, more specific forms of leukocytoclastic vasculitis that will be discussed in greater detail below. For example, HSP is histologically indistinguishable from leukocytoclastic vasculitis/cutaneous leukocytoclastic angiitis. Distinction requires DIF (see below). Systemic forms of leukocytoclastic vasculitis (e.g., Wegener's granulomatosis) tend to affect vessels in the deeper dermis as well as the superficial dermis, but may show significant overlap and be practically indistinguishable if other differentiating features are not present, such as palisading granulomatous inflammation or true granulomatous vasculitis. Changes of leukocytoclastic vasculitis may be seen as a reactive secondary process adjacent to ulcers. It is important to remember that primary leukocytoclastic

vasculitis rarely results in the formation of an ulcer despite the vascular damage. If there is a clinical history of an ulcer, the vasculitis process is likely to be secondary in nature. Practical tips for the diagnosis are summarized in Table 6.2.

Table 6.2 Practical tips: leukocytoclastic vasculitis

- Fully developed features not always present
- Early cases may show perivascular neutrophils, leukocytoclasis, and hemorrhage without significant fibrin deposition or vessels necrosis
- If epidermis is ulcerated, consider secondary vasculitis

Henoch–Schönlein Purpura

Clinical Features

HSP accounts for approximately 10% of all cases of cutaneous vasculitis and almost all pediatric cases of vasculitis (≥90%). Although primarily considered a pediatric disease, it may also be seen in adults. The clinical presentation is that of palpable purpura in addition to various combinations of arthritis, gastrointestinal involvement, and nephritis. Some patients develop chronic renal failure as a result of the renal involvement.

Microscopic Features

The histologic findings are those of a leukocytoclastic vasculitis as outlined above in the preceding section. DIF findings are the key to diagnosis. DIF will reveal perivascular deposits of IgA around both involved and uninvolved vessels in the dermis (Fig. 6.4). As a caveat, the DIF findings may not be evident in biopsies of lesions >48 h old (Table 6.3).

Differential Diagnosis

HSP needs to be differentiated from other forms of vasculitis. Typically, the differential diagnosis is a hypersensitivity type vasculitis as outlined in the preceding chapter. The histologic distinction rests on findings of perivascular IgA deposits and the appropriate clinical context (Table 6.4). Without such information, one needs to use a descriptive diagnosis of leukocytoclastic vasculitis (see sample reports).

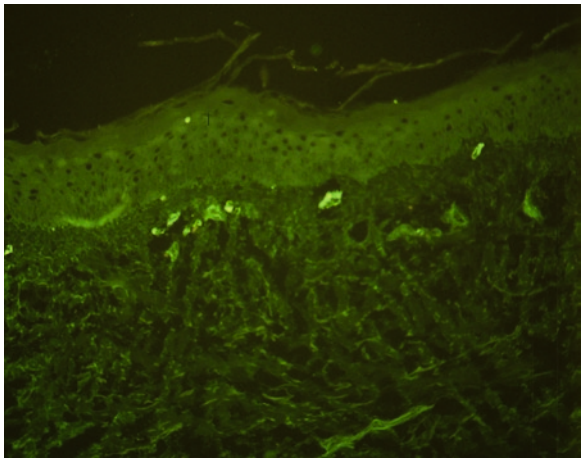

Fig. 6.4 *Henoch–Schönlein purpura (HSP) direct immunofluorescence (DIF)*. DIF demonstrate perivascular deposits of IgA characteristic of HSP

Table 6.3 Key microscopic features: Henoch–Schönlein purpura (HSP)

- Leukocytoclastic vasculitis
- Perivascular IgA deposits on direct immunofluorescence (DIF)

Table 6.4 Practical tips: Henoch–Schönlein purpura (HSP)

- Correlation with clinical history is critical
- More common in children but adult cases are also seen
- DIF requisite for definitive diagnosis

Urticarial Vasculitis

Clinical Features

Urticarial vasculitis occurs in about 20% of patients with chronic urticaria. Unlike leukocytoclastic vasculitis discussed previously, patients have urticarial plaques rather than just palpable purpura. Systemic symptoms such as fever, arthralgias, angioedema, and abdominal pain are common. Urticarial vasculitis can be subdivided into hypocomplementemic or normocomplementemic forms. Hypocomplementemic forms are associated with connective tissue disease (e.g., systemic lupus erythematosus and Sjögren's disease) and more severe disease.

Microscopic Features

Urticarial vasculitis can be quite subtle. The infiltrate tends to be sparse and the vascular damage is focal (Fig. 6.5). Perivascular eosinophils are often present, more commonly in normocomplementemic forms (Table 6.5).

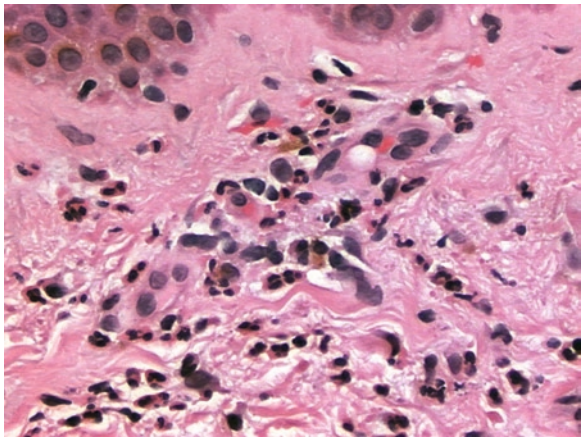

Fig. 6.5 *Urticarial vasculitis*. In urticarial vasculitis the evidence of vascular damage is often very subtle. The presence of a mild perivascular neutrophilic infiltrate and nuclear debris may be the only evidence of a vasculitis. (Courtesy of Dr. J. Andrew Carlson)

Table 6.5 Key microscopic features: urticarial vasculitis

- Subtle leukocytoclastic vasculitis
- Usually mild perivascular neutrophils with leukocytoclasis
- Evidence of vascular damage, typically focal
- Eosinophils are frequently present

Differential Diagnosis

The primary differential consideration is urticaria. Urticaria has a similar sparse infiltrate (see Chap. 5), but no evidence of vascular damage. Because of the subtler findings in most cases of urticarial vasculitis, multiple levels may be necessary to distinguish it from urticaria. In cases with a more prominent inflammatory infiltrate, other forms of leukocytoclastic vasculitis need to be considered. Knowledge of the clinical presentation of the lesions as plaques supports the diagnosis of urticarial vasculitis (Table 6.6).

Table 6.6 Practical tips: urticarial vasculitis

- Deeper levels are often required to make diagnosis
- Lesions are present as urticarial plaques
- Criteria less stringent
  - Neutrophilic infiltrate with any leukocytoclasis sufficient to suggest diagnosis

Wegener's Granulomatosis

Clinical Features

Wegener's granulomatosis (WG) is a systemic vasculitis associated with granulomatous inflammation. Necrotizing granulomas of the respiratory tract and

glomerulonephritis are commonly present, but the disorder can affect any organ system. A subset of patients with WG develops cutaneous manifestations. Most commonly, the cutaneous manifestations present as palpable purpura, but patients may also develop nodules, ulcers and digital gangrene, or polymorphic lesions with rheumatoid papules and pyoderma gangrenosum-like ulcers. Serology for c-ANCA is positive in approximately 80% of cases. Untreated, WG has a high mortality.

Microscopic Features

The microscopic features of cutaneous WG are variable. Biopsies may reveal only small vessel vasculitis. The leukocytoclastic vasculitis of WG overlaps with other forms of leukocytoclastic vasculitis. There does tend to be an involvement of vessels in the deeper dermis as well as the more superficially located vessels (Fig. 6.6). Patients may have ulcers with geographic necrosis resembling pyoderma gangrenosum. Extravascular granulomatous inflammation may also be seen. The granulomas palisade around central karyorrhectic, basophilic debris (Fig. 6.7). True granulomatous vasculitis is rare (Table 6.7).

Differential Diagnosis

The differential diagnosis depends on the clinical manifestations. The most common differential diagnosis in our experience includes other forms of leukocytoclastic vasculitis. The vasculitis of WG has an identical appearance, but the vasculitis in WG tends to be more diffuse with involvement throughout the dermis rather than concentrated in the upper half of the dermis. In this respect, WG is similar to mixed cryoglobulinemia, Churg–Strauss syndrome, and microscopic polyangiitis. In the vabsence of characteristic granulomatous inflammation, WG is rarely a purely

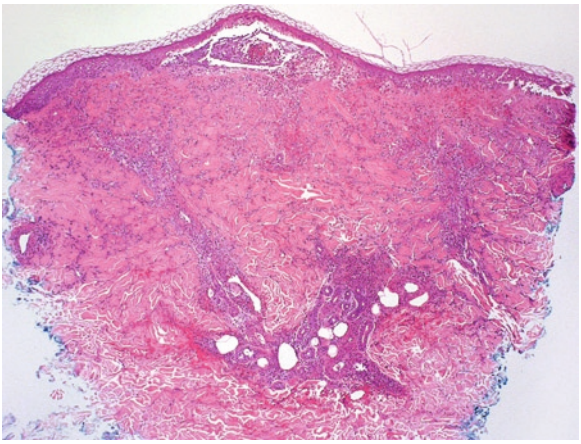

Fig. 6.6 *Wegener's granulomatosis*. In the vasculitis of Wegener's granulomatosis, there is diffuse involvement of dermal vessels

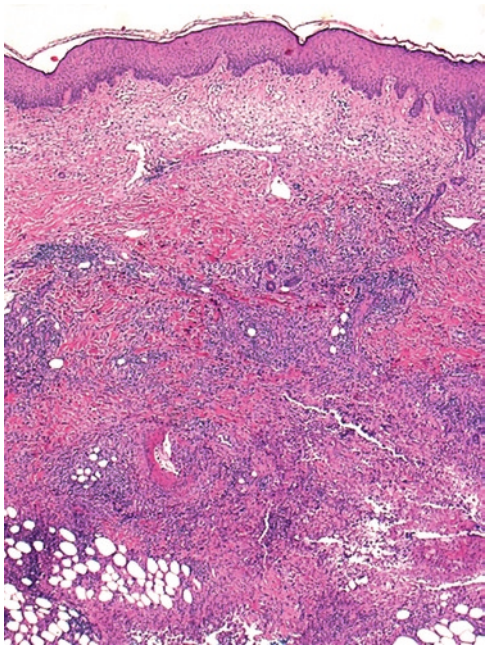

Fig. 6.7 *Wegener's granulomatosis*. Low power image demonstrating the palisading granulomas that can be seen in Wegener's granulomatosis. (Courtesy of Dr. J. Andrew Carlson)

Table 6.7 Key microscopic features: Wegener's granulomatosis

- Leukocytoclastic vasculitis involving superficial and deep dermis
- Pyoderma gangrenosum like ulcers may be present
- Palisading granulomatous inflammation
- True granulomatous vasculitis is rare

histologic diagnosis; correlation with other clinical information is essential (see sample reports) (Table 6.8).

Table 6.8 Practical tips: Wegener's granulomatosis

- Histologic findings are variable
- May present with only one of the histologic features (usually leukocytoclastic vasculitis)
- Correlation with clinical presentation and serology (c-ANCA) critical

Churg–Strauss Syndrome

Clinical Features

This syndrome, also called allergic granulomatosis, is characterized by the combination of asthma, other allergic symptoms (e.g., allergic rhinitis), peripheral and tissue eosinophilia, and systemic vasculitis. Cardiac and peripheral nerve

involvement is relatively common. Asthma and allergic symptoms develop early in the course; vasculitis is a late manifestation. The cutaneous disease presents as palpable purpura, petechiae, ecchymoses, or hemorrhagic bullae. Patients may also develop subcutaneous nodules on the scalp or extremities.

Microscopic Features

The most common finding is an eosinophil-rich, neutrophilic, leukocytoclastic vasculitis in the superficial to mid dermis (Fig. 6.8). Interstitial eosinophils are present, and flame figures characterized by a palisading arrangement of eosinophils and eosinophilic debris encrusting collagen fibers are sometimes seen (Fig. 6.9; Table 6.9).

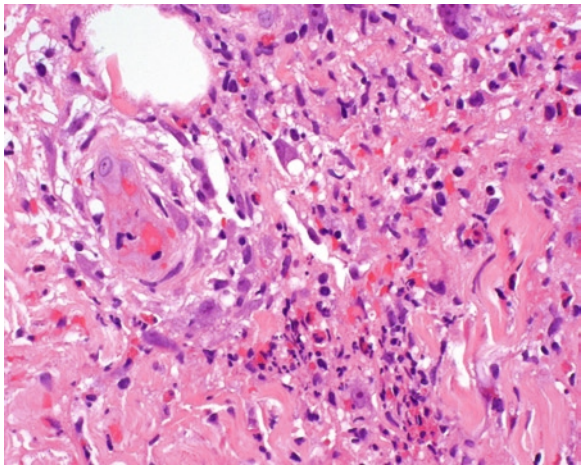

Fig. 6.8 *Churg–Strauss syndrome*. There is leukocytoclastic vasculitis in association with numerous eosinophils

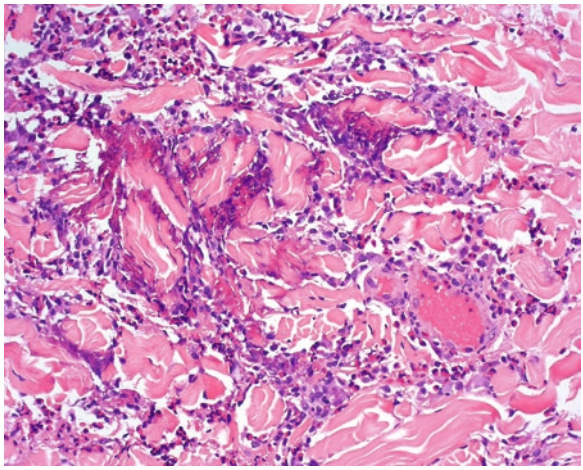

Fig. 6.9 *Churg–Strauss syndrome*. Palisading granulomas with eosinophils and flame figures are a characteristic, though not invariable, feature of Churg–Strauss syndrome

Table 6.9 Key microscopic features: Churg–Strauss syndrome

- Eosinophil-rich neutrophilic leukocytoclastic vasculitis
- Interstitial eosinophils
- Variable flame figures

Differential Diagnosis

The differential diagnosis includes other forms of vasculitis already discussed. Urticarial vasculitis is especially in the differential diagnosis because of the presence of eosinophils in the infiltrate. The perivascular infiltrate of Churg–Strauss syndrome is much denser than that in urticarial vasculitis (Table 6.10). Entities such as Wells' syndrome could be considered, but Wells' syndrome and other dermal hypersensitivity reactions lack vasculitis.

Table 6.10 Practical tips: Churg–Strauss syndrome

- If a leukocytoclastic vasculitis has significant numbers of eosinophils, consider Churg–Strauss syndrome
- Correlation with history is critical

Microscopic Polyangiitis

Clinical Features

Microscopic polyangiitis is a systemic vasculitis that is not associated with granulomatous inflammation or asthma. Associated renal disease in the form of focal segmental necrotizing glomerulonephritis is common. Cutaneous manifestations most commonly include palpable purpura and petechiae. About one-fourth of patients have splinter hemorrhages, palmar erythema, subcutaneous nodules, and/or livedo. Approximately 80% of patients have p-ANCA antibodies.

Microscopic Features

Sections demonstrate leukocytoclastic vasculitis. Vessels throughout the dermis and even subcutis are affected similar to Wegener's granulomatosis (Table 6.11).

Table 6.11 Key microscopic features: microscopic polyangiitis

- Diffuse leukocytoclastic vasculitis involving superficial and deep dermis
- No granulomas

Differential Diagnosis

The differential diagnosis includes any other form of leukocytoclastic vasculitis, especially Wegener' granulomatous or conventional leukocytoclastic vasculitis. There are no truly distinct histologic features of microscopic polyangiitis. Differentiation requires correlation with clinical information (e.g., positive p-ANCA serology) (Table 6.12).

Table 6.12 Practical tips: microscopic polyangiitis

- Histologic features are not distinctive
- Correlation with clinical presentation and serology (p-ANCA) is critical

Cryoglobulinemia

Clinical Features

Cryoglobulinemia is a form of systemic vasculitis associated with the presence of cryoglobulins. Cryoglobulins are immunoglobulins that precipitate at colder temperatures and resolubilize when rewarmed. Cryoglobulinemia can be divided into monoclonal cryoglobulinemia and mixed cryoglobulinemia. In monoclonal, or type I, cryoglobulinemia, there is a monoclonal IgG of IgM cryoglobulin. There is usually an associated underlying disease such as multiple myeloma, Waldenström's macroglobulinemia, or chronic lymphocytic leukemia. Mixed cryoglobulinemia occurs in two forms. In type II, the patients have both a monoclonal IgM rheumatoid factor and polyclonal IgG cryoglobulins. In type III, the patients have polyclonal IgM and polyclonal IgG cryoglobulins. Mixed cryoglobulinemia is seen in association with autoimmune disease, hematologic malignancies, and hepatitis, especially hepatitis C.

As the effects are the result of cryoglobulins, the cutaneous manifestations tend to occur in the distal extremities. Mixed cryoglobulinemia is a vasculitic process, and patients present with intermittent palpable purpura, Raynaud's phenomenon, and polyarthralgia. Patients may develop ulcers and digital necrosis in more severe cases. Glomerulonephritis is sometimes present. In the monoclonal cryoglobulinemia, the disease is primarily thrombotic in nature, and patients present with acral cyanosis and ulcers. By far, the majority of cases are of the mixed type.

Microscopic Features

Mixed cryoglobulinemia is a vasculitic process and biopsies reveal a leukocytoclastic vasculitis throughout the dermis and into the subcutis. Monoclonal cryoglobulinemia

is pauci-inflammatory. The vessels are occluded by intravascular eosinophilic deposits of the monoclonal cryoglobulins. There may be a mild perivascular lymphocytic infiltrate but a true vasculitis is not present (see Table 6.13).

Table 6.13 Key microscopic features: cryoglobulinemia

Mixed cryoglobulinemia
• Leukocytoclastic vasculitis
• Affects superficial and deep dermis to subcutis
Monoclonal cryoglobulinemia
• Dermal vessels occluded with eosinophilic material (immunoglobulin)
• No vasculitis

Differential Diagnosis

Mixed cryoglobulinemia can be indistinguishable from other forms of systemic vasculitis on biopsy. Recognizing this entity requires knowledge of the clinical presentation; ultimately the diagnosis depends on demonstration of cryoglobulins by serologic testing. Lacking that crucial information, a descriptive diagnosis is most appropriate (see sample reports). For monoclonal cryoglobulinemia, the differential diagnosis includes thrombotic processes described in the latter half of this chapter (e.g., antiphospholipid antibody syndrome). Histologically, this form of cryoglobulinemia is indistinguishable from other thrombotic processes. Clinical history and serology are required before this diagnosis can be rendered (Table 6.14).

Table 6.14 Practical tips: cryoglobulinemia

Mixed cryoglobulinemia
• Presents on distal extremities, upper and lower
• Seen in cold weather
• Associated with underlying disease (e.g., hepatitis C)
Monoclonal cryoglobulinemia
• Clinical history of underlying disease
• Presents on distal extremities, upper and lower
• Seen during cold weather

Cutaneous Polyarteritis Nodosa

Clinical Features

Cutaneous polyarteritis nodosa presents in middle-aged to older adults as painful nodules on the extremities, leg more frequently than arm. Patients may have livedo and rarely patients develop acral gangrene or digital necrosis. Associated neuropathy is commonly present.

Microscopic Features

Unlike other forms of vasculitis previously discussed, cutaneous polyarteritis nodosa is a neutrophilic vasculitis involving muscular arteries in the subcutis or dermis–subcutis interface (Fig. 6.10). Later stages may show neovascularization of the adventitia and fibrosis of the vessel wall (see Table 6.15).

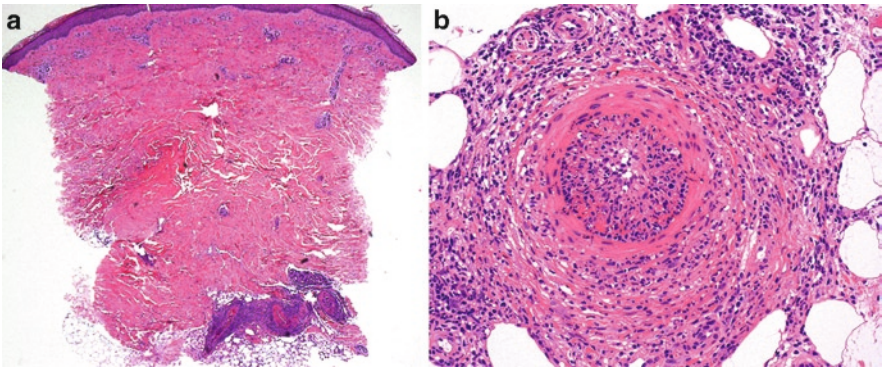

Fig. 6.10 *Cutaneous polyarteritis nodosa*. (**a**) In polyarteritis nodosa the medium sized vessels at the dermoepidermal junction or subcutis are involved. (**b**) In this case there is a leukocytoclastic vasculitis affecting a muscular artery in the subcutis. There is some adjacent fat necrosis

Table 6.15 Key microscopic features: polyarteritis nodosa

- Affected vessels are in deep dermis/subcutis
- Medium-sized muscular arteries are involved by leukocytoclastic vasculitis

Differential Diagnosis

Erythema induratum (nodular vasculitis) has some overlap, but this entity has an associated lobular panniculitis (see Chap. 11). In polyarteritis nodosa, the damage to adjacent adipose tissue is restricted to the area surrounding the vessel (Table 6.16).

Table 6.16 Practical tips: polyarteritis nodosa

- Diagnostic features can be focal
- Deeper levels may be necessary
- No associated diffuse lobular panniculitis

Vaso-Occlusive Disease

This group of disorders is generally characterized by occlusion of vessels, often with associated ischemic necrosis.

Coumadin Necrosis

Clinical Features

Lesions begin several days after initiation of therapy with coumadin. The lesions are ecchymotic and progress to necrotic lesions. It most commonly presents in the thighs, buttocks, and breasts, typically in obese women. It is associated with low levels of protein C.

Microscopic Features

Within the dermis and often subcutis, there are numerous fibrin thrombi within venules and arterioles (Fig. 6.11). There may be associated hemorrhage and ischemic necrosis (Table 6.17).

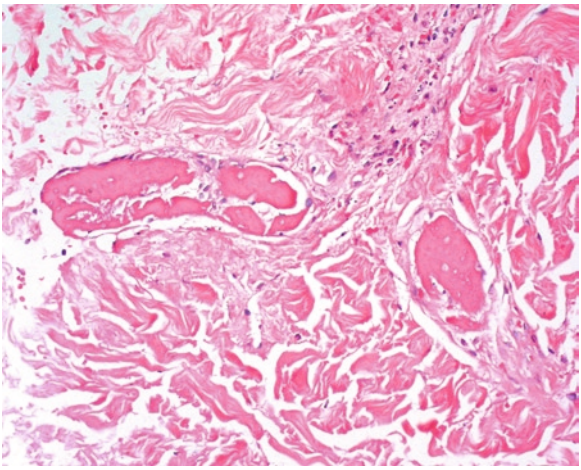

Fig. 6.11 *Coumadin necrosis*. In coumadin necrosis there is thrombosis of dermal venules and arterioles without significant inflammation

Table 6.17 Key microscopic features: Coumadin necrosis

- Thrombi in venules and arterioles
- Non-inflammatory

Differential Diagnosis

The primary differential diagnosis includes other hypercoagulable states such as antiphospholipid antibody syndrome or monoclonal cryoglobulinemia (see above). Distinction rests on clinical information, but it is usually suspected based on history of recent initiation of coumadin therapy (Table 6.18).

Table 6.18 Practical tips: Coumadin necrosis

- Clinical history is critical
- Occurs within days of initiation of anticoagulant therapy
- Histologic features are not distinctive from other hypercoagulable states

Atrophie Blanche (Livedoid Vasculopathy)

Clinical Features

This condition usually presents in elderly women. This disease initially presents as purpuric areas that ulcerate and over time develop into irregular smooth atrophic plaques with a hyperpigmented border and surrounding telangiectasias. The lower extremities are by far the most common site of involvement. The pathogenesis is poorly understood, but at least some cases, patients have an underlying hypercoagulable state such as Factor V Leiden mutation or antiphospholipid antibody syndrome. Therefore, this condition may represent in part a reaction pattern.

Microscopic Features

Biopsies demonstrate fibrin deposition in the walls of superficial dermal vessels and fibrin thrombi in association with hemorrhage (Fig. 6.12). A true vasculitis is not present, but a perivascular infiltrate may develop in later lesions. The overlying epidermis and surrounding tissue may be necrotic. See Table 6.19.

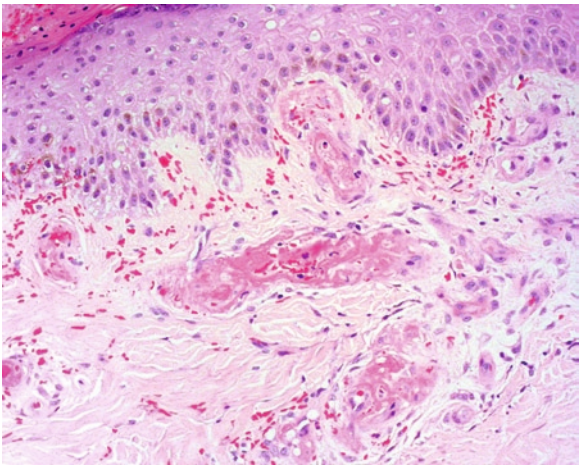

Fig. 6.12 *Atrophie blanche* is characterized by fibrin deposition and thrombosis of superficial dermal blood vessels in association with prominent hemorrhage

Table 6.19 Key microscopic features: atrophie blanche

- Primarily superficial vessels
- Fibrin deposition and thrombosis
- Hemorrhage

Differential Diagnosis

The diagnosis primarily depends on clinical presentation. Histologically, it can be indistinguishable from other hypercoagulable states, and indeed other hypercoagulable states may be the cause of the clinical presentation as alluded to above. See Table 6.20.

Table 6.20 Practical tips: atrophie blanche

- Most common on distal lower extremities
- Clinical correlation critical

Antiphospholipid Antibody Syndrome

Clinical Features

Young adult women are most commonly affected. The syndrome is the result of autoantibodies directed against phospholipid. Patients have recurrent episodes of thrombosis and associated thrombocytopenia and spontaneous abortions. The causative autoantibodies are found in patients with systemic lupus erythematosus in up to 50% of patients with this disease. Other factors play a role in developing sequelae of hypercoagulability as roughly half of the patients with the antibody develop thromboses. Cutaneous lesions manifest as livedo reticularis, Raynaud's phenomenon, ulcerations, necrosis, painful nodules, splinter hemorrhages, and atrophie blanche. The ulcerations and necrosis can be quite severe.

Microscopic Features

Biopsies demonstrate fibrin thrombi in venules and arterioles much like that seen in coumadin necrosis. There is often extensive surrounding necrosis. No true vasculitis is present (Table 6.21).

Table 6.21 Key microscopic features: antiphospholipid antibody syndrome

- Vascular thrombosis without significant inflammation
- Venules and arterioles involved

Differential Diagnosis

The histologic features are not distinctive from other occlusive vasculopathies. Diagnosis requires clinical evaluation and appropriate serologic testing (Table 6.22).

Table 6.22 Practical tips: antiphospholipid antibody syndrome

- Young adult women
- If there is a history of spontaneous abortion or connective tissue disease, suspect antiphospholipid antibody syndrome
- Correlation with serology is critical

Cholesterol Emboli

Clinical Features

This presents in patients who have significant atheromatous plaques in large vessels, especially the abdominal aorta. They can develop spontaneously or as a result of dislodgement from a vascular procedure. Cutaneous lesions manifest on the distal lower extremities as purpura, cyanosis, painful nodules, or necrosis.

Microscopic Features

The affected vessels demonstrate thrombosis with cholesterol clefts (Fig. 6.13). The affected vessels are in the deep dermis or subcutis (Table 6.23).

Differential Diagnosis

The histologic features are sufficiently distinct that essentially no other entity is in the differential diagnosis. However, the finding is often focal and multiple levels may need to be obtained (Table 6.24).

Calciphylaxis

Clinical Features

Calciphylaxis usually presents in patients with end-stage renal disease. It presents as painful, often ulcerated, nodules, and plaques, most commonly on the lower extremities. Breasts, buttocks, penis, and upper extremities may also be involved. Mortality rates approach 60%.

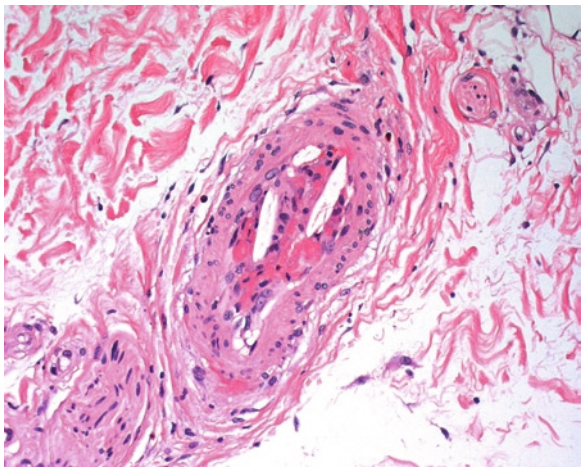

Fig. 6.13 *Cholesterol emboli* are characterized by thrombosis with cholesterol clefts

Table 6.23 Key microscopic features: cholesterol emboli

- Vascular thrombus in deep dermis or subcutis
- Cholesterol clefts are required for the diagnosis

Table 6.24 Practical tips: cholesterol emboli

- Multiple levels are often needed
- Occurs on distal extremities
- History of prior vascular procedure is common

Microscopic Features

Calciphylaxis is characterized by calcification of small to medium-sized arteries and arterioles that may be associated with intimal fibroblastic proliferation and intravascular fibrin thrombi (Fig. 6.14). Associated fat necrosis is common and often extensive (Table 6.25).

Differential Diagnosis

Fat necrosis could be considered in the differential diagnosis. Mönckeberg's calcification could be considered, but that is a sequela of aging, tends to involve larger vessels, and is not associated with necrosis. Calciphylaxis is usually suspected clinically, so this entity is rarely a diagnostic problem. It is important that a sufficiently large and deep biopsy is obtained as the involved vessels are usually in the subcutis (Table 6.26). Superficial biopsies may not be diagnostic (see sample report).

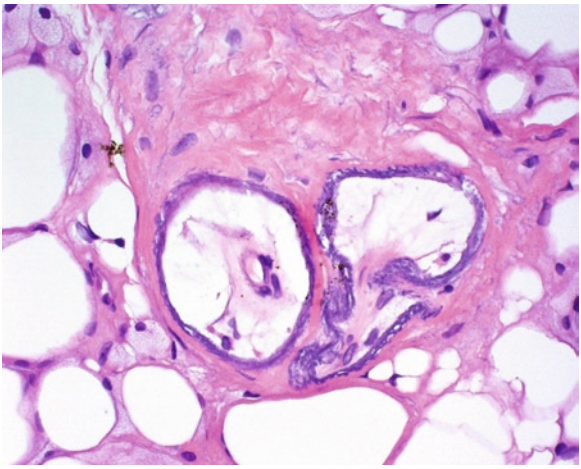

Fig. 6.14 *Calciphylaxis*. There is calcification of the vascular wall. Note the adjacent evidence of fat necrosis

Table 6.25 Key microscopic features: calciphylaxis

- Calcification of small to medium-sized arteries
- Associated necrosis

Table 6.26 Practical tips: calciphylaxis

- Usually requires deep biopsy; affected vessels usually in subcutis
- Clinical history of renal failure

Sample Reports: Leukocytoclastic Vasculitis

Example 1: This report represents a biopsy from an early leukocytoclastic vasculitis in which the findings are not well developed.

Clinical history: Rule out LCV.

Diagnosis: Superficial perivascular neutrophilic infiltrate consistent with leukocytoclastic vasculitis, see comment.

Comment: The epidermis is relatively normal. Within the upper dermis, there is a perivascular infiltrate of neutrophils with some nuclear debris and extravasated erythrocytes. No significant fibrin deposition in vessels of fibrinoid necrosis is seen. The histologic features are consistent with the clinical impression of leukocytoclastic vasculitis. Clinicopathologic correlation is recommended.

Example 2: A classic case.

Clinical history: Palpable purpura.

Diagnosis: Leukocytoclastic vasculitis, see comment.

Comment: The epidermis is relatively normal. Within the upper dermis, there is a perivascular infiltrate of neutrophils with prominent

nuclear debris, extravasated erythrocytes, and fibrin deposition in blood vessel walls.

Example 3:
Clinical history: Ulcer.
Diagnosis: Reactive epidermal changes and mixed dermal infiltrate, see comment.
Comment: The epidermis shows reactive epidermal hyperplasia. Within the dermis, there is a mixed infiltrate with lymphocytes and neutrophils. There is proliferation of blood vessels. Neutrophils are present in some of the blood vessel walls as is fibrin deposition. Given the clinical history of an ulcer, the vasculitis may represent a secondary vasculitis related to the ulcer rather than a primary leukocytoclastic vasculitis.

Sample Report: Henoch–Schönlein Purpura

Example: In this case, a specimen for DIF is not available.
Clinical history: Rule out HSP.
Diagnosis: Leukocytoclastic vasculitis, see comment.
Comment: Within the dermis, there is a leukocytoclastic vasculitis characterized by a perivascular infiltrate of neutrophils with leukocytoclasis, hemorrhage, and fibrin deposition in blood vessel walls. The histologic features are compatible with Henoch–Schönlein purpura in the appropriate clinical context. However, confirmation requires DIF testing. A repeat biopsy submitted in Michel's solution for DIF is recommended.
Note to reader: If a specimen for DIF is submitted and the predominant finding is perivascular deposits of IgA, the diagnosis could be changed to leukocytoclastic vasculitis consistent with Henoch–Schönlein purpura.

Sample Report: Wegener's Granulomatosis

Example: In this case, only vasculitis is present.
Clinical history: Rule out Wegener's.
Diagnosis: Leukocytoclastic vasculitis, see comment.
Comment: Within the dermis, there is a leukocytoclastic vasculitis characterized by a perivascular infiltrate of neutrophils with leukocytoclasis, hemorrhage, and fibrin deposition in blood vessel walls. Superficial and deep vessels are involved. The histologic features are compat-

ible but not entirely specific for the diagnosis of Wegener's granulomatosis. Clinicopathologic correlation is recommended.

Sample Report: Churg–Strauss Syndrome

Example: In this case, Churg–Strauss syndrome is not specifically mentioned in the clinical history.

Clinical history: Rule out vasculitis.

Diagnosis: Leukocytoclastic vasculitis with numerous eosinophils, see comment.

Comment: Within the superficial and deep dermis, there is a leukocytoclastic vasculitis characterized by a perivascular infiltrate of neutrophils with leukocytoclasis, hemorrhage, and fibrin deposition in blood vessel walls. Numerous eosinophils are present. The extent of the dermal infiltrate and the numerous eosinophils suggest the possibility of Churg–Strauss syndrome. Clinicopathologic correlation is recommended.

Note to reader: In this scenario, it might be a good idea to pick up the phone and call the clinician to see if the patient has a history of asthma or allergic rhinitis.

Sample Reports: Hypercoagulable States (e.g., antiphospholipid antibody syndrome)

Example: In this case, a specific diagnosis is not suggested in the clinical history.

Clinical history: Rule out vasculitis.

Diagnosis: Numerous intravascular thrombi, see comment.

Comment: Within the dermis, there are numerous intravascular thrombi in association with hemorrhage and ischemic necrosis. No significant inflammation is present. The histologic features are compatible with an underlying hypercoagulable state. Clinicopathologic correlation is recommended.

Note to reader: If the clinician suggests a specific diagnosis (e.g., coumadin necrosis), the diagnosis can read "Intravascular fibrin thrombi consistent with _____," with the pathologist filling in the blank with what the clinician is suspecting.

Sample Report: Calciphylaxis

Example: In general, the diagnosis of calciphylaxis is relatively easy. However, diagnostic findings may not be present on superficial biopsies. This report reflects that situation.

Clinical history: Ulcerated plaque, rule out calciphylaxis.

Diagnosis: Ulcer with dermal necrosis, see comment.

Comment: The epidermis is ulcerated and there is underlying necrosis. The biopsy is relatively superficial and only a limited amount of subcutaneous fat is present. Diagnostic features of calciphylaxis are not seen, but that possibility cannot be excluded based on this biopsy. A repeat, excisional biopsy including a generous sampling of subcutaneous fat is recommended if calciphylaxis remains a strong clinical possibility. Clinicopathologic correlation is recommended.

Selected References

1. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. American Journal of Dermatopathology. 27:504–528, 2005.
2. Carlson JA, Chen KR. Cutaneous pseudovasculitis. American Journal of Dermatopathology. 29:44–55, 2007.