Vasculitic Neuropathy

13

Vasculitis of the peripheral nerve (VPN) can occur as an isolated process or more commonly as the manifestation, initial or late, of a systemic disease (recently reviewed Vrancken and Said 2013; Collins et al. 2013). Inflammation affects endoneurial and epineurial microvessels, arterioles, and venules; thrombosis and necrosis are often present resulting in ischemia of nerve with varying degrees of axonal degeneration. The vasculitic processes detected in routine nerve biopsy specimens (sural, peroneal, median) occur in medium- and small-sized vessels as the diameter of these structures range from 10 to 350 μm.

With some exceptions the vasculitides found in nerve biopsies (Vital et al. 2006) in many diseases and syndromes are histologically similar; distinction is usually dependent on clinical criteria or biopsy at other sites. In classifying peripheral nerve vasculitis, it is helpful to separate the infectious etiologies and subdivide the remainder into those diseases in which inflammation selectively affects vessels in nerve and those in which vascular involvement is part of a systemic process, acknowledging that sometimes this separation is difficult to establish. Polyarteritis nodosa (PAN), ANCA-related microscopic polyangiitis, Churg–Strauss angiitis (CSA), Wegener granulomatosis (WG), and rheumatoid vasculitis account for about 50 % of cases with systemic vasculitis neuropathy. Attempts to classify vasculopathic diseases, on the basis of the size and type of vessels involved or through putative pathogenic mechanisms, have been unsatisfying (Collins et al. 2010a). Several schemes are in use and we will draw, for the discussion in this chapter, from the nomenclature of the Chapel Hill Consensus Conference (Jennette et al. 2013) and from the classifications proposed by Vrancken and Said (2013) and Gwathmey et al. (2014). We will review the most important types of peripheral nerve vasculitis, followed by a general discussion of the pathological spectrum of peripheral nerve vasculitis and the differential diagnosis. Table 13.1 classifies vasculitis into isolated

Table 13.1 Peripheral neuropathy due to vasculitis

Isolated PNS vasculitis
Primary systemic vasculitis
Polyarteritis nodosa (PAN)
Churg–Strauss syndrome
Microscopic polyangiitis
Wegener granulomatosis
Essential mixed cryoglobulinemia
Behçet's disease
Henoch–Schönlein purpura
Collagen vascular diseases
Rheumatoid arthritis
Systemic lupus erythematosus (SLE)
Sjögren syndrome
Scleroderma
Other vasculitis and vasculopathies
Giant cell arteritis
Paraneoplastic[a] (hematological or solid malignancy)
Hypersensitivity vasculitis
Essential mixed cryoglobulinemia
Sarcoidosis[a]
Lymphomatoid granulomatosis[a]
Cholesterol embolus syndrome[a] (Bendixen et al. 1992)
Infection-associated vasculitis
Leprosy in ENL reaction
HIV infection
CMV related
Unknown basis
Lyme disease
Various arthropod stings[a]
Bacterial endocarditis[a] (Jones and Siekert 1968; Pamphlett and Walsh 1989)
Tuberculosis[a] (Stubgen 1992)
Other
Eosinophilia–myalgia syndrome[a]
Toxic oil syndrome[a]

[a]Necrotizing vasculitis not proven

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vasculitis of peripheral nerves, primary systemic vasculitis, vasculitis of connective tissue disease, and less common vasculopathies.

13.1 Clinical Manifestations

13.1.1 Mononeuritis Multiplex

Mononeuritis multiplex is regarded as the classic manifestation of vasculitic neuropathy, as the multifocal process affects nerves throughout the body (more often peroneal, ulnar, tibial, and the sural) including the cranial nerves. Patients experience an abrupt onset of pain, paresthesia, and paralysis in the distribution of a single nerve trunk evolving over hours to days, with newly involved nerves appearing over days to months. Atypical forms of presentation include pure sensory ataxia and radiculoplexopathy (Vrancken and Said 2013). When the lesions are disseminated, and their territories overlap, the presentation is in the form of an asymmetric polyneuropathy. Notwithstanding that biopsy is more likely to be performed in patients with mononeuritis multiplex, an acutely, subacutely, or chronically progressive symmetric distal sensorimotor polyneuropathy, where vasculitis is often not suspected, has been described in 19–76 % of biopsy-proven vasculitic neuropathies (Harati and Niakan 1986; Dyck et al. 1987; Hawke et al. 1991; Wees et al. 1981; Kissel et al. 1985; Panegyres et al. 1990; Said et al. 1988). This indicates that progressive symmetric distal polyneuropathy is a common clinical presentation of vasculitic neuropathy. Experience with vasculitic neuropathy at St. Michael's Hospital includes 39 cases, for which adequate clinical information was available in 32. Fourteen (44 %) presented with a distal symmetrical pattern, 12 (38 %) with obvious mononeuritis multiplex, 5 (16 %) with asymmetrical polyneuropathy, and 1 was asymptomatic. Evolution can occur rapidly enough to result in an initial clinical diagnosis of GBS (Suggs et al. 1992).

Nerve conductions give evidence of axonal abnormalities and are invaluable for demonstrating the asymmetry and multifocality that are most suggestive of a vasculitic neuropathy (Hawke et al. 1991; Kissel et al. 1985; Olney 1992). Although demyelination is generally not a significant element of the histologic picture, conduction block has occasionally been documented as part of an ischemic or vasculitic neuropathy (Hughes et al. 1982; Jamieson et al. 1991; Kaku et al. 1993). Significant demyelinating electrophysiological features were observed in 3 of 32 adequately documented cases of vasculitic neuropathy identified in our laboratory.

In patients known to have a systemic vasculitic illness, nerve biopsy is of questionable value. Of greater interest to the pathologist are those situations where a diagnosis of vasculitis is unsuspected, either because the disease seems confined to the peripheral nervous system, or because it is not yet fully evident

13.1.2 Nonsystemic (Isolated) Peripheral Nervous System Vasculitis (NSVN)

Vasculitis involving the peripheral nerves can be seen in isolation and results in a peripheral nerve syndrome indistinguishable from that of vasculitic neuropathy in multisystem disease. Approximately 25 % of cases with vasculitis neuropathy are diagnosed with primary vasculitis neuropathy. These patients usually present with a subacute or chronic neuropathy, often with a mononeuritis multiplex, and have few or no systemic abnormalities on history, physical, or laboratory investigation. Cases fulfilling these criteria are found in all large series of vasculitic neuropathy (Dyck et al. 1987; Hawke et al. 1991; Vincent et al. 1985; Harati and Niakan 1986; Kissel et al. 1985; Panegyres et al. 1990), and the pathogenesis is probably heterogeneous, as the pathology seems to be (vide infra). It has been argued that these cases do not represent a truly isolated PNS disease because a very high incidence of concurrent vasculitis was found in muscle biopsy (Said et al. 1988). The apparent selectivity of peripheral nerve involvement may reflect an increased vulnerability of this tissue to multifocal microvascular insults, and the presence of a milder disease sufficient to clinically affect nerve but no other tissues might explain the better outcome observed in these patients (Said et al. 1988; Said 1989; Dyck et al. 1987). Some authors have suggested that NSVN should be considered a low-grade systemic vasculitis that is symptomatic in nerves only (Said and Lacroix 2005).

13.1.3 Primary Systemic Vasculitis

13.1.3.1 Classic Polyarteritis Nodosa (PAN)

Classic polyarteritis nodosa (PAN) is a necrotizing arteritis associated with fibrinoid change. It is not uncommonly seen in patients suffering from hepatitis B infection (70 % of cases) and, less often, in patients with hepatitis C or HIV infections (Siva 2001). Although in its presentation PAN may appear limited to skin, muscles or nerves, PAN is a primary systemic vasculitis. Mononeuritis multiplex is recognized in 50–67 % of patients, and it may be the presenting manifestation in most (Hawke et al. 1991; Guillevin et al. 1988; Chumbley et al. 1977; Frohnert and Sheps 1967; Vrancken and Said 2013). Positivity for pANCA is exclusionary for classic PAN. Involvement of medium-sized vessels in epineurium is the domain of classic PAN.

13.1.3.2 Churg–Strauss Angiitis (CSA)

Churg–Strauss angiitis (CSA) is also designated eosinophilic granulomatosis with polyangiitis. In a large series of VPN, CSA accounted for the largest number of cases followed by PAN and WG (Mathew et al. 2007). This disease affects small- and medium-sized vessels. Patients display prominent pulmonary symptoms and eosinophilia, and vasculitic neuropathy develops in 20–65 % of cases, which can be the initial manifestation (Hattori et al. 2002; Uchiyama et al. 2012; Vrancken and Said 2013), CSA is a member of the family of ANCA-associated vasculitides that also includes WG and MPA. Perinuclear ANCA/MPO-ANCA is the pattern most often detected in CSA. The necrotizing vasculitis exhibits PAN-like fibrinoid change and an eosinophilic-rich lymphocytic and histiocytic infiltrate. Extravascular necrotizing granulomata are a feature of CSA, but not PAN (Chumbley et al. 1977).

13.1.3.3 Wegener Granulomatosis (WG)

Wegener granulomatosis (WG) (also termed *granulomatosis with polyangiitis*) is not a primary vasculitis, but rather a systemic disease characterized by necrotizing granulomata and granulomatous cytoplasmic-ANCA/PR3-ANCA-associated vasculitis (Gross and Csernok 2008; Suppiah et al. 2011) of small- and medium-sized vessels. Paranasal sinuses, lungs, and kidneys (resulting in necrotizing glomerulonephritis) are most severely involved. Peripheral neuropathy, most often with a mononeuritis multiplex pattern due to vasculitis, is the most common neurological manifestation, seen in 10–22 % of patients (Fauci et al. 1983; Drachman 1963; Nishino et al. 1993; Mahr 2009).

13.1.3.4 ANCA-Associated Microscopic Polyangiitis (MPA)

ANCA-associated microscopic polyangiitis (MPA) (formerly designated as microscopic periarteritis nodosa, Wohlwill 1923) is a necrotizing vasculitis affecting predominantly small-sized vessels, associated with antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase (MPO-ANCA) with a perinuclear pattern and sparse immune deposits. The most characteristic clinical feature is rapidly progressive glomerulonephritis, pulmonary involvement, and palpable purpura due to cutaneous vasculitis. Peripheral neuropathy (with frequent features of mononeuritis multiplex) occurs in about 57 % of patients (Guivellin et al. 1999; Mahr 2009; Chung and Seo 2010). Frequently affected nerves include the peroneal, ulnar, and median nerves. Cranial nerves are rarely involved (Vrancken and Said 2013). MPA may develop insidiously with nonspecific constitutional signs and symptoms or may be disguised as polymyalgia rheumatica.

13.1.3.5 Henoch–Schönlein Purpura (HSP)

Henoch–Schönlein purpura (HSP) is a systemic vasculitis of unknown etiology that involves the small vessels, most notably those in the skin (palpable purpura), gastrointestinal tract, and glomeruli, accompanied by arthralgia or arthritis. HSP is seen predominantly in children and its main histopathological features are leukocytoclastic vasculitis (LCV) mainly in papillary dermis associated with the deposition of IgA immune complexes in small vessels. Peripheral nerves are rarely affected (Mathew et al. 2007; Linskey et al. 2012). The prognosis of HSP is excellent as progressive renal disease occurs only in a minority of patients.

13.1.3.6 Behçet's Disease (BD)

Behçet's disease (BD) is a systemic disorder of unknown etiology. The criteria for diagnosis require the presence of oral ulceration plus any two of the following manifestations: genital ulcerations, papulopustular lesions, erythema nodosum-like nodular lesions, positivity of skin pathergy reaction, and uveitis (Walker et al. 1990, Melikoglu et al. 2008). BD also features a systemic vasculitis with a predilection to affect large veins and arteries including vena cava and aorta and its branches. Pseudoaneurysm formation in affected vessels is common. Involvement of small vessels is rare and manifestation of mononeuritis multiplex is exceptional (Takeuchi et al. 1989; Walker et al. 1990).

13.1.3.7 Connective Tissue Diseases

Vasculitis is suspected when a patient with multisystem disease develops symptoms and signs of peripheral nerve dysfunction. However, nerve biopsies in many such patients show nonspecific changes and normal vessels (Olney 1992). Clinicopathological review of our material revealed that non-vasculitic neuropathy-associated with systemic inflammatory disease (NASID) was the fourth most common diagnosis (Table 1.2), and the histological correlates of this included any combination of axonal, demyelinating, and inflammatory changes (Table 1.3). It is impossible to determine whether this represents a sampling error or whether a non-vasculitic pathologic process is at work.

Vasculitis and vasculitic neuropathy are typically seen in rheumatoid arthritis (RA) only after many years of disease activity, in the presence of erosive joint disease, cutaneous nodules, and high titers of rheumatoid factor (Scott et al. 1981; Hawke et al. 1991). Vasculitic neuropathy can rarely precede the diagnosis (Peyronnard et al. 1992; Chang et al. 1984). The development of vasculitis in a patient with RA indicates a poor prognosis (Vollertsen et al. 1986; Hawke et al. 1991). In rheumatoid arthritis a mild predominantly sensory neuropathy is more frequent than the more severe sensorimotor neuropathy associated with vasculitis

(Olney 1992). In rare biopsied cases the underlying pathology has been mild axonal loss with segmental demyelination in the absence or paucity of vascular changes, but whether this is primary or secondary demyelination has not been determined (Weller et al. 1970; Beckett and Dinn 1972). Patients suffering from rheumatoid arthritis are also prone to developing other types of neuropathy including entrapments (e.g., median mononeuropathy at the wrist and digital nerve compression secondary to tenosynovitis and arthritis of the carpal bones and digits (Pallis and Scott 1965; Gwathmey et al. 2014). The most devastating type of neuropathy is a progressive multifocal neuropathy, with features similar to those of PAN.

Sjögren syndrome is an autoimmune disease caused by inflammation of the salivary and lacrimal glands. Patients develop the sicca complex (dry eyes and dry mouth), and peripheral neuropathy may be the presenting manifestation (Mellgren et al. 1989; Peyronnard et al. 1992). The clinical picture is usually not a mononeuritis multiplex, but rather a distal sensorimotor neuropathy. Pure sensory neuropathy is also seen and has features suggestive of dorsal root ganglionitis (Pavlakis et al. 2012). Vasculitis (with no other systemic manifestations) has been reported to account for about 15 % of Sjögren-related neuropathies. Important to the diagnosis of Sjögren syndrome is the presence of SS-A (Ro)/SS-B (La) antibodies (Theander and Jacobsson 2008). In Sjögren syndrome a pure sensory neuropathy is occasionally seen and is likely due to spinal ganglionitis (Chap. 21)

Peripheral neuropathy develops in about 10–20 % of patients with systemic lupus erythematosus (SLE) (Chalk et al. 1993; Richardson 1982; Wallace and Metzger 1993; Collins and Periquet 2008; Florica et al. 2011). A distal sensorimotor polyneuropathy, a mononeuritis multiplex, and rarely a CIDP-like picture (Richardson 1982; Rechthand et al. 1984) may be seen. The neuropathy is usually seen after the disease is well established, but can be the presenting manifestation (McCombe et al. 1987; Hughes et al. 1982). The vasculitis affects small vessels and has leukocytoclastic characteristics. PAN-like necrotizing vasculitis may be observed in medium-sized blood vessels. In SLE, CIDP has been infrequently reported (Rechthand et al. 1984; Richardson 1982). Some of the vasculitides encountered in mixed connective tissue disease are similar to the morphologic vascular changes in SLE-associated vasculitis.

Peripheral neuropathy (excluding trigeminal sensory neuropathy and carpal tunnel syndrome) is present in 1–10 % of patients with Scleroderma (Olney 1992; Lee et al. 1984; Averbuch-Heller et al. 1992; Dierckx et al. 1987; Hietaharju et al. 1993). Histological data is scanty, but there are several reported cases of biopsy-proven vasculitic neuropathy in progressive systemic sclerosis (PSS), most often in the presence of Sjögren syndrome (Oddis et al. 1987; Dyck et al. 1987; Vincent et al. 1985). A neuropathy in which vasculitis cannot be implicated, and which can precede generalized clinical manifestations, may be seen in PSS (Di Trapani et al. 1986). Several histological reports have documented prominent epineurial and perineurial collagenization and microangiopathic but non-vasculitic changes similar to those seen systemically with this disease (Richter 1954; Di Trapani et al. 1986; Corbo et al. 1993).

13.1.4 Other Vasculitides

A peripheral neuropathy is said to occur in as many as 14 % of patients with giant cell (temporal) arteritis and frequently precedes the diagnosis by several months (Caselli et al. 1988). Isolated reports exist documenting necrotizing vasculitis, with or without giant cells, involving neural vessels of all sizes in cases of clear-cut temporal cell arteritis (Bridges et al. 1989; Torvik and Berntzen 1968; Merianos et al. 1983; Pons et al. 1987; Nesher et al. 1987). Sites involved include brachial plexus, peroneal nerve, mononeuropathies, and polyneuropathies. Histopathologic features consist of transmural lymphohistiocytic inflammation in the absence of fibrinoid necrosis. Multinucleated giant cell formation occurs associated to degeneration of internal elastica.

A group of nonsystemic, localized vasculopathies termed diabetic lumbosacral radiculoplexus neuropathy and nondiabetic lumbosacral radiculoplexus neuropathy (LRPM) are characterized by intense pain and weakness in the thighs and progressing to affect lower extremities including feet and toes. The clinical course is monophasic but results in protracted morbidity (Gwathmey et al. 2014). Histopathological studies revealed reduction in the number of nerve fibers, perineurial thickening, neuroma formation, neovascularization, and half of the cases featured changes suggestive of microvasculitis.

A heterogeneous group of diseases termed hypersensitivity vasculitis or cutaneous small-vessel vasculitis may present as an idiopathic condition, or secondary to infections, adverse reaction to pharmaceuticals, in the setting of malignancy or autoimmune diseases. Peripheral neuropathy occurs only rarely, except in patients suffering from autoimmune disorders. The hypersensitivity vasculitis that results from the administration of heterologous sera has received the most interest in the past (Iqbal and Arnason 1984).

Paraneoplastic Vasculitic Neuropathy. The most common paraneoplastic vasculitis is leukocytoclastic vasculitis, 75 % of which are caused by hematological malignancies. Second in frequency is small-cell carcinoma of the lung followed by malignancies of the colon, breast, and kidney (Solans-Laqué et al. 2008). In a review of 14 cases, nine cases involved microvasculitis and five cases involved necrotizing vasculitis in medium-sized vessels (Oh 1997; Naka et al. 1991; Choi et al. 2013; Paul 1996).

The most frequently described neuropathy in chronic hepatitis C is a vasculitic neuropathy in the setting of essential cryoglobulinemia (Ferri 2008; Gwathmey et al. 2014; Ramos-Casals et al. 2006). Peripheral neuropathy is more common in essential mixed cryoglobulinemia, but reports of pathological studies are rare (Vrancken and Said 2013).

Vasculitic neuropathy is rare in sarcoidosis, but it is well documented (Said et al. 2002; Vital et al. 2008), including epineurial necrotizing vasculitis in the vicinity of granulomata. Our experience with this disease indicates the presence of naked granuloma in perivascular spaces of epineurial medium-sized vessels, with intrusion into the vessel wall. Some patients suffering from sarcoidosis exhibit the clinical syndrome of mononeuritis multiplex.

VPS may develop in association with leprosy (ENL), HIV, CMV, HCV, and Lyme disease (see Chaps. 11 and 12).

13.2 Pathology

13.2.1 General Considerations: Sensitivity of Biopsy

Nerve biopsy is critical for the diagnosis of vasculitis in two clinical situations: "atypical" presentation of systemic vasculitis masquerading as a cryptogenic polyneuropathy and isolated vasculitis of the peripheral nervous system.

The sensitivity of nerve biopsy in the detection of vasculitis is not known because of the variability of selection criteria in published series and the absence of a "gold standard" against which to measure the biopsy. In a study which identified 35 consecutive patients with mononeuritis multiplex from a hospital EMG laboratory, 11 had a previously known rheumatic disease, 9 had the simultaneous onset of systemic disease, and 15 showed only peripheral nerve manifestations (Hellmann et al. 1988). Biopsies showed definite vasculitis in 3 of 5 patients strongly suspected of having polyarteritis nodosa clinically, but in none of 7 biopsies in patients with isolated PNS disease. In the latter group, however, nerve "infarction" was seen in 5 of 7. Dyck et al. (1987) noted that of 45 patients with a biopsy-proven systemic vasculitic illness with neuropathy, nerve biopsy was positive in 58 % in patients, suggestive in 29 %, and nondiagnostic in 23 %. It is possible to find necrotizing vasculitis in an electrically normal nerve (Kissel and Mendel 1992), as has been our experience with 3 patients who underwent nerve and muscle biopsy for suspected systemic vasculitis despite normal nerve conductions studies and EMG. However, the yield is lower than in clinically or electrically involved nerves (Wees et al. 1981). Such data do not make possible estimation of the sensitivity of sural nerve biopsy for the diagnosis of vasculitic neuropathy.

Epineurial vascular involvement usually predominates over endoneurial involvement and is often exclusive; thus, fascicular biopsy is not appropriate when vasculitis is suspected (Dyck et al. 1972; Oh 1990); this is the strongest argument against the utility of fascicular nerve biopsy for diagnostic purposes.

If muscle biopsy can be added to the procedure, the yield may increase an additional 15–45 % (Hawke et al. 1991; Vincent et al. 1985; Dyck et al. 1987). In one series of 83 patients who underwent nerve and muscle biopsy, necrotizing arteritis in the muscle alone was found in 45 %, as compared with 20 % in the nerve alone, and 30 % in both, including patients with seemingly isolated PNS vasculitis (Said et al. 1988). We thus advocate combined nerve and muscle biopsy whenever vasculitis is being considered.

13.2.2 Some Pathological Considerations

Perivascular inflammation is a common and nonspecific finding in peripheral nerve pathology and should be differentiated from "vasculitis." Throughout this book, the term "vasculitis" indicates inflammation of the vessel and evidence of destruction such as fibrinoid necrosis, thrombosis, hemorrhage, or disruption of the endothelium (Fig. 13.1a, b). Transmural inflammation accompanied by karyorrhexis has substantially the same value as fibrinoid necrosis (Fig. 11.2), whereas the presence of leukocytes within the vessel wall is suggestive but not diagnostic of vasculitis. At times, what seems to be prominent perivascular cuffing around small vessels (Fig. 13.2) has been called "microvasculitis" by some (Oh et al. 1991; Vincent et al. 1985), but in our experience this lesion does not have the same diagnostic specificity as necrotizing vasculitis. For example, some of the patients reported by Leger et al. (1988) as showing neural "vasculitis" likely suffered from CIDP. Vasculitis can involve small-sized endoneurial and epineurial vessels for which the designation of microvasculitis is preferred. The anatomy of peripheral nerve vasculature is reviewed in Chap. 6.

13.2.2.1 Light Microscopy

The hallmark of acute vasculitis is destruction and disorganization of muscularis and endothelial layers of the vessel, with deposition of fibrinoid material in the presence of transmural mononuclear or polymorphonuclear inflammatory cells and thrombosis. The damage is often focal, involving only a segment of the vessel wall (Fig. 13.3a, b). Hemorrhage into the surrounding tissue may be seen (Fig. 13.4a), sometimes in a perineurial or subperineurial crescentic pattern. Perl's ferrocyanide stain (Fig. 13.4b) will highlight old hemorrhages (Adams et al. 1989), but the specificity of this finding is uncertain (Winer et al. 1992). The use of MSB or PTAH staining (Fig. 13.5a, b) may bring out inconspicuous fibrinoid change. The pattern of involvement in vasculitis is often patchy, with unscathed vessels

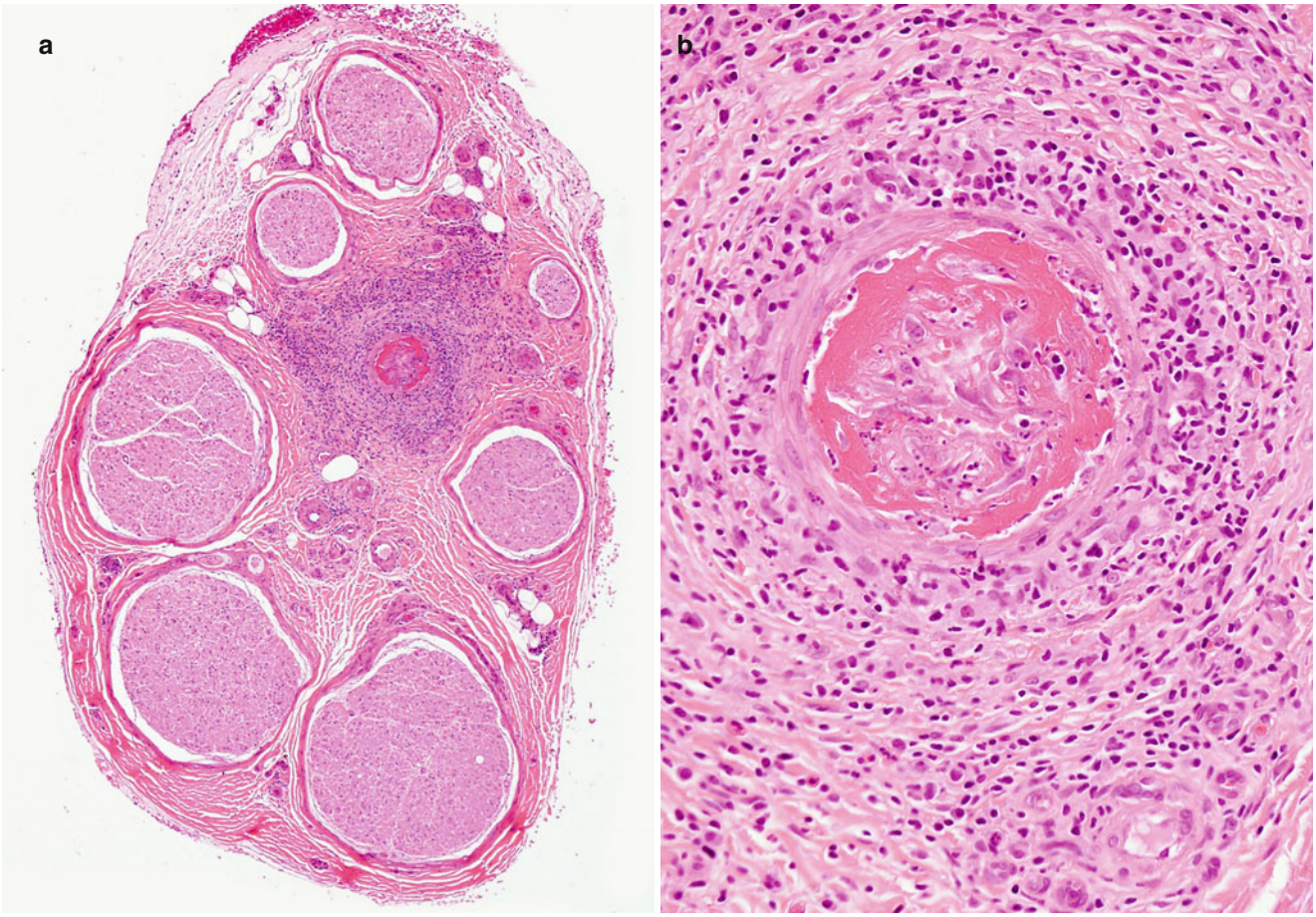


Fig. 13.1 Vasculitic neuropathy: (**a**) recent fibrinoid necrosis and thrombosis of an epineurial vessel, with perivascular hemorrhage. (**b**) Transmural inflammation and karyorrhexis are associated with perivascular accumulation of polymorphonuclear leukocytes and mononuclear cells (**b**) (paraffin, H&E stain; magnification: **a**, 100×; **b**, 400×)

and nerve fascicles adjacent to severely damaged ones (Fig. 13.6a, b). Epineurial vessels, predominantly arterioles, are much more frequently damaged than endoneurial vessels (Fujimura et al. 1991). The size of vessels affected has diagnostic implication (Table 13.2). Step sections encompassing the entire thickness of the tissue block may be necessary to arrive at the correct diagnosis if initial examination shows nonspecific features such as lymphocytes in the form of large aggregates or perivascularly (Fig. 13.2). The internal elastic lamina is fragmented, and the use of elastic stains alternating with H&E is helpful in the search for vascular damage.

In the acute stage of vasculitis, polymorphonuclear leukocytes can be prominent (Fig. 13.1b and 13.7a–e), but usually T lymphocytes predominate in the vessel wall and perivascular area, with variable numbers of macrophages (Kissel et al. 1989). Any nerve biopsy showing extravasation of neutrophils should be regarded as suspicious for vasculitis, as polymorphonuclear infiltrates are almost never seen in any other cause of neuropathy. However, neutrophils may also be seen in any biopsied tissue if an inordinate amount of time is taken to perform the procedure (30 min or more) (Fig. 7.13). The presence of inflammatory cells within the vessel wall is also suggestive but not diagnostic of vasculitis (vide supra). The inflammatory cells may include epithelioid elements, which can be loosely clustered, palisading, or tightly packed in association with multinucleated giant cells. Eosinophils commonly and plasma cells less frequently contribute to the cellularity. Two of four patients with Churg–Strauss angiitis whose nerve biopsies we have studied had large numbers of eosinophils within the vessel wall in perivascular spaces of epineurium (Fig. 13.8a–e). Conspicuous in one case were Charcot–Leyden crystals within the inflammatory infiltrate (Fig. 13.8d, e). The inflammatory damage

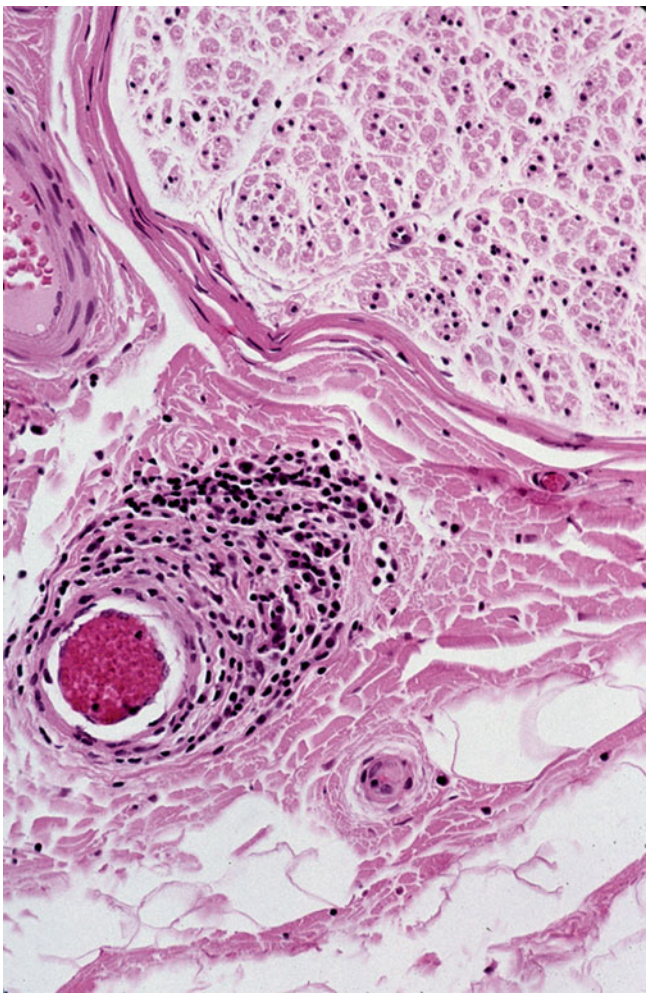


Fig. 13.2 Epineurial perivascular inflammation in the absence of necrosis does not meet the gold standard of angionecrosis, although additional adjacent sections may meet that criterion (paraffin, H&E, 400×)

to the vessel usually results in narrowing and thrombotic occlusion (Figs. 13.5b and 13.8c). Accumulation of mucoid "edema" in endoneurium, subperineurium, and around vessels is occasionally seen.

Findings indicative of the disease underlying the vasculitis are rarely present, but include such observations as CMV inclusions in endothelial cells (Fig. 11.4), detection of intravascular cholesterol crystals in cholesterol embolus syndrome (Bendixen et al. 1992), or the presence of an atypical cellular infiltration in lymphomatoid granulomatosis (vide infra).

With time, the inflammation subsides or disappears and vessels may show marked narrowing (Fig. 13.9a), fibrous obliteration or asymmetric mural fibrosis (Fig. 13.9b), calcification (Fig. 13.9c), recanalization (Fig. 13.9d–f), fragmentation of the internal elastica (Fig. 13.9g), or increased numbers of small vessels (Fig. 13.9h). This should be distinguished from vessel retraction and invagination caused by surgical trauma (Fig. 13.10a–c). A specimen displaying both acute and healed vascular lesions is typical of the polyphasic course of polyarteritis nodosa (Lie 1990). Hemosiderin-laden macrophages indicative of past hemorrhage may be found clustered in a periadventitial location (Fig. 13.4a). We have occasionally observed miniature bundles of aberrantly regenerating axons, much like a traumatic neuroma, growing into the perineurium, and regard this as suggestive evidence of a previous infarction. Schroder (1986) has drawn attention to the reactive proliferation of capillaries that can occur in the epineurium after a vascular insult (Fig. 13.9a), although this is not specific to vasculitis.

Vasculitis of endoneurial vessels is uncommon and would theoretically be classified with hypersensitivity vasculitides (Fig. 13.11). Involvement of capillaries and postcapillary venules is seen as infiltration by polymorphonuclear leukocytes and leukocytoclasis. Fibrinoid necrosis, thrombosis, and hemorrhage may also be present (Figs. 13.11, 13.12, 13.13, and 13.14). In skin biopsies the inflammatory process may show mononuclear, neutrophilic, or eosinophilic predominance and even granulomatous characteristics (Lie 1990), but whether this wide spectrum of pathology is also seen in nerve biopsy material is uncertain. In ischemic neuropathy, nerve fiber degeneration ranges from none at all to universal and from chronic to hyperacute (Fig. 13.15a, b). The geography of endoneurial damage is variable; centrofascicular or perineurial-based wedge-shaped regions of nerve fiber loss are infrequently seen in biopsy material (Fig. 13.12a, b). More typically there is multifocal axonal degeneration, and a striking variability in the severity of involvement may be seen between different fascicles (Fig. 13.6a, b) (Fujimura et al. 1991). The fibers may all be in the same stage of degeneration, suggesting a single massive insult, but more commonly evidence of both acute and chronic axonal changes is seen. Large myelinated axons can be selectively affected, but in severe lesions, all fiber types are involved (Vital and Vital 1985; Fujimura et al. 1991). Regenerating clusters will appear in the recovery phase, but may be less prominent with more severe insults, perhaps because loss of Schwann cells impairs the regenerative process (Fujimura et al. 1991).

While segmental demyelination and/or remyelination may occur, it is always subordinate to prevailing axonal degeneration (Panegyres et al. 1990; Vital and Vital 1985). Remarkably, Harati and Niakan (1986) observed segmental demyelination/remyelination in a majority of patients with vasculitic neuropathy using teased fibers, but most other workers (Said et al. 1988; Fujimura et al. 1991; Dyck et al. 1987; Hawke et al. 1991) have reported minor segmental

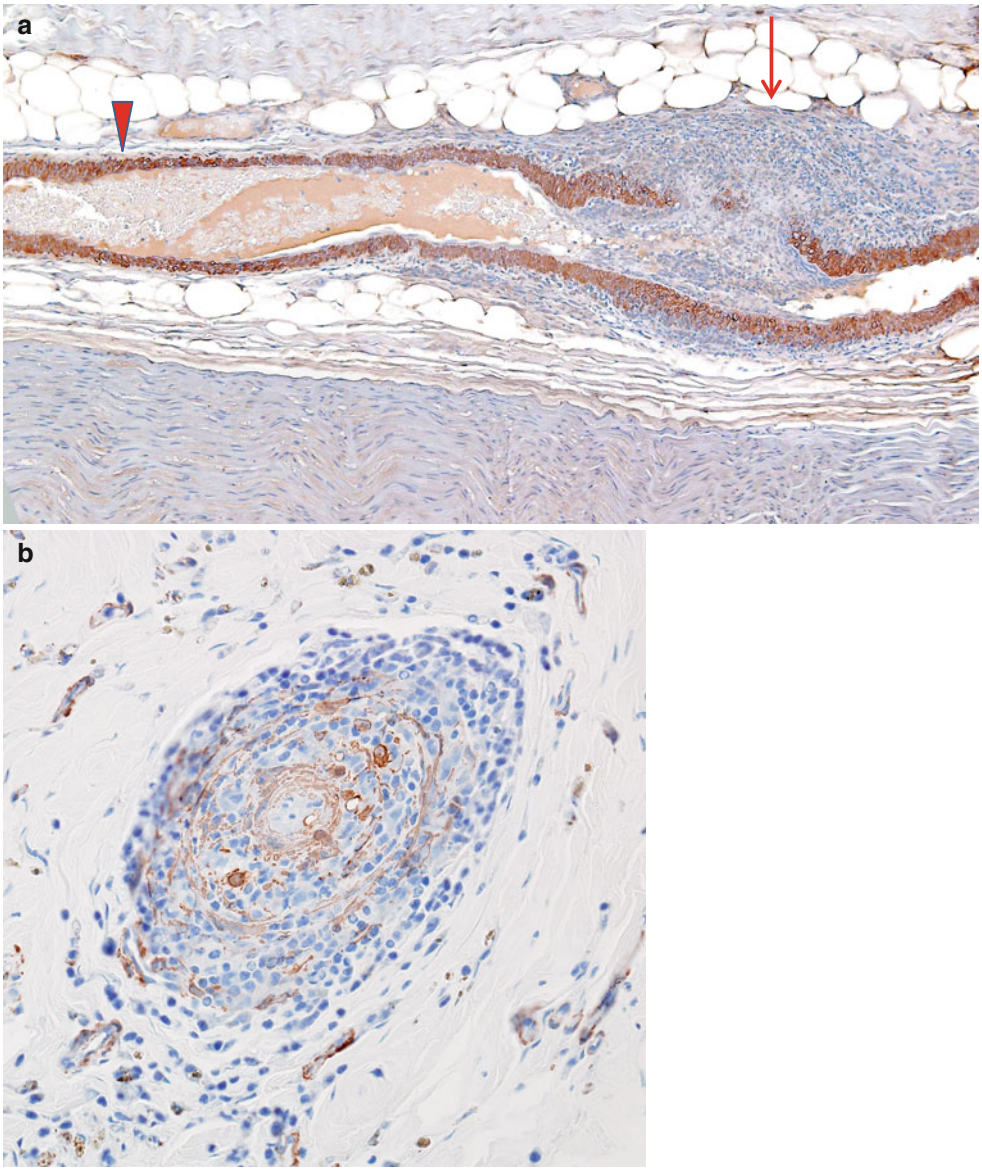


Fig. 13.3 (**a**) Vasculitis: longitudinal section of epineurial artery shows the focal nature of vasculitis. At the distalmost aspect shown (*arrow*) marked inflammation has resulted in complete thrombosis and mural destruction only a few hundred microns from a portion of the vessel exhibiting only a perivascular lymphocytic infiltrate (*arrowhead*). (**b**) Vascular cross section shows destruction of the entire smooth muscle component of the vessel wall (paraffin, anti-smooth muscle actin (anti-SMA) immunohistochemistry; magnification: **a**, 100×; **b**, 200×)

myelin pathology in a distribution suggestive of a process secondary to axonal disease, as has been amply demonstrated in experimental material.

13.2.3 Electron Microscopy

The superior resolution of electron microscopy may reveal endothelial cell necrosis and disruption of basal laminae in cases where light microscopy showed inflammation only. It has been suggested that hypertrophied endothelial cells with prominent intraluminal projections may be a helpful clue (Nemni et al. 1988), but we find this to be nonspecific.

Nonspecific axonal degenerative changes may be seen. Vesicular "demyelination" has been observed in neuropathy associated with necrotizing vasculitis, but in contrast to the picture in GBS or CIDP, the axons showed concomitant damage (Hughes et al. 1982; Vital and Vital 1985). In ischemic damage unmyelinated fibers may be as prominently involved as myelinated fibers or may show relative sparing (Said et al. 1988). Segmental demyelination may be detected, as has been shown in human material and in experimental models of ischemic neuropathy. Other than in the setting of HIV infection, tubuloreticular inclusions are a very rare finding in peripheral nerve, but we have observed them in vasculitis associated with SLE (Fig. 13.16a, b) (Case 13.1).

13.2.4 Immunohistochemistry

The predominant inflammatory cell in any vasculitis is the lymphocyte, of which 95 % or more are CD4+/helper and

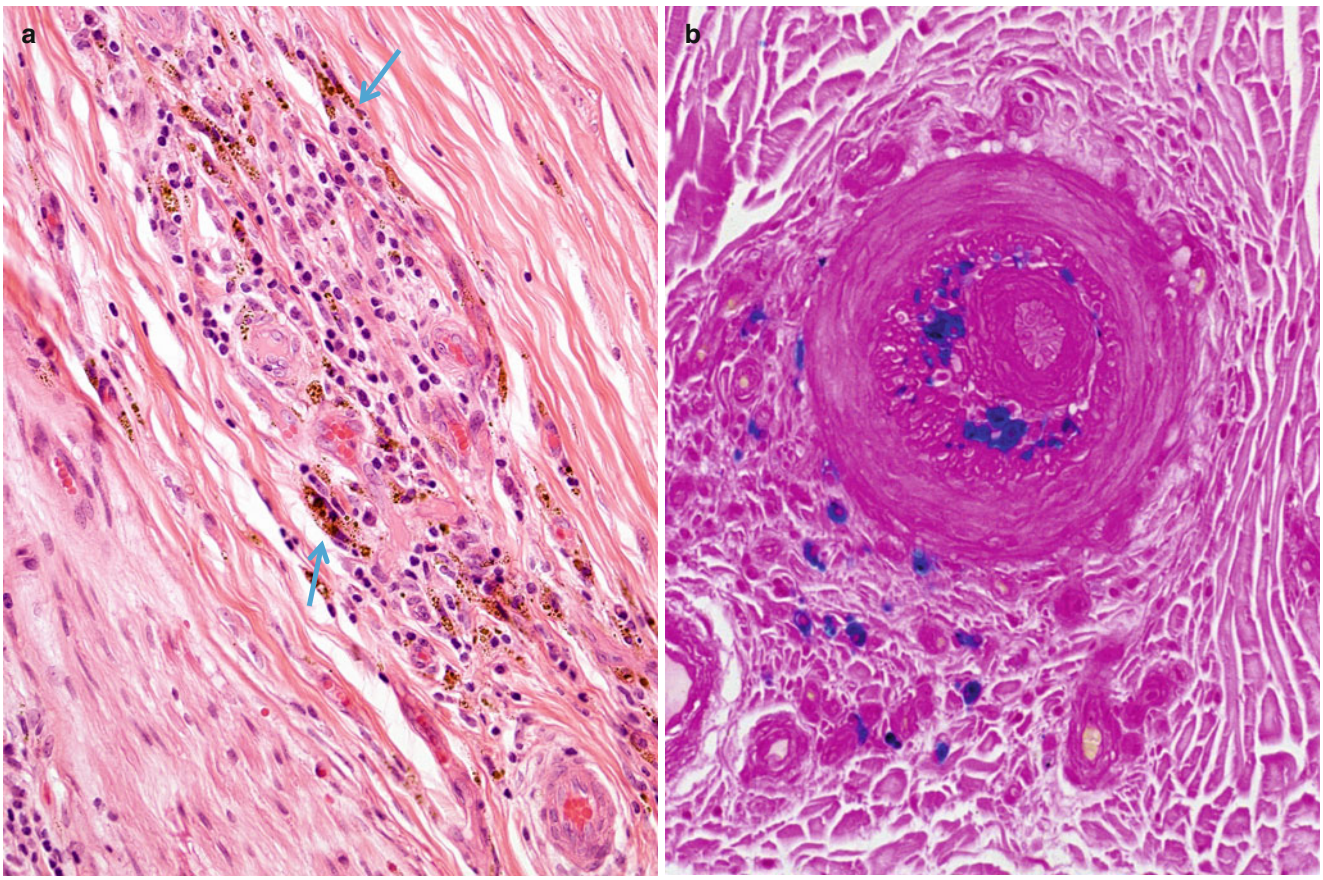


Fig. 13.4 Vasculitis, hemorrhagic residua: perivascular inflammation and hemosiderin deposition (*arrows*, **a**) are highlighted by Prussian blue stain (**b**) for iron (paraffin, **a**, H&E; **b**, Perls' iron stain; magnification: **a**, **b**, 200×)

CD8+/cytotoxic T cells (Fig. 13.17a, b) and macrophages. Depending on the acuteness of the process, variable number of neutrophils and eosinophils may also be present. Collins et al. (2010b), using combined peroneal nerve/peroneus brevis muscle biopsies, direct immunofluorescence revealed immunoglobulin, complement, or fibrinogen (DIF, IgG, IgM, and complement 3) deposits in epineurial vessel walls in 70–80 % of nerve biopsies in patients with suspected peripheral nervous system vasculitis and diabetic radiculoplexus neuropathy (Collins et al. 2010b). These authors concluded that epineurial/perimysial vascular deposits of immunoglobulin/C3 by DIF are a specific marker of vasculitic neuropathy. The less sensitive DIF may be more specific for identifying vasculitis-relevant immune deposits by not labeling low concentrations of vascular immunoglobulin and complement found in "normal" and non-vasculitic cases.

13.3 Pathogenesis

Nerve dysfunction is presumed to occur on the basis of ischemia secondary to vessel destruction, with the areas of maximal clinical involvement (mid-arm and mid-thigh), representing vascular watershed regions, as demonstrated in a remarkable study by Dyck et al. (1972). In patients with a symmetrical sensorimotor neuropathy, the mechanism is probably multiple random minor lesions which will summate to affect the longest nerve fibers more severely (Waxman et al. 1976). Axonal destruction is invariably the dominant process, but segmental demyelination attributable to ischemia is shown by the occasional finding of conduction block in biopsy-proven vasculitic neuropathy (Ropert and Metral 1990) and experimental studies of nerve ischemia.

Epineurial arterioles are in the 75–350 μm diameter size range, while perineurial and endoneurial vessels fall well below 75 μm in diameter. It is thought that this sharp size separation between the two classes of vessels relates to the far more frequent finding of epineurial damage, as most vasculitic process are vessel size specific (Dyck et al. 1972).

Activated complement and immunoglobulin deposits are found in 63–100 % of inflamed vessel walls regardless of etiology (Kissel et al. 1989; Hawke et al. 1991; Panegyres et al. 1990), and immune complexes have long been known to be associated with vasculitis (Smiley and Moore 1989). In animal models deposition of these complexes within vessel walls follows the introduction of a foreign antigen, and

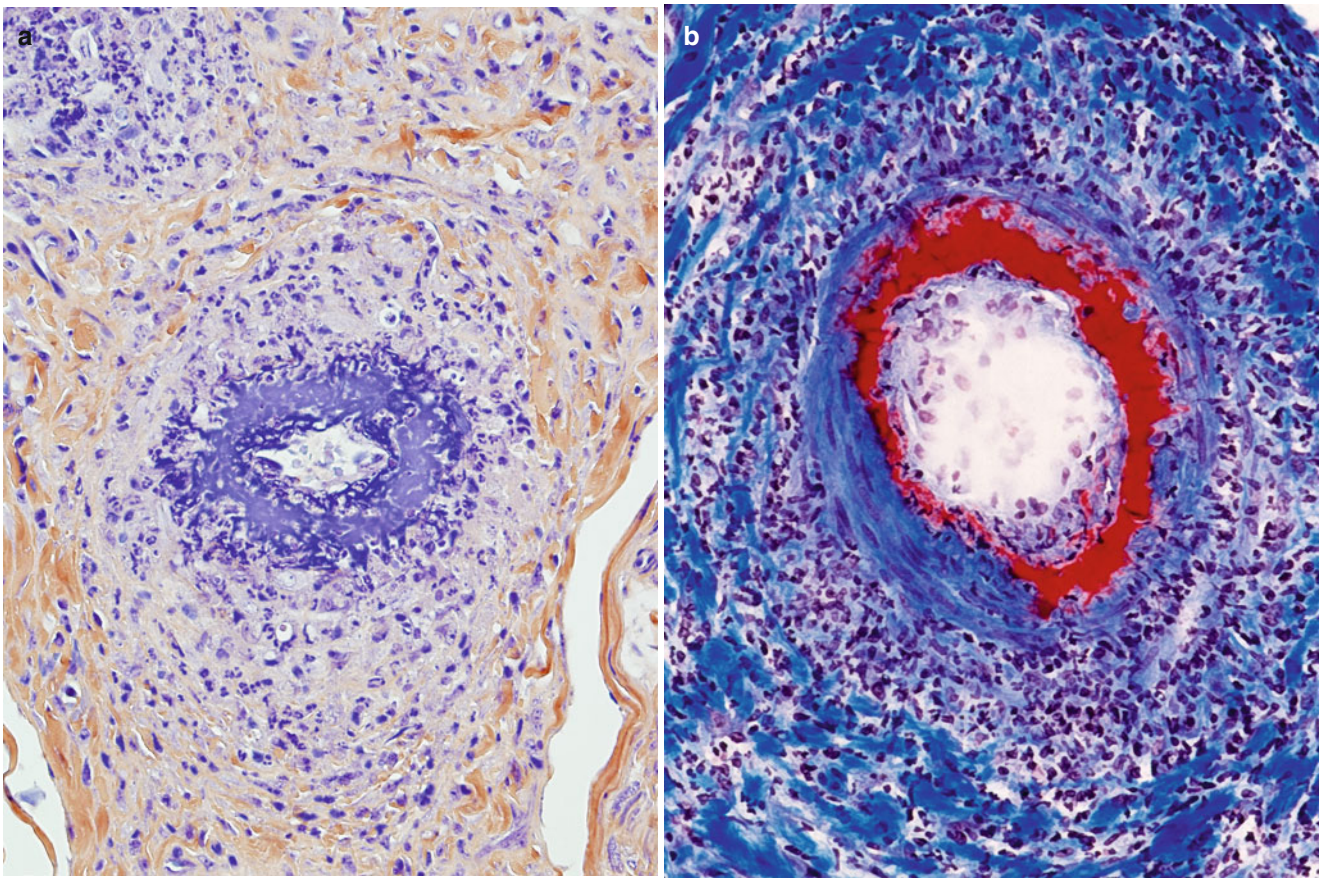


Fig. 13.5 (**a**, **b**) Fibrinoid necrosis/fibrin deposition in vasculitis (**a**) phosphotungstic acid (PTAH) stain; B, Landrum stain for fibrin (magnification: **a**, **b** ~400×)

results in activation of complement, attraction of neutrophils and other inflammatory cells, and release of toxic substances that can cause vessel wall necrosis. In human disease, a putative antigen source is sometimes found, as exemplified by hepatitis B antigen in PAN (Guillevin et al. 1988). Serum sickness and amphetamine-associated hypersensitivity vasculitis are examples of a clear-cut source of antigen for the formation of antigen–antibody complexes. It is unlikely that the immunoglobulins identified in vessel walls are generated at the site of the lesion, as B cells are very infrequent in the vascular lesion (Kissel et al. 1989). Despite the lack of a source of antigen–antibody complexes, immunoglobulin and complement deposits are also seen in patients with isolated PNS vasculitis (Kissel et al. 1989).

Immunohistochemical studies of the cells involved in vasculitis suggest that other mechanisms may be at play. Activated T cells form a major component of the inflammatory infiltrate regardless of underlying disease (Kissel et al. 1989; Panegyres et al. 1990), and the observation that they are predominantly of the CD8 subtype suggests an important role for cytotoxic T-cell-mediated damage, perhaps directed at a vascular antigen (Panegyres et al. 1990), or an antigen presented by endothelial cells (Kissel and Mendel 1992; Panegyres et al. 1992). It may be that the deposition of immunoglobulin and complement is not a primary cause of the vasculitis, but follows the cell-mediated attack (Kissel and Mendel 1992).

Mechanisms of vasculitis are probably heterogeneous, disease specific (Panegyres et al. 1990), and perhaps tissue specific. Excellent reviews in the pathogenesis of vasculitic neuropathy are available (Younger 2004; Pagnoux and Guillevin 2005; Gwathmey et al. 2014).

13.3.1 Significance of Size of Involved Vessels

Epineurial vascular involvement is said to be typical of PAN, CSS, WG, and isolated PNS vasculitis (Dyck et al. 1987; Marazzi et al. 1992; Fujimura et al. 1991). Epineurial arterioles are usually 75–350 μm in diameter, and there may be a tendency towards involvement of vessels in the lower part of this size range in isolated PNS vasculitis (Dyck et al. 1987). Involvement of veins is more common in WG and CSS than in PAN (Lie 1990). Endoneurial vessels are usually <30 μm in size, and arterioles, venules, and capillaries of this caliber in both endoneurium and epineurium are the typical

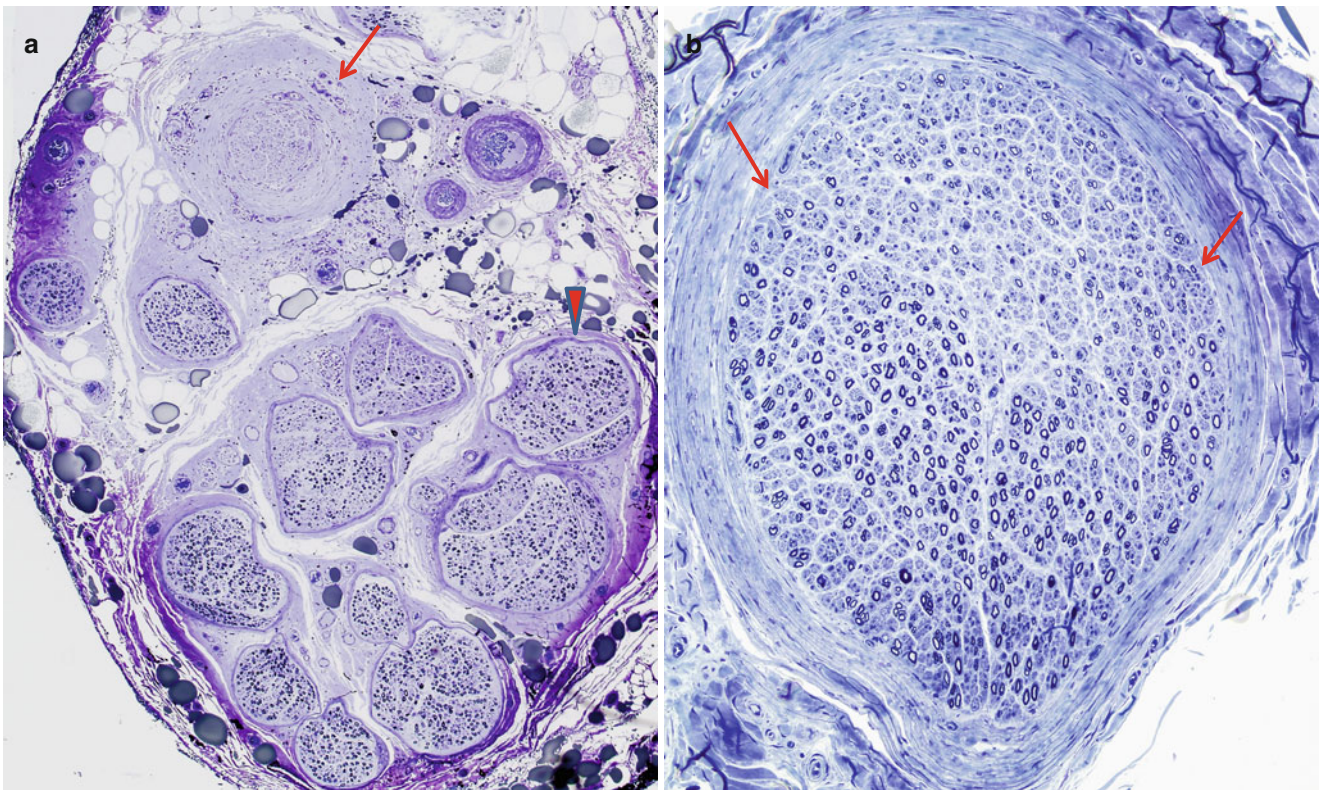


Fig. 13.6 Ischemic pattern of axon loss: (**a**) typical pattern of fascicle-to-fascicle variability of axon loss is characterized by marked axon loss (*arrow*) compared to more modest loss (*arrowhead*). Note that none of the vessels in the cross section demonstrate vasculitis. (**b**) Individual fascicles show intrafascicular variability with patches of axon loss (delimited by *arrows*) (1 μ thick plastic sections; magnification: **a**, 100×; **b**, 200×)

Table 13.2 Clues to the presence of remote vasculitis

Luminal narrowing or thrombosis
Disorganization of vessel: intimal hyperplasia, thinning or proliferation of the media, breakup of circumferential ring of internal elastic lamina
Vessel sclerosis, recanalization
Proliferation of epineurial capillaries
Old hemorrhage in nerve (hemosiderin, positive Perl's Prussian blue)
Nonuniform fascicular or multifocal axonal degeneration
Vascular immunoglobulin and complement deposition
Focal calcification of or near vessel walls
Focal perineurial damage with aberrant regenerating nerve bundles

site of injury in SLE, hypersensitivity vasculitis, Henoch–Schönlein purpura, and essential mixed cryoglobulinemia. Vessels in either size range can be involved in the collagen diseases. While these guidelines are useful in the differential diagnosis, any conclusion drawn must consider that overlap syndromes, in which vessels of all sizes are involved, are not uncommon. Review of the literature on vasculitis, based on histology of nerve or other tissues, indicates that PAN, Wegener's granulomatosis, Churg–Strauss angiitis, rheumatoid arthritis, SLE, Sjögren syndrome, cryoglobulinemia, and scleroderma may all show involvement of vessels in a size range considered atypical for that disease (Bouche et al. 1986; Dyck et al. 1987; Vincent et al. 1985; Lie 1989; Fauci et al. 1978; Leavitt and Fauci 1986; Vincent et al. 1985). Because of this overlap, the caliber or type of vessels involved does not point to a specific diagnosis. Vincent and colleagues reviewed 40 biopsies where only vasculitis involving arterioles, venules, and capillaries less than 70 μm in diameter was present (Vincent et al. 1985). The clinical diagnoses include PAN, RA, CSA, and SLE, despite the absence of arteriolar necrotizing vasculitis. Eleven patients had an isolated neuropathy in association with "microvasculitis," contradicting the suggestion that only epineurial vessels are involved in isolated PNS vasculitis (Dyck et al. 1987).

13.3.2 Significance of Inflammatory Cell Types

Eosinophils are seen in vasculitis of various etiologies and are especially well demonstrated by Giemsa histostain. Their presence does not necessarily correlate with peripheral eosinophilia (Vincent et al. 1985; Lie 1990; Ijichi et al. 1991). The finding of eosinophils in the vasculitic infiltrate has little diagnostic specificity, but if they are very prominent Churg–Strauss angiitis (CSA) should be considered more

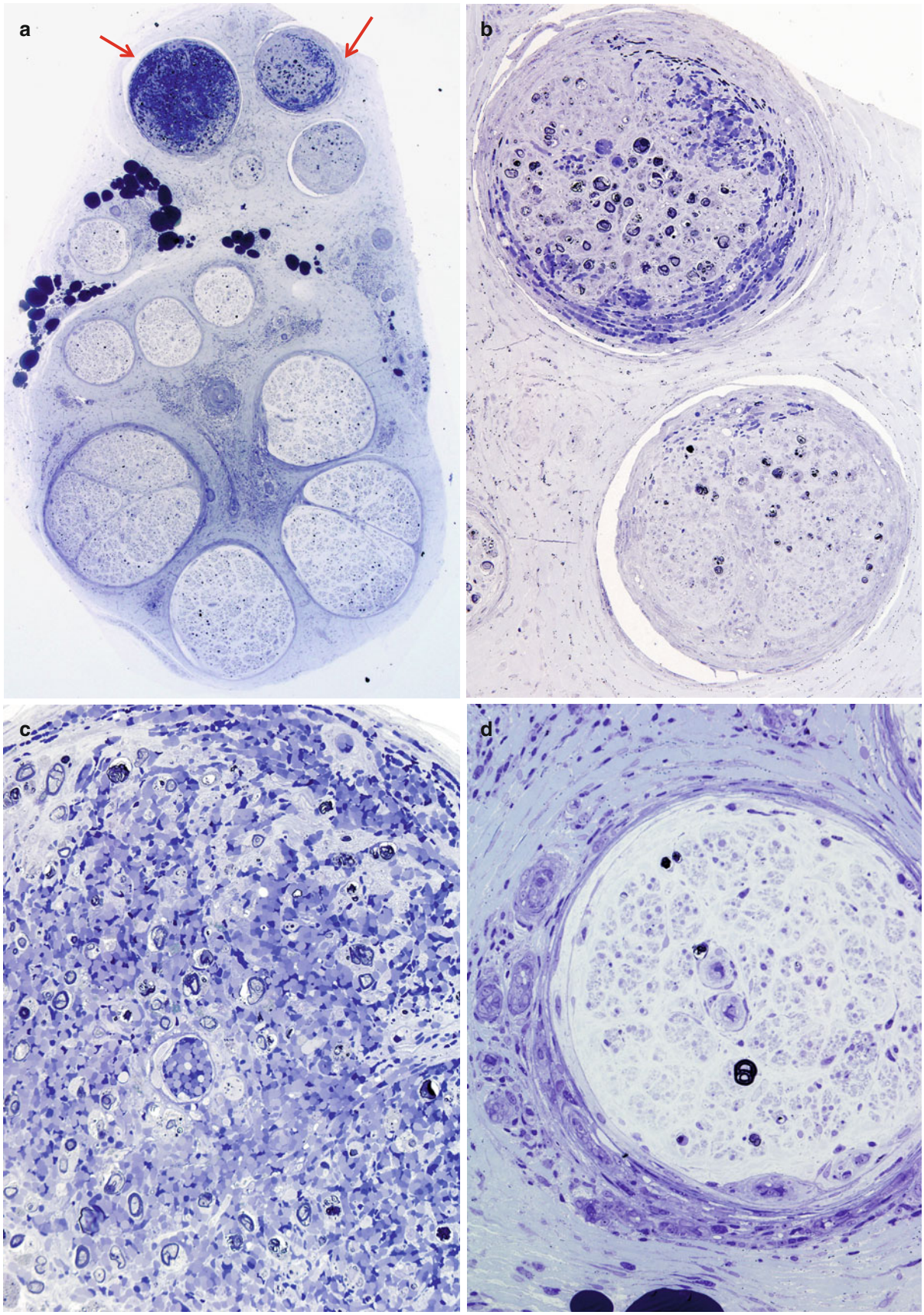


Fig. 13.7 Polyarteritis nodosum (PAN): (**a**) two fascicles show hemorrhagic necrosis (*arrows*). (**b**, **c**) Higher magnification of involved fascicles show hemorrhage and axonal degeneration. (**d**) Axonal depletion is the cardinal feature in all other fascicles. (**e**) Epineurial perivascular chronic inflammation is accompanied by a vessel showing resolving vasculitis (*arrow*). (**f**) Perivascular inflammation in the absence of angionecrosis is also common. (**a**–**f** 1 μ thick plastic sections, **f** paraffin, H&E; magnification: **a**, 40×; **b**, 200×; **c**, **d** 600×; **e**, 100×; **f**, 400×)

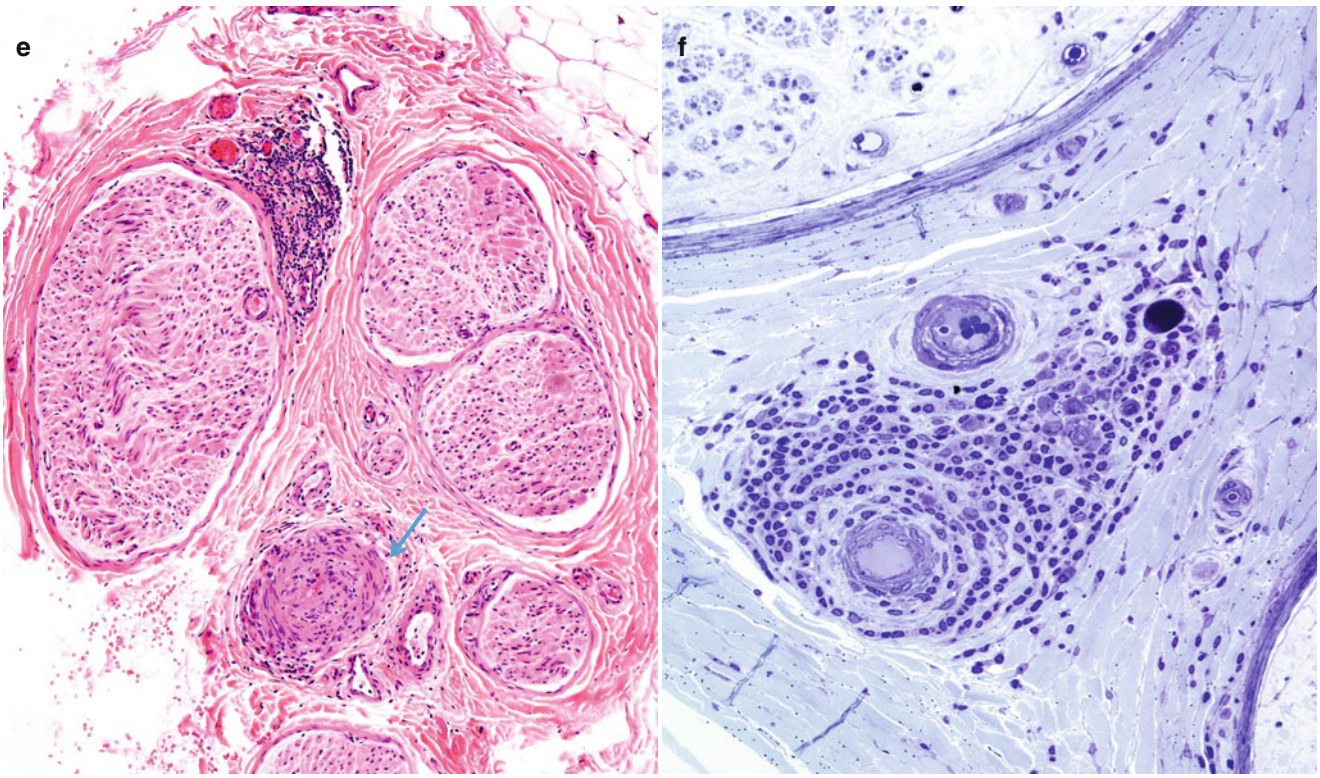


Fig. 13.7 (continued)

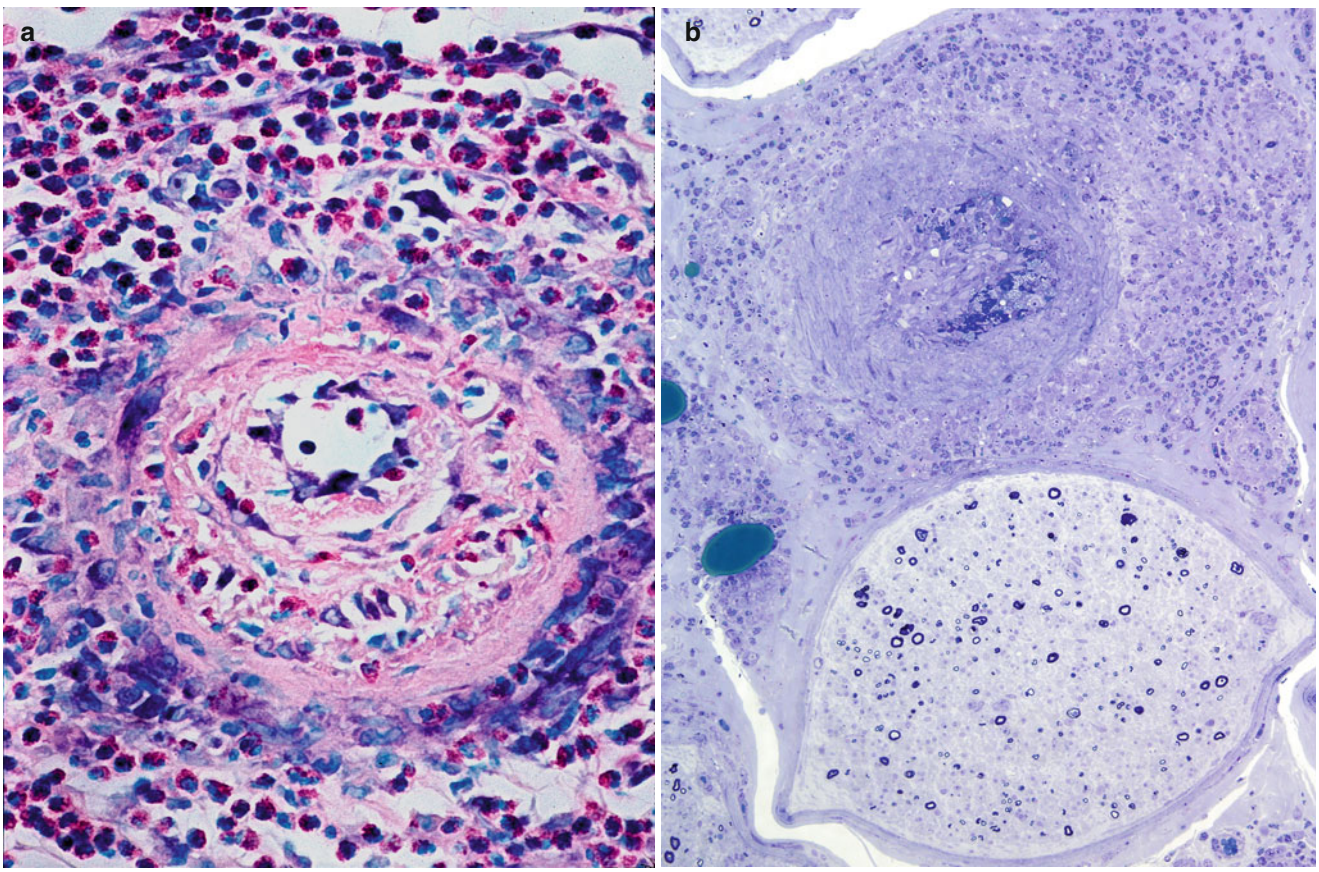
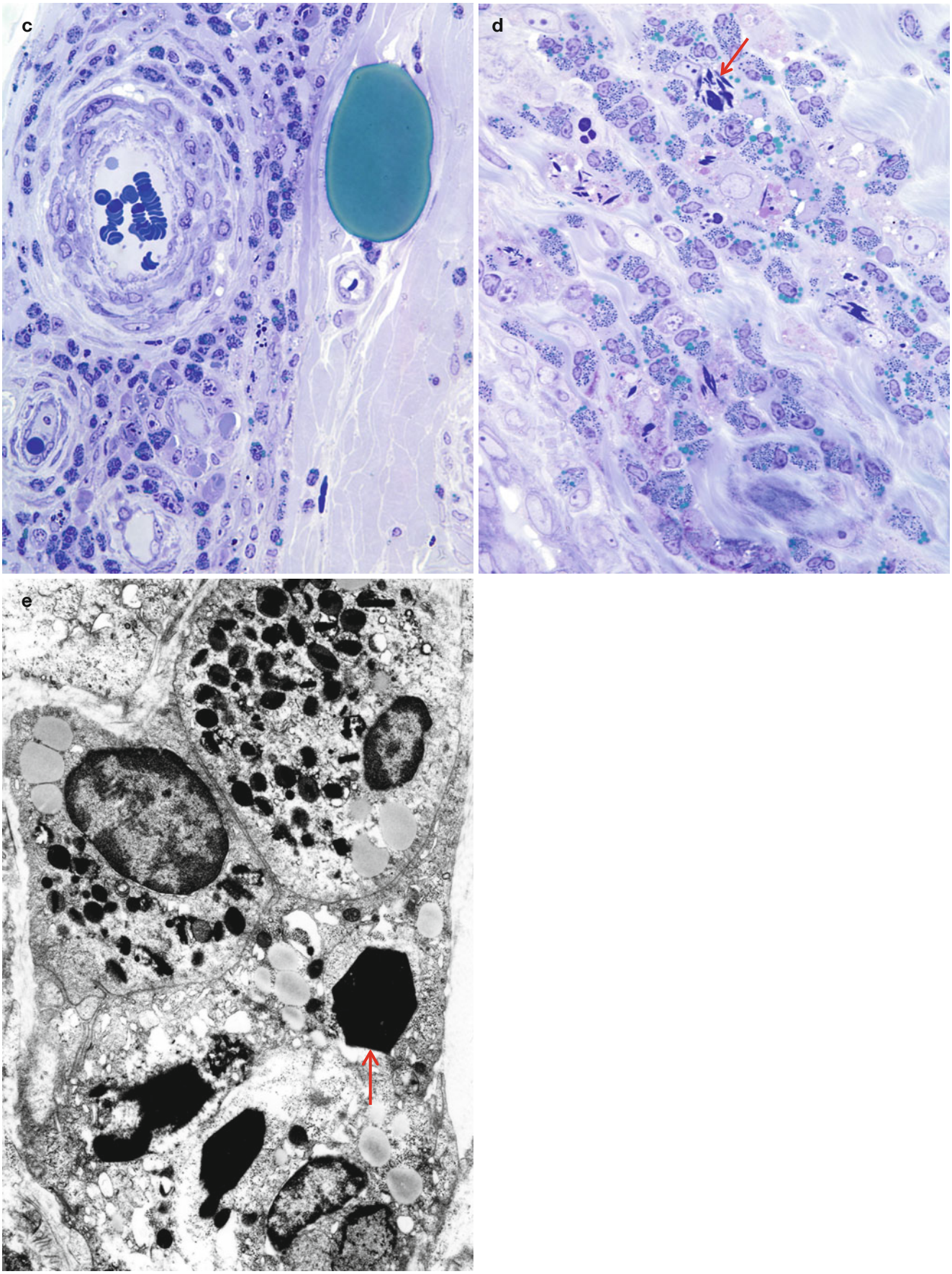


Fig. 13.8 Churg–Strauss angiitis: (**a**) eosinophils predominate in vascular and perivascular inflammation, which ranges from fibrinoid necrosis/thrombosis (**b**) to marked inflammation lacking angionecrosis. (**c**) Note Charcot–Leyden crystal formation (*arrows*, **d**, **e**) (**a**, paraffin, H&E; **b**–**d** 1 μ thick plastic sections; **e**, electron micrograph) (magnification **a**, **c**, 400×; **b**, 300×; **d**, 600×; **e**, 6,000×)



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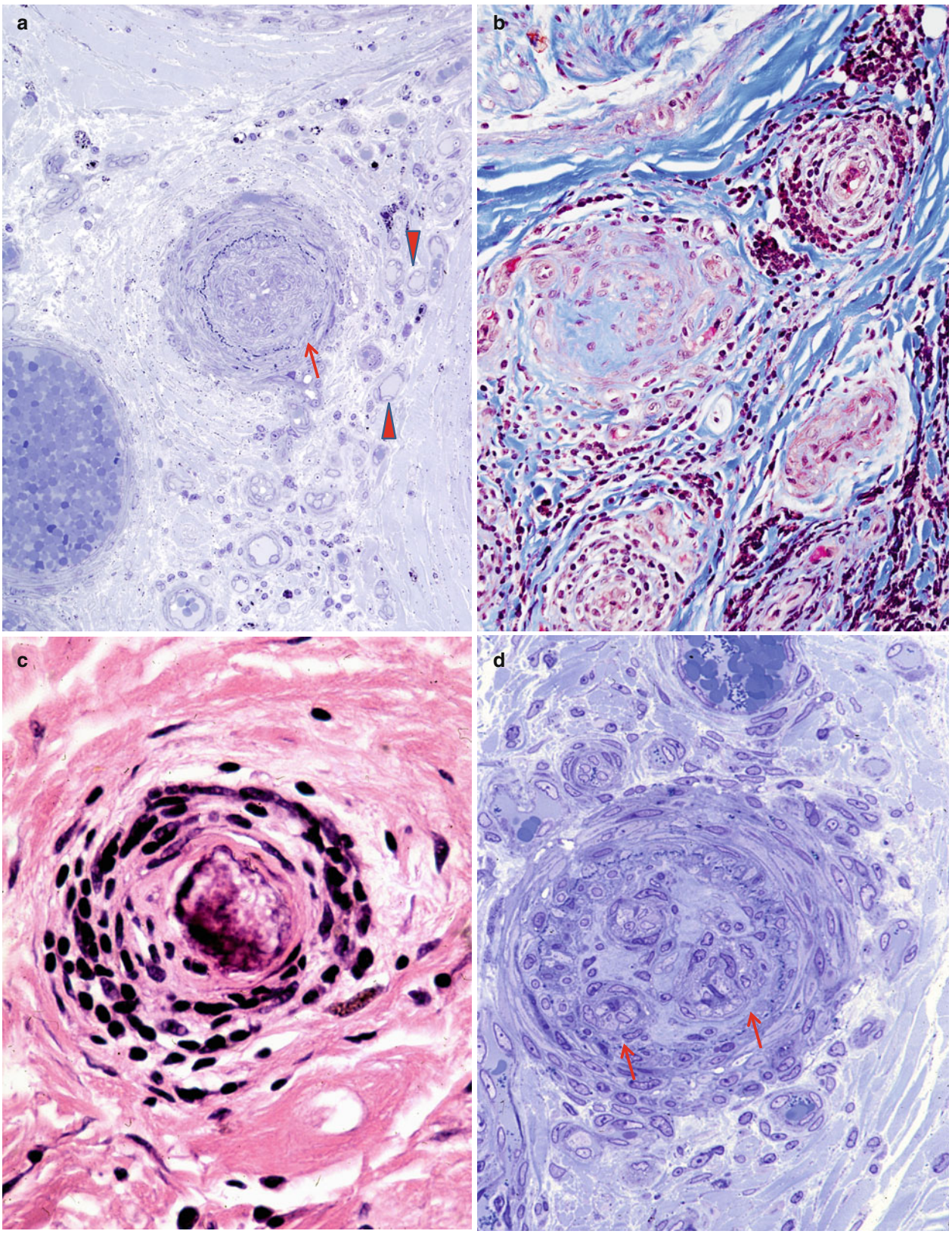
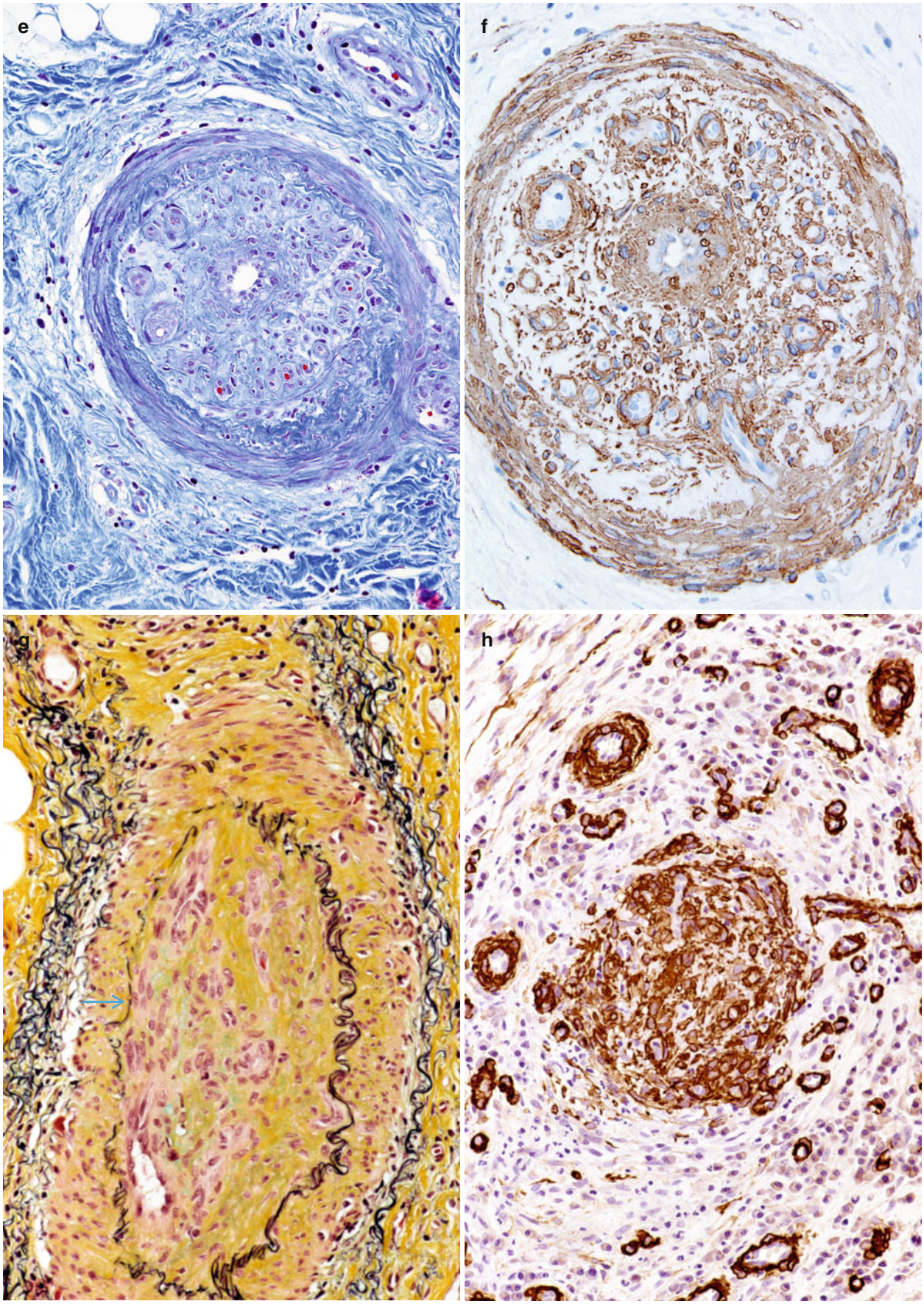


Fig. 13.9 Remote vasculitis. (**a**) A small epineurial vessel shows luminal thrombosis, loss of part of the internal elastic lamina (*arrow*) and increased numbers of small telangiectatic vessels (*arrowheads*). (**b**) One destroyed vessel shows occlusion and patchy fibrosis in this trichrome stain for collagen in the presence of damage to adjacent inflamed vessels. (**c**) Chronic inflammation surrounds a calcified epineurial vessel. (**d**) An obstructed vessel has recanalized to form small channels (*arrows*). (**e**, **f**) Recanalized small vessel has formed multiple channels resembling an intraneural vascular malformation, within its original adventitia as seen in trichrome (**e**) and smooth muscle actin immunostain (**f**). (**g**) Elastin stain shows recanalization within the remnants of the internal elastic lamina (*arrow*). (**h**) Proliferation of reactive vessels is highlighted by CD34 immunohistochemistry and elastin stain (**g**) (**a**, **d** 1 μ thick plastic sections; **b**, **c**, **e**,**f**, **g** paraffin) (magnification: **a**, **b** 400×;**c**–**f**, 400×)



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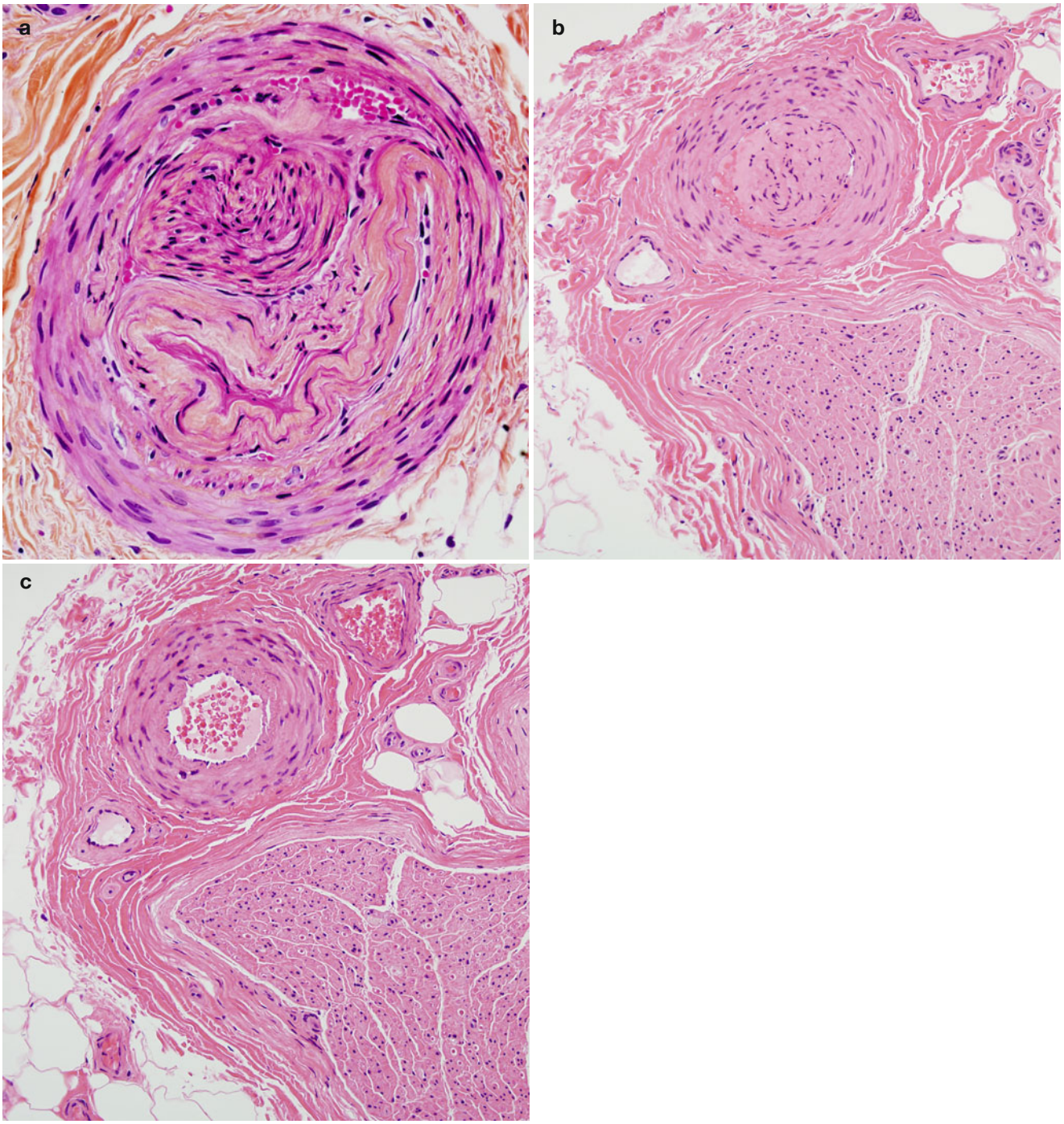

Fig. 13.10 (**a**) Retraction and invagination of arterial wall near resection site is a crushing artifact which should not be confused with healed vasculitis. Epineurial artery shows the effect of artifactual crush injury (**b**) which disappears in deeper section (**c**) (paraffin, **a** HPS trichrome, **b**, **c**: H&E) (magnification 400×)

strongly (Oh et al. 1986). This has also been our experience: eosinophils were prominent in the inflammatory infiltrate in only two of the four cases of vasculitic neuropathy in CSA that we have examined. In a study of 7 nerve biopsies in patients with neuropathy and CSA, only nonspecific perivascular inflammatory infiltrates and one perineurial granulomatous lesion were seen (Inoue et al. 1992). In three cases reported by Marazzi et al. (1992), epineurial necrotizing vasculitis was seen in 2, but eosinophils did not form a significant part of the inflammatory infiltrate, and were only occasionally seen in the necrotizing vasculitis described by other authors (Weinstein et al. 1983; Aupy et al. 1983). Eosinophils in perivascular infiltrates and peripheral nerve "inflammatory angiopathy" have also been described in eosinophilia myalgia syndrome (Smith and Dyck 1990). The idiopathic hypereosinophilic syndrome only rarely demonstrates inflammatory infiltrates, and the distinction between this syndrome and CSA may be unclear.

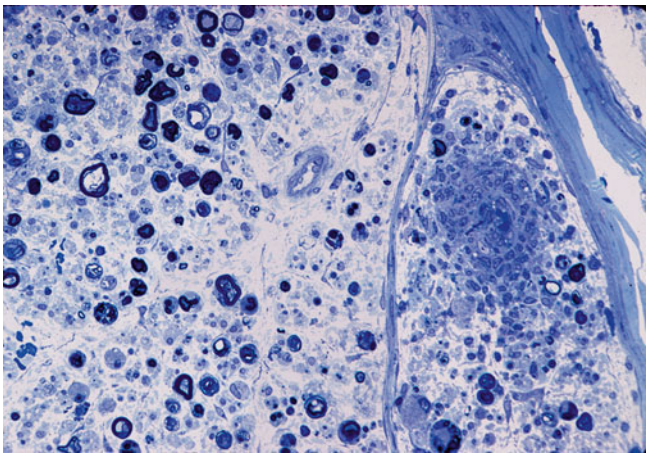

Fig. 13.11 Churg–Strauss angiitis: against a background of acute axonal degeneration, an endoneurial vessel shows transmural and perivascular inflammation (1 μ thick plastic sections, 600×)

The cellular content and characteristics of the vascular inflammatory infiltrate does not distinguish reliably between the most important disease processes: PAN, CSA, WG, and isolated PNS vasculitis (Dyck et al. 1972, 1987; Stern et al. 1965). Frankly granulomatous angiitis is infrequently seen in peripheral nerve, but the literature on systemic vasculitis suggests that granulomatous angiitis can be seen in PAN, SLE (Lie 1989,1990), or RA (Yoshioka et al. 1989), although it is more typical of Wegener's granulomatosis and CSA (Aupy et al.1983; Stern et al. 1965; Evans et al. 1992). Conversely, granulomatous angiitis is not always seen in vasculitis associated with CSA or WG (Marazzi et al. 1992; Lie 1990). Thus, classification of a systemic vasculitis cannot be based solely on peripheral nerve biopsy findings (Evans et al. 1992). The differential diagnosis of granulomatous angiitis also includes leprosy, sarcoidosis, and lymphomatoid granulomatosis.

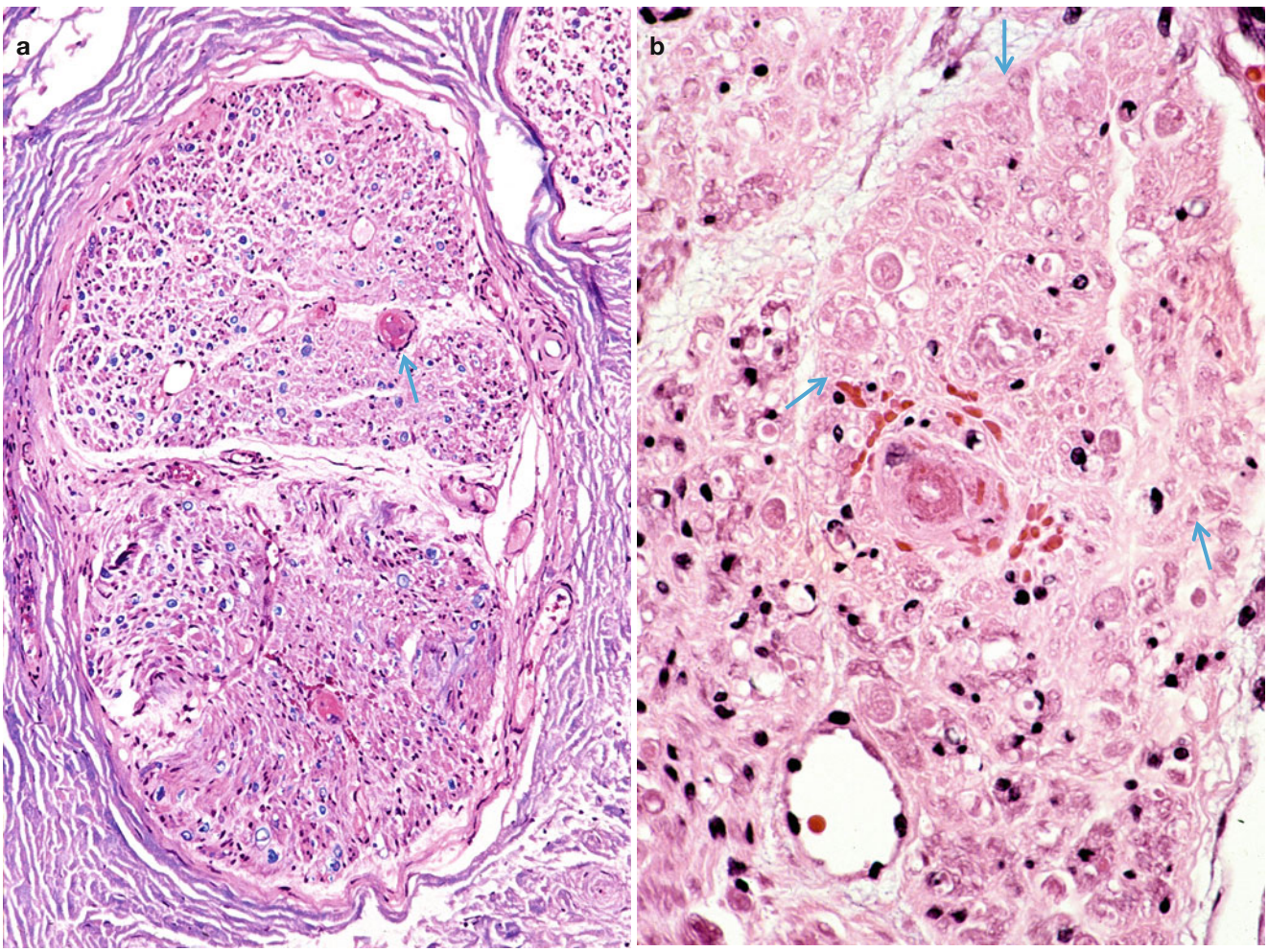

Fig. 13.12 SLE. Ischemia appears as pallor around a thrombosed microvessel (*arrow*, **a**) at the center of fascicle resulting in confluent area of necrosis (*arrow*, **b**) (paraffin, H&E, ~400×)

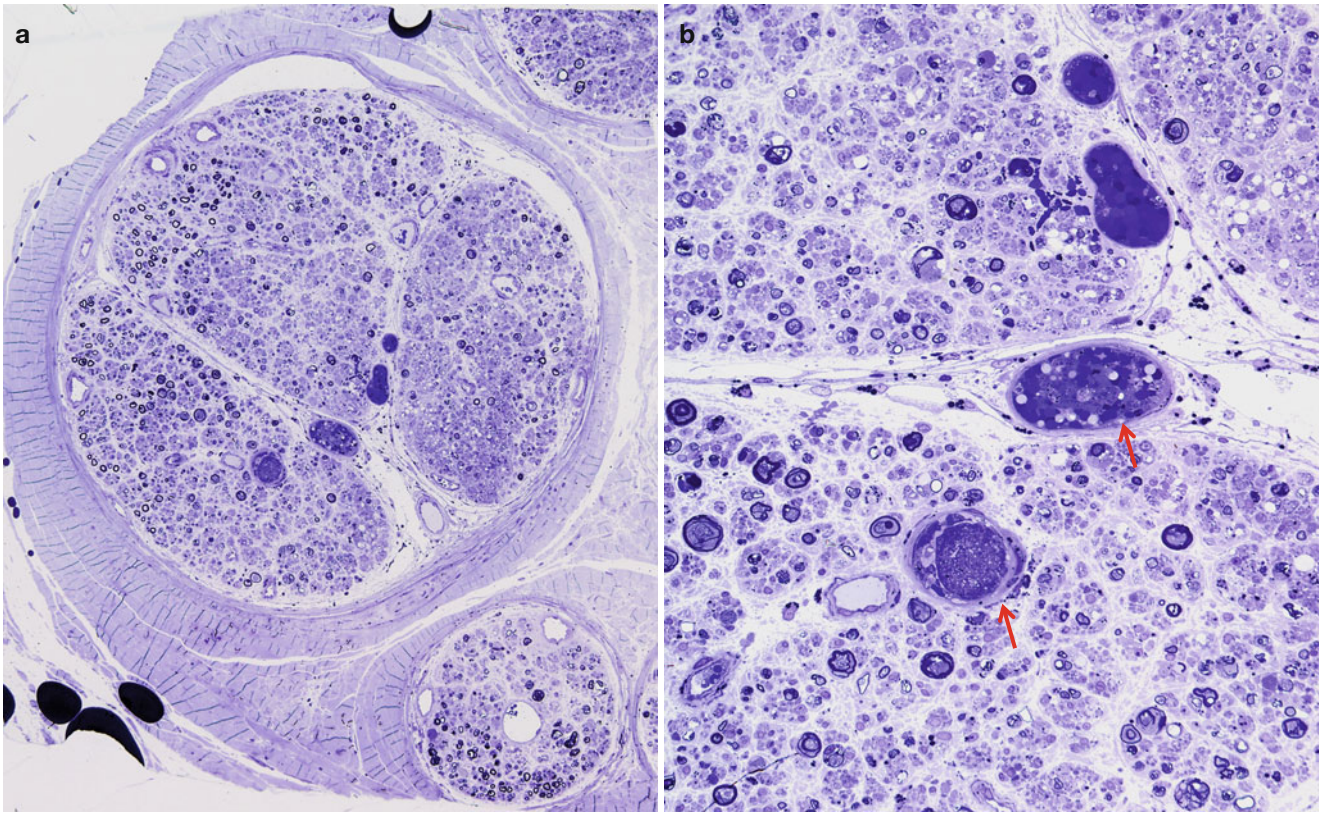

Fig. 13.13 SLE. Plastic sections demonstrate axon loss at the center of the fascicle (**a**, **b**) and thrombosis of the adjacent microvasculature (*arrows*) (1 μ thick plastic sections, magnification: **a**, 400×; B, 1,000×)

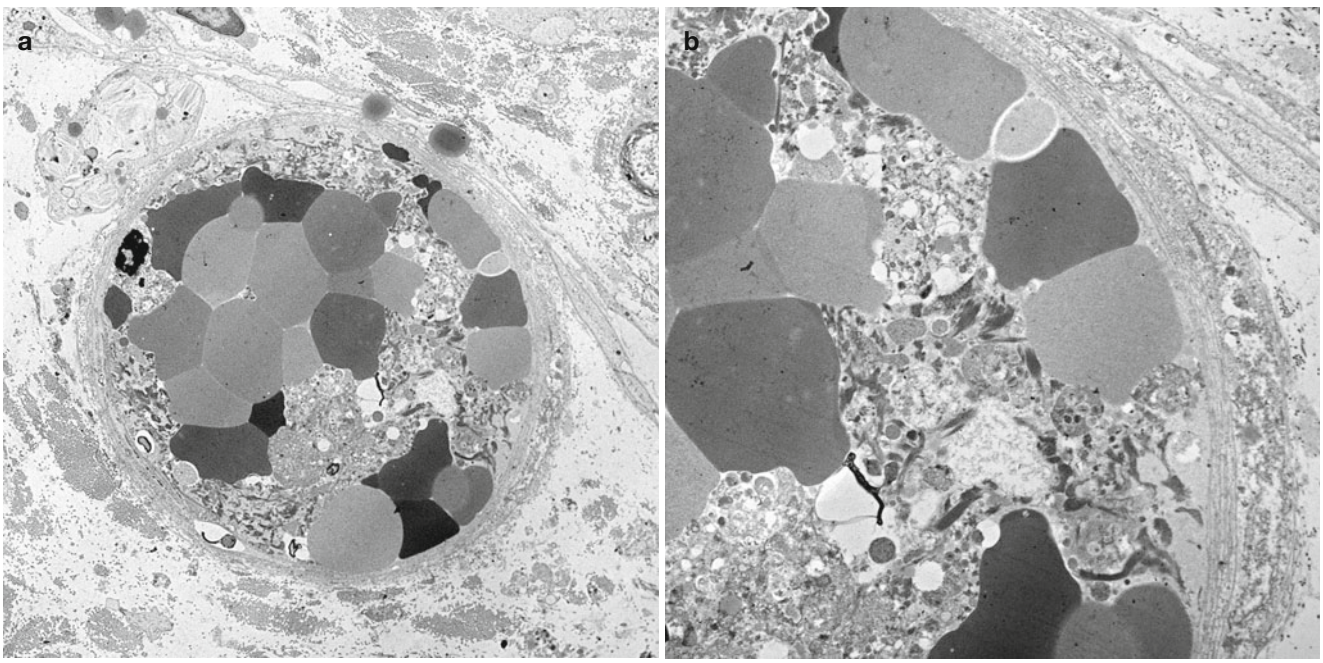

Fig. 13.14 SLE. (**a**, **b**) Ultrastructural appearance of thrombosed vessels shows an admixture of red cells, platelets, and fibrin leading to dissolution of the endothelium (magnification: **a**, 3,000×; **b**, 7,500×)

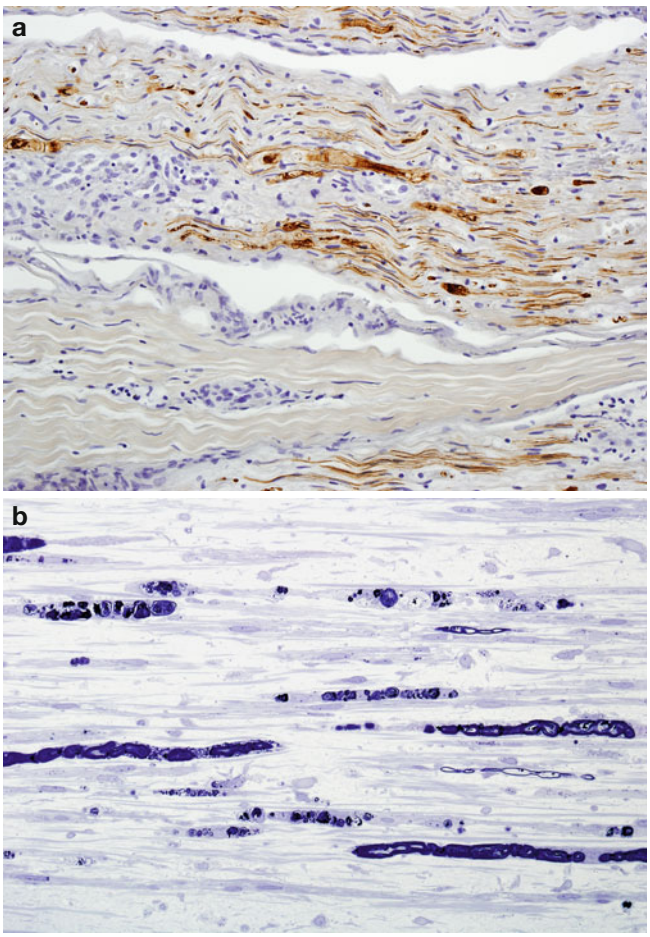

Fig. 13.15 Vasculitis. (**a**, **b**) Actively degenerating axons shown in longitudinal section as seen with neurofilament immunohistochemistry (**a**) and in plastic section (**b**) (magnification: paraffin section, **a**, 400×; **b**, 1 μ thick plastic sections, 600×)

Hemorrhage in vessel wall can be used to support a diagnosis of vasculitis, but other evidence of vasculitis should be seen, as neural hemorrhage can also be seen in hemorrhagic diathesis, which can present with a mononeuritis multiplex (Greenberg and Sonoda 1991).

13.3.3 Other Elements of Differential Diagnosis

Primary PNS vasculitis may be difficult to distinguish from CIDP if only perivascular inflammation, without typical vascular lesions, is seen. Acute axonal degeneration favors the former, while prominent segmental demyelination is characteristic of the latter. Inflammation is typically predominantly endoneurial in CIDP, but epineurial in most vasculitides. Florid perivascular inflammation is quite uncommon in CIDP.

Neural vasculitis may be seen in infectious causes of vasculitis, including leprosy in acute erythema nodosum leprosum reaction, CMV- or HIV-associated vasculitis, and Lyme neuritis. Usually the clinical information provides the necessary information, but appropriate histochemical and immunostaining can provide confirmation.

Case 13.1
Ten years prior to nerve biopsy, a 49-year-old woman was diagnosed as having SLE when she presented with fever of unknown origin, arthralgia, serositis, epilepsy, hematological abnormalities, and positive ANF. A sister also was said to suffer from SLE. Long-term treatment with steroids (5 mg/2.5 mg, alternate days) was instituted. Three years prior to nerve biopsy, the patient developed burning paresthesia in the left foot, progressing over 2 years to numbness and paresthesia of both feet. Initial neurological assessment disclosed wasting of foot muscles, no weakness, and absence of the ankle jerks only. All sensory modalities were reduced in a stocking distribution to the ankles. Electrophysiological tests revealed a mild symmetrical sensorimotor neuropathy, with borderline normal conduction velocities and reductions in CMAP and sensory amplitudes. EMG disclosed mild denervation and evidence of chronic re-innervation in foot muscles. Following sural nerve biopsy, the patient's steroid dose was increased to 30 mg/day, with reduction in ESR from 55 to 10, but little change in her symptoms. The neuropathy did not progress further and remained a relatively insignificant part of her general medical illness for the next 10 years. Following death due to cardiac arrest at the age of 68, autopsy examination revealed multisystem chronic disease consistent with longstanding SLE.

Discussion of pathology: We are aware of no other cases in the literature where tubuloreticular (undulating tubules) inclusions were detected in peripheral nerve in association with a collagen disease (discussion of TRI's: Sect. 7.5.4), although this finding is commonly seen in endothelial cells of HIV-infected patients (clinical material courtesy of Dr. D. McGillivray)

13.4 Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) is a rare, angiocentric lymphoproliferative disease EBV driven, most often affecting the lungs of affected individuals (Katzenstein et al. 2010; Dunleavy et al. 2012). Most LYG patients are middle aged with male predominance, and most do not have a history of immunodeficiency. Multisystem involvement is often seen, including peripheral neuropathy in 7–15 % (Liebow et al. 1972; Katzenstein et al. 1979). Tissues involved in LYG show an infiltrative lymphocytic, angiodestructive,

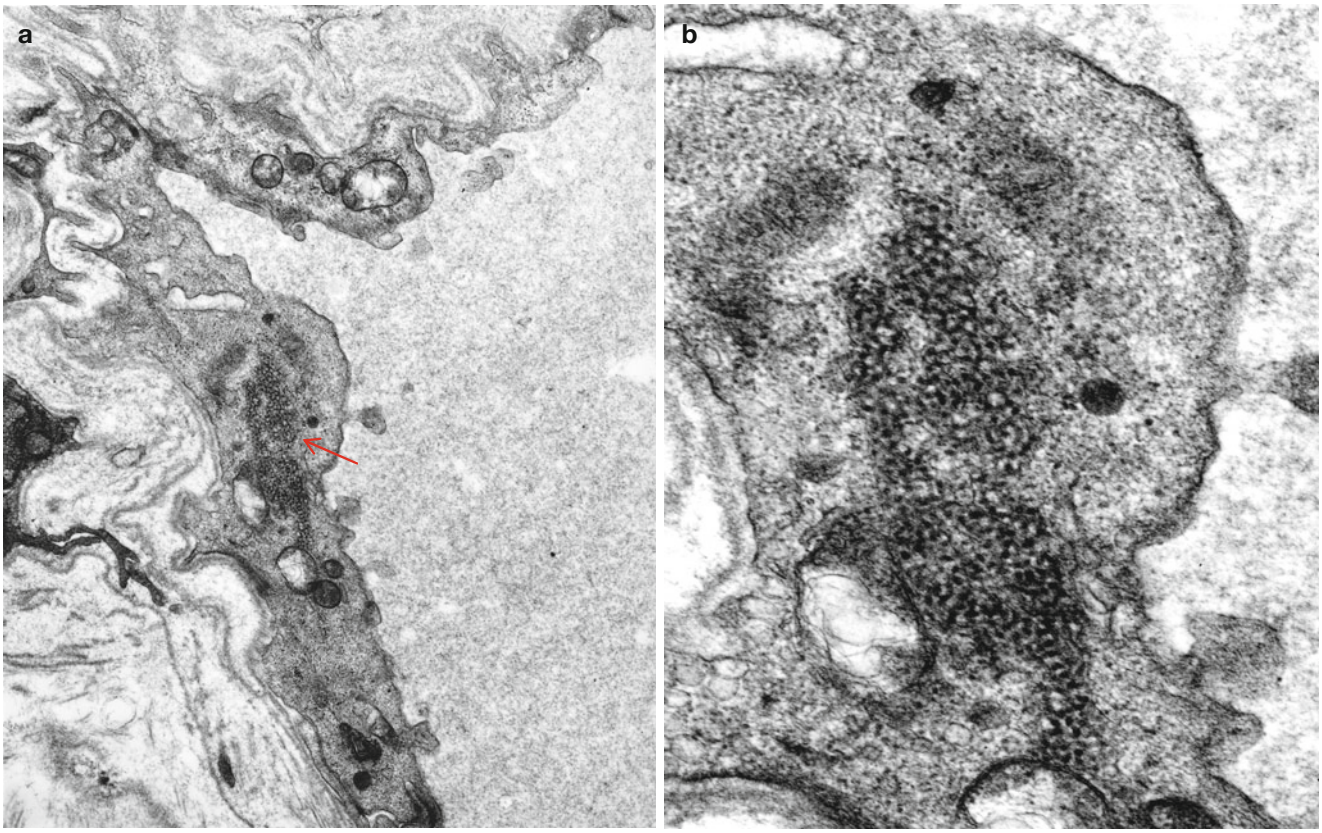

Fig. 13.16 SLE. (**a**, **b**) Endoneurial endothelial cell contains intracytoplasmic inclusion (*arrow*, **a**) also shown at higher magnification (**b**) (electron micrographs, **a**, magnification 10,000×; **b**, 39,100×)

non-leukocytoclastic process with varying numbers of large, often atypical, CD20 and CD30 and EBV-positive B lymphocytes accompanied by numerous CD3-positive small T lymphocytes and scattered admixed plasma cells and histiocytes but lack giant cells or epithelioid cell palisading. Intimal thickening of blood vessels and accompanying necrosis are demonstrable in many cases. LYG can be divided into three grades according to the prevalence and proportion of large atypical EBV-positive B cells and necrosis against a background of reactive lymphocytes (Peiper 1993; Katzenstein et al. 2010). Dunleavy et al. (2012) hypothesize that progressive oncogenic events transform lower-grade to higher-grade disease: grades I and II are polyclonal or oligoclonal, and grade III is polyclonal.

It has been suggested that LYG with increased atypia (grades 2 and 3) be classified as LYG-derived lymphoma either T-cell-rich large B cell lymphoma or diffuse large B cell lymphoma (Katzenstein et al. 2010). We discuss LYG in this chapter because vascular necrosis is part of the pathology (Dunleavy et al. 2012).

Peripheral nerve material is scanty, with Liebow's original article mentioning peripheral nerve examination in three patients, revealing atypical lymphoid cell infiltration, loss of myelin, and fibrosis, but without specific mention of vasculitis or discussion of the clinical picture in these patients (Liebow et al. 1972). Henson and Urich (1982) illustrate an example of a LYG in a woman with "unclassified lymphoma" who late in the course of her illness developed mononeuritis multiplex. Biopsy showed a necrotizing arteritis with massive lymphoplasmacytoid infiltration (Henson and Urich 1982, p 246). In another report of LYG with mononeuritis multiplex, thickened perineurium and massive diffuse and perivascular inflammatory infiltrates without necrosis of epineurial vessels were described. The two cases mentioned in this latter report mimicked tuberculoid or borderline leprosy clinically and histologically (Garcia et al. 1978). In a case we have examined (Fig. 13.18, Case 13.2), low-power views were indeed reminiscent of leprosy, but higher magnification revealed atypical mononuclear cells infiltrating all compartments of the peripheral nerve, with an angiocentric predominance (Fig. 13.18a–e). Fibrinoid necrosis was not seen, but the infiltrating cells obliterated epineurial vessels which at times showed recanalization (Fig. 13.18d, e). The atypical cellular infiltrate immunostained positively for T-cell markers (UCHL-1, CD43).

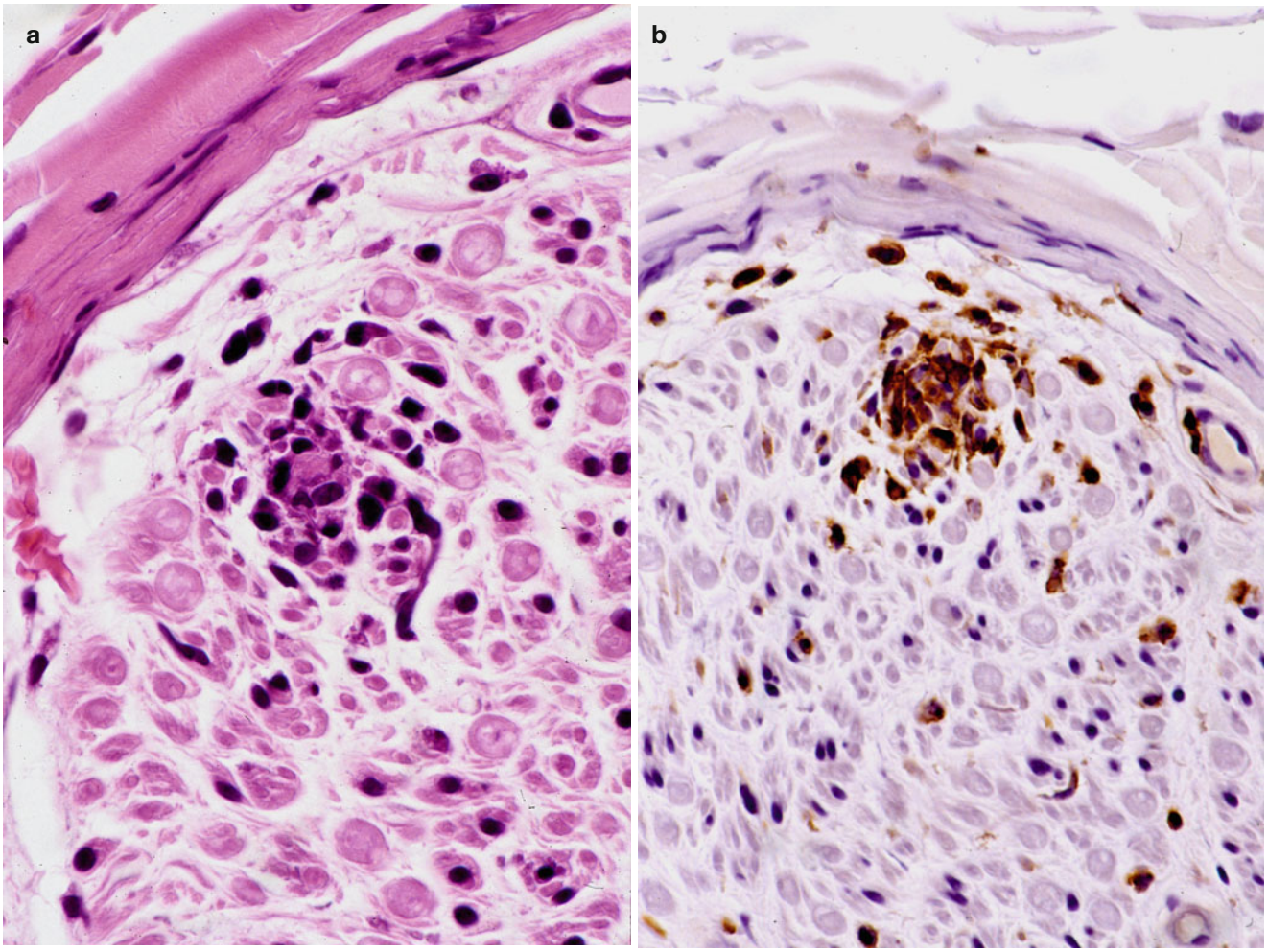

Fig. 13.17 The predominant inflammatory cell in any vasculitis is the lymphocyte (**a**), in this case involving a small endoneurial venule, of which 95 % or more are T cells (**b**) (paraffin, **a**, H&E, 600×; **b**) CD3 immunohistochemistry, 600×)

Case 13.2

A 30-year-old nickel worker experienced painful paresthesias initially involving the forearms, progressing over 3–4 months to affect almost the entire body in a multifocal distribution. At this time he began to note worsening hand weakness and wasting, more prominent on the right than on the left. A multifocal macular rash appeared, affecting his forearms most severely. During this period he experienced generalized malaise, but no fever or respiratory symptoms. Physical examination revealed a well-looking man with no evidence of pulmonary disease, organomegaly, or lymphadenopathy. No abnormalities were detected on examination of the cranial nerves. In the limbs striking atrophy and weakness were seen in the distribution of the ulnar nerves, more severe on the right. Reflexes were easily obtainable and symmetrical. There was a glove-stocking distribution of light touch and pinprick deficit, extending to mid-thigh and elbows.

Electrophysiological testing revealed a multifocal axonal neuropathy superimposed on a mild diffuse axonal sensorimotor neuropathy. CSF examination revealed a normal cell count and slightly elevated protein at 0.57 g/L. ESR, ANA, RF, C3, C4, ANCA, immunoelectrophoresis, cryoglobulins, chest X-ray, and abdominal ultrasound were normal. Bone marrow biopsy was unremarkable. Sural nerve biopsy revealed findings suggestive of lymphomatoid granulomatosis or an angiocentric lymphoma (Fig. 13.18). Because of the marked angiodestruction, the former diagnosis was favored despite the absence of pulmonary findings. Treatment with oral cyclophosphamide and prednisone resulted in a dramatic improvement of sensory symptoms within a month. Over a period of several years, he also showed clinical and electrophysiological evidence of recovery in his ulnar nerves. A second nerve biopsy performed 1 year after the first revealed only nonspecific chronic degenerative changes without cellular infiltration.

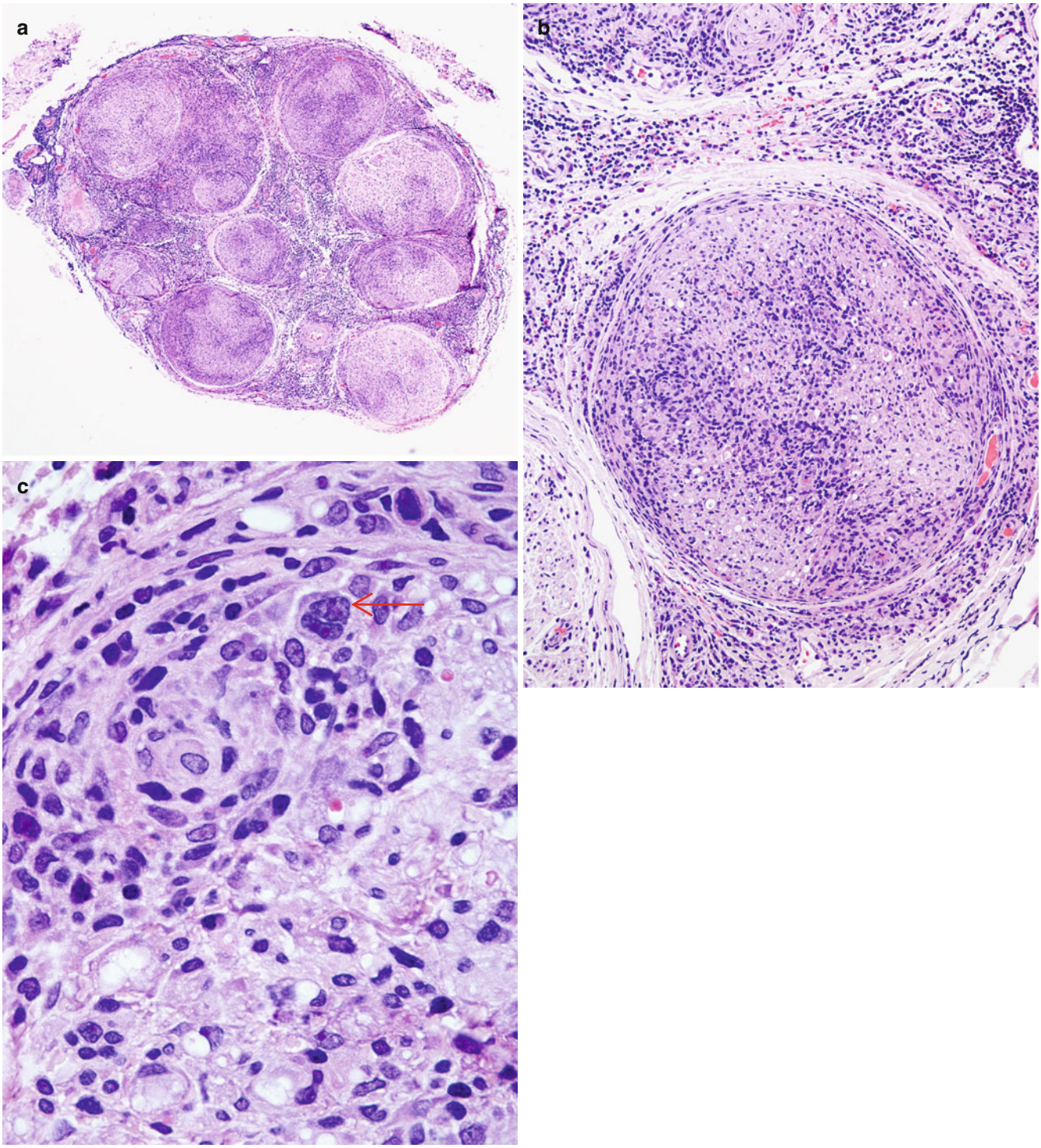

Fig. 13.18 Lymphomatoid granulomatosis. (**a**) Pleomorphic mononuclear cell infiltrate involving all compartments of sural nerve (**a**). (**b**, **c**) Note angiocentricity and the atypical appearance of scattered cells (*arrow*, **c**). (**d**, **e**) The epineurial vasculature is damaged and overrun by the inflammatory infiltrate, with recanalization (*arrows*, **d**), as shown in H&E (**d**) and PAS (**e**) (magnification: **a**, 40×; **b**, 200×; **c**, 1,000×; **d**, **e**, 400×)

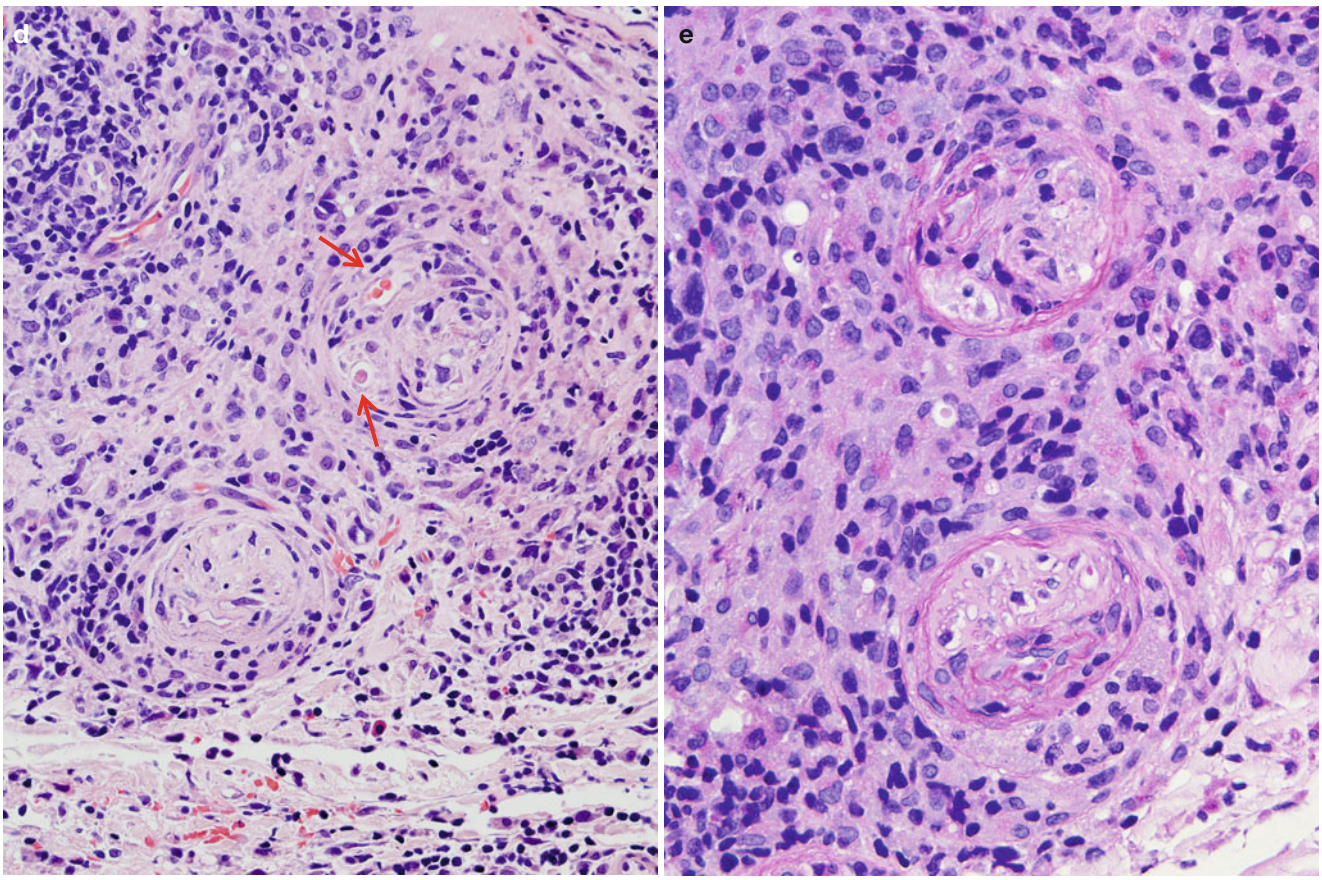

Fig.13.18 (continued)

Neuropathy has been described as preceding pulmonary findings for as long as 5 years (Katzenstein et al. 1979). This patient has now been followed for 10 years and has not developed pulmonary symptomatology or frank lymphoma (tissue courtesy of Dr. J Deck).

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