Vasculitis

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Contents

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Introduction

Vasculitis, characterized by inflammation and necrosis, manifests a wide spectrum of presentation by involving a vasculature of various sizes and locations. It can present clinically as urticaria, purpura, papules, nodules, erythema, ulcer, infarct, or livedo reticularis. A definitive diagnosis of vasculitis invariably requires histologic confirmation since there are no diagnostic clinical, imaging, or laboratory findings. A skin biopsy would provide information regarding the size of the involved vessels and the nature of the inflammatory infiltrate (neutrophils, lymphocytes, or histiocytes). The optimal time frame would be 24–48 hours after lesion onset. Vasculitis can be primary or secondary to drugs, infection, underlying systemic disease, or trauma. Therefore, a diagnosis of vasculitis cannot be based on histologic ground alone. It requires clinical pathologic correlation.

Several classifications have been proposed to differentiate one type of vasculitis from other vasculitides. The initial classification scheme was proposed by the American College of Rheumatology (ACR) in 1990 based mainly on clinical symptoms [1]. The subcommittee on Classification of Vasculitides analyzed 1000 consecutive patients with definitive vasculitis and proposed classification criteria for hypersensitivity vasculitis, Henoch-Schonlein purpura, Churg-Strauss syndrome, polyarteritis nodosa, Wegener granulomatosis, Takayasu arteritis, and giant cell arteritis (Table 7.1) [1–3]. The criteria present in one type of vasculitis but absent or infrequent in the other types were excluded; thus, sensitivity and specificity were low for hypersensitivity vasculitis. In a recent series of 1095 patients with primary vasculitis and 415 with comparable diseases, using ACR criteria the sensitivity of each type of vasculitis has decreased although specificity remains high [4]. In 2010 the European League Against Rheumatism and Pediatric Rheumatology European Society have outlined consensus criteria for the classification of childhood vasculitis [5].

The most widely adopted vasculitis classification is the Chapel Hill Consensus Conference (CHCC) nomenclature of systemic vasculitis which integrated clinical symptoms, histopathologic features, and laboratory findings [2]. This classification allows differentiation of immune complex-mediated vasculitis such as Henoch-Schonlein purpura and essential cryoglobuline-

Table 7.1 Clinical features of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

	Microscopic polyangiitis	Eosinophilic granulomatosis with polyangiitis	Granulomatosis with polyangiitis
Constitutional symptoms (fever, arthralgias, myalgia)	++	++	+++
Cutaneous purpura	++	++	++
Destructive sinusitis, nose deformity	–	–	**+++**
Alveolar hemorrhage	++	– transient infiltrate	++
Asthma	–	**+++**	–
Glomerulonephritis	+++	+	+++
Peripheral neuropathy	+	++	+
Eosinophilia	–	**+++**	–
ANCA	60–80% MPO-ANCA (P-ANCA)	30–40% MPO-ANCA (P-ANCA)	90% PR3-ANCA (C-ANCA)

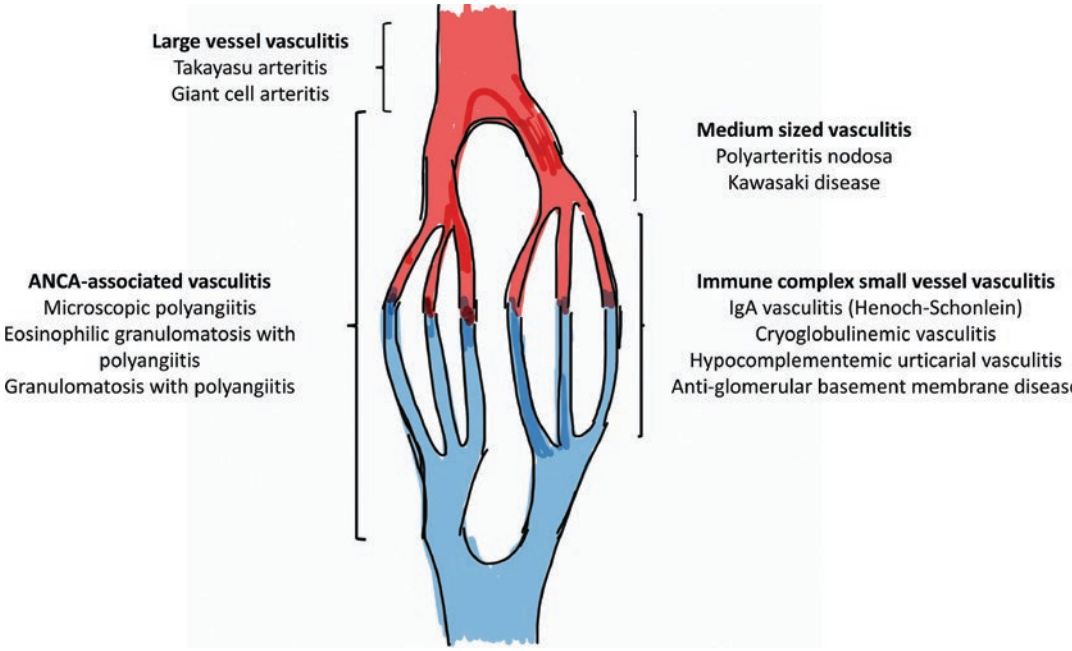


Fig. 7.1 Diagram of vasculitis classification

mic vasculitis from nonimmune complex ones. It also classifies vasculitides based on the size of the involved vessels: small vessel (<50 um), medium vessel (50–100 um), and large vessel (>150 um) (Fig. 7.1). However, classification by vessel size is imperfect due to overlapping vessel sizes. There is an overlap with arterial involvement since all three major categories of vasculitis can affect any artery size. While microscopic polyangiitis affects mainly the small vessels, polyarteritis nodosa involves medium-sized arteries. The criteria have been modified by the CHCC in 2012 (Table 7.2) [1–3]. These criteria are for classification and they are not for diagnostic purposes.

Recently several entities have been proposed to be included under the category of cutaneous single-organ vasculitis. These include IgM/IgG immune complex vasculitis, nodular vasculitis (erythema induratum of Bazin), erythema elevatum diutinum, recurrent macular arteritis in hypergammaglobulinemia (hypergammaglobulinemic purpura of Waldenstrom), and normocomplementemic urticarial vasculitis [6].

The frequency of various types of vasculitis is summarized in Table 7.3 [7–23]. While Wegener granulomatosis is more common in the Northern Hemisphere, polyarteritis nodosa and microscopic polyangiitis are more common in Southern Europe and especially in Arab countries. HLA-

Table 7.2 Vasculitis nomenclature proposed by the 2012 International Chapel Hill Consensus Conference [1–3]

ACR 1990	CHCC 1994	CHCC 2012
	Small-vessel vasculitis	*Small-vessel vasculitis*
Hypersensitivity vasculitis	Cutaneous leukocytoclastic vasculitis	Cutaneous leukocytoclastic vasculitis
		Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
	Microscopic polyangiitis (microscopic polyarteritis)	Microscopic polyangiitis (microscopic polyarteritis) (MPA)
Churg-Strauss syndrome	Churg-Strauss syndrome	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
Wegener granulomatosis	Wegener granulomatosis	Granulomatosis with polyangiitis (Wegener) (GPA)
		Immune complex small-vessel vasculitis
Henoch-Schonlein purpura	Henoch-Schonlein purpura	IgA vasculitis (Henoch-Schonlein)
	Essential cryoglobulinemic vasculitis	Cryoglobulinemic vasculitis (CV)
		Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis) (HUV)
		Anti-glomerular basement membrane disease
	Medium-sized vessel vasculitis	*Medium-sized vessel vasculitis*
Polyarteritis nodosa	Polyarteritis nodosa (classic)	Polyarteritis nodosa (PAN)
	Kawasaki disease	Kawasaki disease (KD)
	Large-vessel vasculitis	*Large-vessel vasculitis*
Giant cell (temporal) arteritis	Giant cell arteritis	Giant cell arteritis (GCA)
Takayasu arteritis	Takayasu arteritis	Takayasu arteritis (TAK)
		Variable-vessel vasculitis
		Behcet disease (BD)
		Cogan syndrome (CS)
		Vasculitis associated with systemic disease
		Lupus vasculitis
		Rheumatoid vasculitis
		Sarcoid vasculitis
		Vasculitis associated with probable etiology
		Hepatitis C virus-associated cryoglobulinemic vasculitis
		Hepatitis B virus-associated vasculitis
		Syphilis-associated aortitis
		Drug-associated immune complex vasculitis
		Drug-associated ANCA-associated vasculitis
		Cancer-associated vasculitis

Table 7.3 Incidence of vasculitis [7–23]

Type of vasculitis	Incidence per million	Location	Years of study (Reference)
Hypersensitivity vasculitis	17.8	Norwich, UK	1990–1994 [7]
IgA vasculitis/HSP	84.9 (children)	Lugo, Spain	1980–1989 [8]
	126.4 (adults)	Lugo, Spain	1990–1999 [8]
	13.0 (adults)	Norwich, UK	1990–1994 [7]
Microscopic polyangiitis	8.0	Norwich, UK	1988–1997 [9]
	2.7	Tromso, Norway	1988–1998 [10]
	1.6	Olmsted County, Minnesota, USA	1996–2015 [11]
	94	Southern Sweden	2003 [12]
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	2.7	Norwich, UK	1988–1997 [9]
	0.5	Tromso, Norway	1988–1998 [10]
	0.4	Olmsted County, Minnesota, USA	1996–2015 [11]
	14	Southern Sweden	2003 [12]
Granulomatosis with polyangiitis (Wegener granulomatosis)	10.6	Norwich, UK	1988–1997 [9]
	63	United Kingdom	1988–1997 [9]
	12.0	Tromso, Norway	1994–1998 [13]
	95	Northern Norway	1988–1997 [9]
	58	Northern Germany	1994 [14]
	42	Southern Germany	1994 [14]
	160	Southern Sweden	2003 [12]
	1.3	Olmsted County, Minnesota, USA	1996–2015 [11]
	23.7	US	[15]
Polyarteritis nodosa	8.0	Norwich, UK	1988–1997 [9]
	4.4	Tromso, Norway	1988–1998 [10]
	31	Southern Sweden	2003 [12]
Kawasaki disease	2648	Japan	2011–2012 [16]
	3080	Japan (0–4 years)	2013–2014 [17]
	196	Canada (5 years)	2004–2014 [18]
	64	Canada (5–9 years)	2004–2014 [18]
	13	Canada (10–14 years)	2004–2014 [18]
	2648	Japan	2000–2012 [19]
	1344	Korea	2000–2012 [19]
	828	Taiwan	2000–2012 [19]
	514	Singapore	2000–2012 [19]
	219	Canada	2000–2012 [19]
	181	USA	2000–2012 [19]
Giant cell arteritis	290	Tromso, Norway	1987–1994 [20]
	102	Lugo, Spain	1981–1998 [21]
	167	Western Norway	1972–2012 [22]
	87	Northern Germany	1994 [14]
	94	Southern Germany	1994 [14]
Takayasu arteritis	22 (Northern Europeans) 78.1 (Asian whites) 108.3 (Africans)	Southern Norway	1999–2012 [23]

DRB1 alleles have been shown to be associated with disease susceptibility in giant cell arteritis and Henoch-Schonlein purpura.

Small-Vessel Vasculitis

Cutaneous Leukocytoclastic Vasculitis

Cutaneous small-vessel vasculitis or leukocytoclastic vasculitis (LCV) affects postcapillary venules and is limited to the skin. It can be idiopathic or associated with an underlying disease such as connective tissue diseases, rheumatoid arthritis, infections, medications, or malignancies. Approximately 10–24% of LCV cases are caused by drug hypersensitivity [24].

Clinical Presentation

It affects both children and adults, with a predilection for women. The most common cutaneous presentation is palpable purpura on sites of dependency, but also livedo reticularis, urticarial lesions, and ulcers [24]. Extravasation of erythrocytes from dermal blood vessel results in purpura which does not blanch under pressure (Fig. 7.2). Resolution of purpura progresses to post-inflammatory hyperpigmentation.

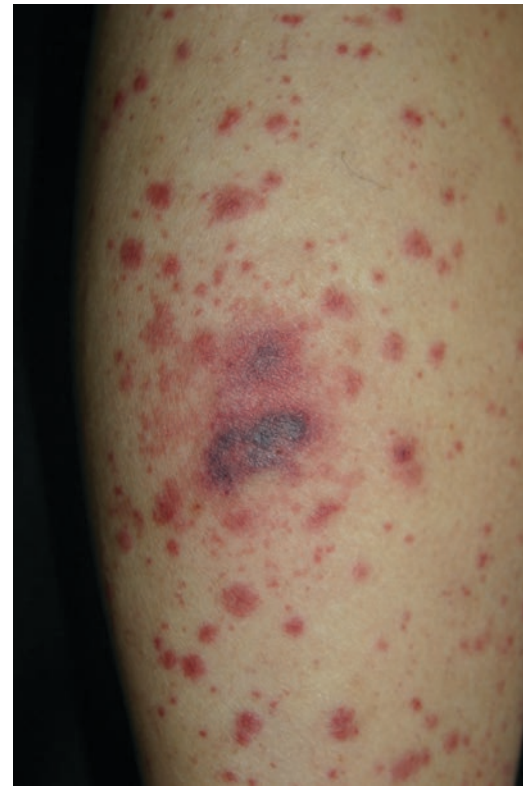


Fig. 7.2 *Cutaneous small-vessel vasculitis*. Non-blanching and palpable purpura is noted on the lower extremity

Prognosis or Clinical Course

Patients with LCV confined to the skin have better prognosis than those with systemic vasculitis. Most episodes of cutaneous LCV are self-limited and resolve over 3–4 weeks with residual hyperpigmentation.

Histopathology

Features characteristics of LCV including fibrinoid necrosis of the vessel walls and perivascular infiltrate of neutrophils and erythrocytes are seen (Fig. 7.3). On direct immunofluorescence studies, perivascular C3 and IgM can be seen.

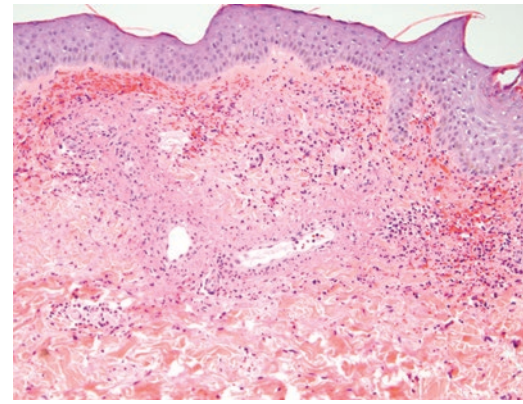


Fig. 7.3 *Cutaneous small-vessel vasculitis*. Features of leukocytoclastic vasculitis are seen on skin biopsy (×100)

Differential Diagnosis

It is important to exclude associated systemic diseases and identifiable offending agent. The main differential diagnosis for a primary small-vessel vasculitis would be the immune complex small-vessel vasculitis and ANCA-associated vasculitis. Systemic disease (lupus erythematosus) and infection-associated (hepatitis virus) vasculitis

can present as LCV. Localized forms of chronic cutaneous small-vessel vasculitis include granuloma faciale and erythema elevatum diutinum (see Case Study 1). The small-vessel vasculitis can also be a process secondary to infections, insect bites, and ulceration; therefore, clinicopathologic correlation is important.

Summary

Clinical Presentation
- Palpable purpura on dependent areas, urticarial lesions, and ulcers.
- Extracutaneous manifestations are uncommon.

Histologic Features
- Leukocytoclastic vasculitis.
- Direct immunofluorescence studies would be negative.

Differential Diagnosis
- Immune complex small-vessel vasculitis
- ANCA-associated vasculitis
- Secondary vasculitis due to infections, insect bites, and ulceration

Takeaway Essentials

Clinical Relevant Pearls
- Cutaneous small-vessel vasculitis or leukocytoclastic vasculitis is a diagnosis of exclusion. It is important to exclude associated systemic diseases and identifiable offending agent.
- Clinicopathologic pathologic correlation is essential to exclude the secondary small-vessel vasculitis.

Immune Complex Small-Vessel Vasculitis

This category of small-vessel vasculitis is caused by immune complex deposition on the vessel walls. It includes IgA vasculitis (Henoch-Schonlein purpura), cryoglobulinemic vasculitis, hypocomplementemic urticarial vasculitis (anti-C1q vasculitis), and anti-glomerular basement membrane disease.

Immunoglobulin A Vasculitis (Henoch-Schonlein Purpura)

Immunoglobulin A (IgA) vasculitis or Henoch-Schonlein Purpura (HSP) is a systemic vasculitis arising from IgA deposition in blood vessel walls of the skin, gastrointestinal tracts, joints, and kidneys. The diagnosis is made by following the criteria published in 2010 by the European League Against Rheumatism (EULAR)/Paediatric Rheumatology International Trials Organisation (PRINTO)/Paediatric Rheumatology European Society (PRES) with sensitivity (100% and 99.2%) and specificity (87% and 86%) for children and adults, respectively [5]. Purpura or petechiae with lower limb predominance is a mandatory criterion plus at least one of the following: abdominal pain, leukocytoclastic vasculitis or proliferative glomerulonephritis on histopathology with IgA deposits, arthritis or arthralgia, and proteinuria or hematuria [5].

The consensus to replace "Henoch-Schonlein purpura" with IgA vasculitis is based on evidence indicating that abnormal vascular IgA deposits are the defining pathophysiologic feature. Genetic predisposition may play a role with a reported strong association with HLA-DRB1∗01 phenotype [25]. The risk of HSP development and SNP7 subunit polymorphisms of the *C1GALT1* gene as well as *MCP1/CCL1-2518 T* polymorphisms has been proposed. In addition, an association between disease severity and nephritis with RANTES/CCL5 and RANTES/

CCL5-403T polymorphisms has been reported, respectively [25].

Clinical Presentation

It is the most common form of vasculitis in children presenting between the ages of 2 and 10 years (median of 4 years). The patients typically present in autumn or winter with a tetrad of symptoms: cutaneous palpable purpura, abdominal pain, joint pain, and renal involvement. The cutaneous lesions present in all cases often start as petechiae and palpable purpura on the lower extremities and buttocks, likely attributed to gravity-dependent areas (Fig. 7.4). About one-third of the patients have trunk and upper extremity involvement. Glomerulonephritis indistinguishable from IgA nephropathy may occur. A majority of cases have preceding upper respiratory tract infections.

Prognosis or Clinical Course

The hemorrhagic skin lesions will resolve into skin discoloration between several weeks to a few months. IgA vasculitis is generally self-limited in the pediatric population; however, 20–80% of adult patients have renal involvement, and end-stage renal failure can develop in 1% of cases. The risk of chronic renal failure is related to the development of nephrotic syndrome. Therefore, although IgA vasculitis is more common in children, it has a more severe course in adults.

Histopathology

Vasculitis affects small vessels (predominantly capillaries, venules, or arterioles). Skin biopsy would typically demonstrate fibrinoid necrosis of the vessel walls and perivascular infiltrate of neutrophils, leukocytoclasis, and extravasated erythrocytes in 92% of cases (Fig. 7.5) [26]. On direct immunofluorescence (DIF) studies, vascular IgA and C3 would be identified in 81% of cases (Fig. 7.6) [26]. Although there is a strong correlation between IgA deposition on DIF and

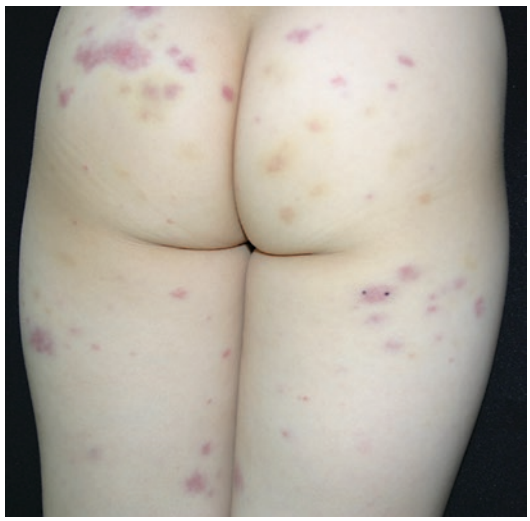


Fig. 7.4 *IgA vasculitis*. Petechiae and palpable purpura are seen on the buttocks and lower extremities of a child

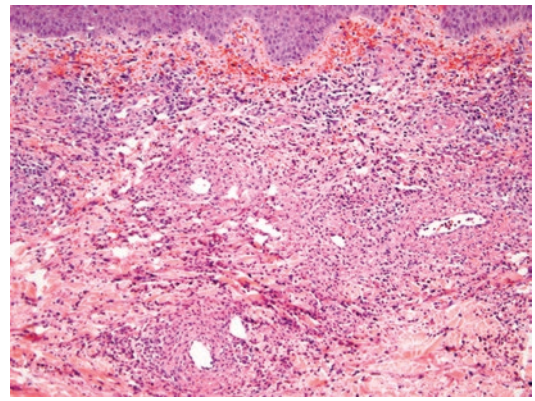


Fig. 7.5 *IgA vasculitis*. A skin biopsy demonstrates features of leukocytoclastic vasculitis (×100)

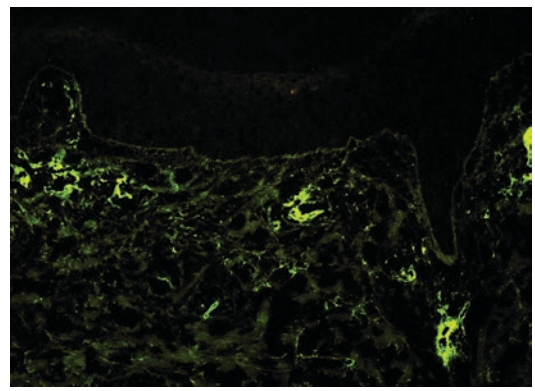


Fig. 7.6 Vascular IgA deposition is noted on direct immunofluorescence studies

IgA vasculitis, there is a subset of patients in which there is absent cutaneous vascular IgA deposition [27].

Differential Diagnosis

Acute hemorrhagic edema, hypersensitivity vasculitis, Wegener disease, and microscopic polyangiitis can have similar clinical presentation. In addition, features of leukocytoclastic vasculitis can be seen on histologic sections of skin biopsies. Vascular IgA deposition can be seen in dermatitis herpetiformis, IgA nephropathy, and chronic alcohol intake [28].

Summary

Clinical Presentation

- Purpura or petechiae with lower limb predominance is a mandatory criterion plus at least one of the following: abdominal pain, leukocytoclastic vasculitis or proliferative glomerulonephritis on histopathology with IgA deposits, arthritis or arthralgia, and proteinuria or hematuria.

Histologic Features

- Leukocytoclastic vasculitis.
- Vascular IgA and C3 deposition on direct immunofluorescence studies would be identified in 81% of cases.

Differential Diagnosis

- Hypersensitivity vasculitis
- Granulomatosis with polyangiitis (Wegener) and microscopic polyangiitis

Takeaway Essentials

Clinical Relevant Pearls

- A tetrad of symptoms: cutaneous palpable purpura, abdominal pain, joint pain, and renal involvement.
- Although IgA vasculitis is more common in children, it has a more severe course in adults.
- 20–80% of adult patients have renal involvement, and end-stage renal failure can develop in 1% of cases.

Pathology Interpretation Pearls

- There is a subset of patients in which there is absent cutaneous vascular IgA deposition.

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) is a vasculitis with cryoglobulin immune deposits within small vessels (capillaries, venules, or arterioles) and associated serum cryoglobulins [3]. Skin, peripheral nerves, joints, and kidneys are often involved. Cryoglobulins are circulating antibodies that precipitate below core body temperature. Based on the composition of the cryoprecipitate, cryoglobulinemia is divided into three types: monoclonal IgM or IgG (rarely IgA) in type I, a mixture of polyclonal IgG and monoclonal IgM with rheumatoid factor activity in type II, and polyclonal IgG and polyclonal IgM with rheumatoid activity in type III. Type II and III cryoglobulins are mixed cryoglobulinemia that frequently lead to systemic vasculitis due to immune complex deposition.

Type I is invariably associated with B-cell lymphoproliferative disorders such as Waldenstrom's macroglobulinemia and multiple myeloma. The main etiology of mixed cryoglobulinemia is hepatitis C virus (HCV) infection accounting for more than 90% of all cases of CV. Although circulating cryoglobulins can be detected in 25–30% of chronic HCV-positive patients, CV would develop in only 10–15% of these patients. There is no correlation between HCV genotype and the development of CV. Others include connective tissue diseases (Sjogren's syndrome, systemic lupus erythematosus, rheumatoid arthritis) or human immunodeficiency virus (HIV) infection. CV is classified as essential or idiopathic when there is no apparent underlying disease process [29].

Clinical Presentation

The disease severity varies ranging from petechial eruptions to life-threatening presentation. Fatigue, the main symptom, is noted in 80–90% of patients. The characteristic cutaneous presentation is palpable purpura, but also ecchymoses, erythematous papules, and nodules on the lower extremities and less often the trunk and upper extremities. The cutaneous purpura is sporadic and intermittent, lasts for 3–10 days, and resolves with post-inflammatory hyperpigmentation. Raynaud's phenomenon, acral cyanosis, and livedo reticularis are common cutaneous lesions seen in type I. Arthralgia is noted in 40–60% of patients and usually as intermittent mono- or oligo-arthralgia affecting large joints. Glomerulonephritis and symmetric peripheral neuropathy can be seen in type II and III cryoglobulinemias, respectively [29]. Neurologic manifestations can be seen in 60–70% of patients and affect sensory nerves more frequently than motor nerves. Renal manifestations are seen in 20–30% and associated with a poor prognosis.

Prognosis or Clinical Course

Significant morbidity and mortality is seen with CV. The 10-year survivals for type I, HCV-negative mixed CV, and HCV-positive mixed CV are 87%, 65%, and 63%, respectively [29]. The presence of liver fibrosis, central nervous system (CNS) involvement, kidney involvement, and heart involvement are associated with poor prognosis. In patients with mixed cryoglobulinemia due to HCV, viral eradication was associated with clinical improvement. HCV-positive patients with mixed cryoglobulinemia had a poorer course than non-HCV type II and III cryoglobulinemia due to infections and end-stage liver disease. Therefore, the main treatment for HCV-positive CV is antiviral therapy [30]. The use of immunosuppressant is associated with poor outcome [29]. Both pure and mixed CV have an increased risk of developing B-cell non-Hodgkin lymphoma [31].

Histopathology

Thrombotic occlusion of vascular lumens is seen in type I (see Chap. 8), whereas a necrotizing vasculitis is seen in type II and type III cryoglobulinemias (Fig. 7.7). Vascular IgM, IgG, and C3 deposition would be seen on DIF studies. Immunoexpression of HCV-related proteins within vascular walls supports the etiologic role of HCV.

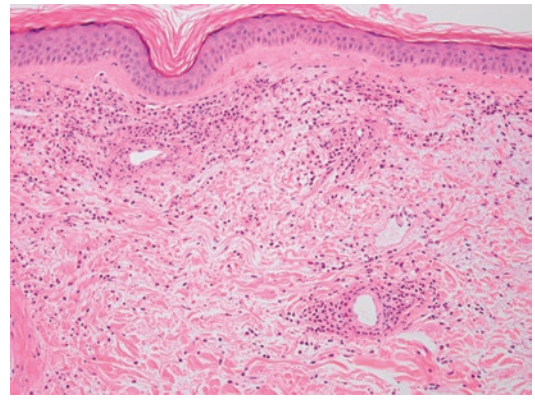


Fig. 7.7 Mixed cryoglobulinemia is characterized by leukocytoclastic vasculitis (×100)

The cryoglobulin level is considered significant when greater than 0.05 g/L at two separate testings performed with at least a 12-week interval. Immunoblotting is a sensitive and specific method which detects cryoglobulin in 98% of cases. Ex vivo cryoprecipitation can result in artifacts; therefore, serum should be transported and tested at 37 °C. In the second phase of testing, serum should be incubated at 4 °C for 3 to 7 days. In the typing of cryoglobulin phase, immunofixation or immunoelectrophoresis allows classification as types I–III. Other surrogate laboratory indicators include decreased complement C4 levels and the presence of an immunoglobulin with rheumatoid activity [29]. A monoclonal B-cell lymphocytosis can be seen.

Differential Diagnosis

HCV-related polyarteritis nodosa affects mainly the medium-sized vessels; therefore, life-threatening vasculitis, severe multifocal sensorimotor mononeuropathies, malignant hypertension, cerebral angiitis, and kidney and liver microaneurysms would be present more frequently in comparison to CV.

Summary

Clinical Presentation

- A small-vessel vasculitis with cryoglobulin immune deposits within small vessels and associated serum cryoglobulins.
- It affects skin, peripheral nerves, joints, and kidneys.

Histologic Features

- A necrotizing vasculitis is seen in type II and type III cryoglobulinemias.
- Thrombotic vasculopathy is seen in type I.

Differential Diagnosis

- HCV-related polyarteritis nodosa

Takeaway Essentials

Clinical Relevant Pearls

- In HCV-negative patients with cryoglobulinemic vasculitis, pulmonary, gastrointestinal, and renal involvement and age >65 years are associated with death.
- In HCV-positive patients with cryoglobulinemic vasculitis, antivirals and immunosuppressant are associated with good and poor outcome, respectively.
- There is an increased risk of B-cell non-Hodgkin lymphoma.

Pathology Interpretation Pearls

- Surrogate laboratory indicators include decreased complement C4 levels and the presence of an immunoglobulin with rheumatoid activity.

Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Hypocomplementemic urticarial vasculitis (HUV) is an uncommon systemic and relapsing immune complex-mediated vasculitis of unknown etiology. HUV is characterized by urticaria, hypocomplementemia, and vasculitis affecting small vessels (capillaries, venules, or arterioles) and anti-C1q antibodies [3]. Schwartz et al. [32] have proposed two major criteria (chronic urticaria and low complement levels) together with at least two minor criteria (leukocytoclastic vasculitis, arthralgias or arthritis, uveitis or episcleritis or conjunctivitis, glomerulonephritis, abdominal pain, and/or positive anti-C1q antibody). These symptoms should be present for at least a 6-month duration.

Urticarial vasculitis can be either normocomplementemic (NUV) or hypocomplementemic (HUV). Although most HUV cases are idiopathic, approximately 25% of cases may be associated with systemic diseases such as systemic lupus erythematosus (SLE), primary Sjogren's syndrome, serum sickness reaction, monoclonal gammopathy, hematologic disorders, and drug hypersensitivity [33]. In a study of a family with three affected children with HUV, Ozcakar et al. [34] reported mutations in *DNASE1L3*, encoding an endonuclease that has previously been associated with SLE. Therefore, it is not surprising that some authors have proposed that HUV syndrome is a subset of SLE.

The pathophysiology of urticarial vasculitis has been thought to be a type III immune complex-mediated hypersensitivity reaction. C1q is the subunit of the C1 complex of the complement activation cascade. The C1q antibodies and associated immune complexes activate the complement pathway resulting in mast cell degranulation, subsequent increased vascular permeability, and urticaria and/or angioedema.

Clinical Presentation

There is a female predominance and affects patients in the fourth to fifth decade of life. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common clinical manifestations. Urticarial lesions in this setting are often painful, associate with angioedema, persist more than 24 hours, and resolve with hyperpigmentation (Fig. 7.8). In addition to urticaria, annular lesions, targetoid lesions, palpable purpura, livedo reticularis, and bullae can be other cutaneous manifestations [33]. Pruritic urticarial lesions can be seen in 51% of patients, purpura in 35%, and livedo reticularis in 14% [33].

Extracutaneous manifestations include constitutional symptoms (fever, fatigue, malaise) (56%), musculoskeletal (82%), ocular (56%), pulmonary (19%), gastrointestinal (18%), and kidney (14%) involvement [33]. Arthralgias and arthritis frequently affect the joints of the hands, wrists, elbows, knees, and ankles. Often mild in adults, renal involvement manifested as proteinuria and microscopic hematuria can be severe in children. Pulmonary manifestations include dyspnea, coughing, hemoptysis, pleural effusion, and chronic obstructive pulmonary disease which is the most frequent cause of death. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and ascites. Uveitis, episcleritis, are conjunctivitis are common ocular involvements. Laboratory studies reveal low complement levels (C1q, C2, C3, and C4), low C1q levels, normal C1 inhibitor levels, and anti-C1q antibodies in 55% [33]. The detection of anti-C1q antibodies is not a major criterion since it can be negative [33].

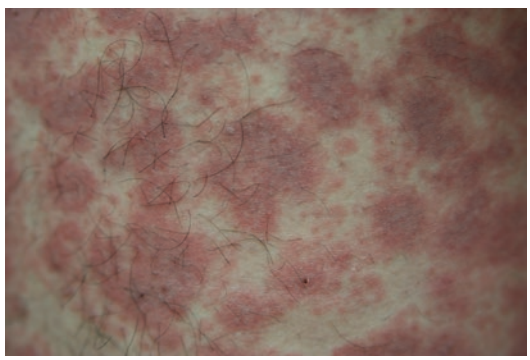


Fig. 7.8 *Urticarial vasculitis*. Edematous plaques are seen on the skin

Prognosis or Clinical Course

High morbidity and mortality are observed due to chronic obstructive pulmonary disease. Patients with hypocomplementemic urticarial vasculitis have a greater risk than those with normocomplementemic urticarial vasculitis for multiorgan involvement.

Histopathology

Histologic features of leukocytoclastic vasculitis such as fibrinoid necrosis of the vessel walls, leukocytoclasis, and perivascular erythrocytes are typically seen. Dermal infiltrate of eosinophils and edema can be seen. Direct immunofluorescence studies show granular IgG, less commonly IgM and C3 at the basement membrane zone and C3 in walls of blood vessels.

Differential Diagnosis

The differential diagnosis of urticarial vasculitis includes common urticaria, serum sickness, systemic lupus erythematosus (SLE); neoplasia; mixed cryoglobulinemia; Cogan syndrome; Muckle-Wells syndrome; arthritis, hives, and angioedema (AHA) syndrome; and Schnitzler syndrome. Although the presence of anti-C1q antibody has often been used to distinguish HUV from connective tissue disease, the antibody can be seen in both primary and secondary vasculitis [35]. Inflammatory ocular disease, a prominent feature of HUV, would be unusual in SLE. Cogan syndrome, a disease of young adults, presents with interstitial keratitis and Meniere's-like episodes [36]. Cogan syndrome can be accompanied by a systemic vasculitis resembling either

Takayasu arteritis or polyarteritis nodosa, depending on the size of the involved vasculature. Muckle-Wells syndrome is a dominantly inherited autoinflammatory disease characterized by urticarial rashes, fever, arthralgia, progressive sensorineural deafness, and frequent association with systemic AA amyloidosis [37]. In AHA syndrome, urticarial vasculitis is accompanied by angioedema [38]. Monoclonal IgM gammopathy, intermittent fever, and hyperostoses would be noted in Schnitzler syndrome.

Summary

Clinical Presentation

- Key diagnostic features are urticarial vasculitis and hypocomplementemia.
- To render a diagnosis, one would need two major criteria (chronic urticaria and low complement levels) together with at least two minor criteria (leukocytoclastic vasculitis, arthralgias or arthritis, uveitis or episcleritis or conjunctivitis, glomerulonephritis, abdominal pain, and/or positive anti-C1q antibody).

Histologic Features

- Leukocytoclastic vasculitis on skin biopsy
- Granular IgG at the basement membrane zone and C3 in walls of blood vessels on direct immunofluorescence studies
- Laboratory findings: elevated erythrocyte sedimentation rate; hypocomplementemia with low C1q, C3, and C4; C1q antibodies; ANA without anti-double-stranded DNA

Differential Diagnosis

- The main differential diagnosis includes systemic lupus erythematosus and mixed cryoglobulinemias.
- Cogan syndrome.
- Muckle-Wells syndrome.
- Arthritis, hives, and angioedema syndrome.
- Schnitzler syndrome.

Takeaway Essentials

Clinical Relevant Pearls

- In contrast to urticaria, urticarial vasculitis lasts more than 24 hours.
- The systemic vasculitis of this syndrome involves skin, eyes, joints, kidneys, and gastrointestinal tract.
- Pulmonary complication is the most life-threatening complication.

Pathology Interpretation Pearls

- The detection of anti-C1q antibodies is not a major criterion since it can be negative.

Anti-glomerular Basement Membrane (Anti-GBM) Disease

Anti-glomerular basement membrane (anti-GBM) disease, previously known as Goodpasture's disease, is a rare yet often life-threatening small-vessel vasculitis caused by in situ immune complex deposition. Anti-GBM affects glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies [3]. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents. Anti-GBM is a misnomer since anti-GBM antibodies react not only with GBM but also with pulmonary alveolar capillary membranes. "Goodpasture's syndrome" has been used in the past for combined pulmonary and renal expression of anti-GBM disease.

Type II antigen-antibody reaction plays the role in this disease. The autoantibodies bind to epitopes in the basement membrane, activate the complement cascade, and cause subsequent tissue damage. This interaction between antigen and antibody can be visualized as linear IgG deposition along glomerular basement membrane and on occasion the alveolar basement membrane on direct immunofluorescence studies. A 28-kd monomeric subunit of the non-collagenous-1 (NC1) domain of the α3 chain of type IV collagen, α345NC1, has been identified as the target

antigen of anti-GBM disease [39]. Conformational alteration of the quaternary structure of α345NC1 at residues 17-31 and 127-141 of α3(IV)NC1 is likely the responsible trigger of immune response [39]. The α3(IV) chain is expressed in few specialized basement membranes including the glomerular, alveolar, testicular, inner ear, and eye [40]. Only the glomerular and alveolar basement membranes are preferentially affected, likely attributed to the greater accessibility of epitopes to the circulating antibodies [39]. The principal component of the glomerular filtration barrier is type IV collagen. In the absence of any of the type IV collagen chains, progressive renal failure develops. Anti-GBM disease has a strong association with human leukocyte antigen (HLA)-DRB1∗1501 and a lesser extent with HLA-DRB1∗1502, suggesting that additional factors such as genetic or environmental are necessary for disease progression [41].

Clinical Presentation

The disease affects 0.5–1 per million persons per year [41]. The disease has a bimodal presentation, 20–30 years and 60–70 years, and affects preferentially men in the younger group and equally men and women over 60 years of age. It is characterized by both pulmonary hemorrhage and renal failure, ranging from mild to lethal outcome, in 60–80% of the patients. Solely renal symptoms are seen in 20–40%, whereas less than 10% have only pulmonary symptoms. The patients invariably have hematuria in addition to constitutional symptoms such as fever, weight loss, and arthralgias. Lung involvement is manifested clinically as exertional dyspnea and hemoptysis. Anemia secondary to iron deficiency can develop.

Prognosis or Clinical Course

The titer of the circulating autoantibodies correlates with disease severity [41]. ANCA positivity is present in patients with extrarenal and extrapulmonary manifestations and recurrent renal or pulmonary disease. In a series of 221 Chinese patients with anti-GBM disease in 1998–2008, the authors reported milder renal damage and less frequent pulmonary involvement in patients older than 65 years of age [42]. A combination treatment composed of plasmapheresis, corticosteroids, and immunosuppressive drugs has helped to improve the 1-year survival to 70–90% [41]. The 5-year survival is more than 80%, and less than 30% of the patients would require long-term dialysis.

Histopathology

Percutaneous renal biopsy provides much higher diagnostic yield than transbronchial or open lung biopsy. Renal biopsy typically demonstrates a necrotizing crescentic glomerulonephritis (Fig. 7.9). Histologic hallmark is linear IgG deposition along the glomerular basement membrane seen on direct immunofluorescence studies (Fig. 7.10) [41].

Serologic testings such as radioimmunoassays or enzyme-linked immunosorbent assays (ELISA) for anti-GBM antibodies are highly sensitive and specific. ELISA invariably shows the presence of anti-GBM antibodies in serum of these patients. One-third of the patients can have circulating ANCA, mainly MPO-ANCA, in addition to anti-GBM antibody [43]. ANCA can precede the development of anti-GBM antibody by months or years. The patients can be doubly positive for anti-GBM and C-ANCA or P-ANCA [43]. Double-positive patients have characteristics similar to those of ANCA-associated vasculitis including older age and longer symptom

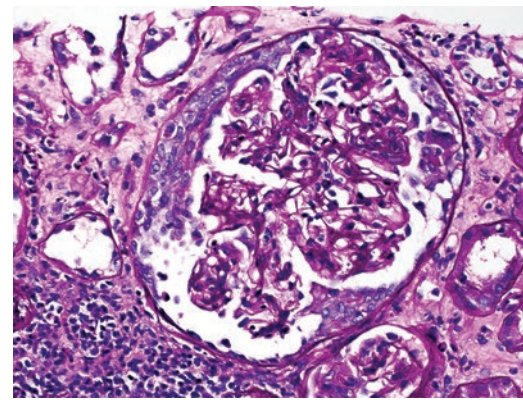


Fig. 7.9 *Anti-glomerular basement membrane disease*. Renal biopsy typically demonstrates a necrotizing crescentic glomerulonephritis (PAS, ×400). (Courtesy of A. Bernard Collins, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA)

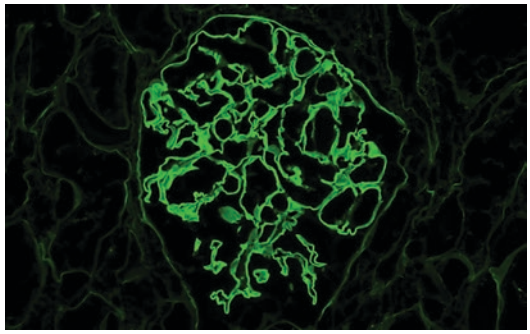


Fig. 7.10 *Anti-glomerular basement membrane disease*. Linear IgG deposition along the glomerular basement membrane seen on direct immunofluorescence studies. (Courtesy of A. Bernard Collins, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA)

duration before diagnosis and features of anti-GBM disease such as kidney and lung involvement at presentation [43]. The clinical course however is similar to those with anti-GBM only.

Differential Diagnosis

Conditions that cause pulmonary-renal syndromes include ANCA-associated vasculitides (MPA, GPA, and EPGA), IgA vasculitis, SLE, undifferentiated connective tissue disease, and rarely rapidly progressive glomerulonephritis. Anti-GBM antibodies can be detected in GPA and other ANCA-associated vasculitides and inflammatory conditions characterized by renal and pulmonary involvement. Since MPO-ANCA can be detected in patients with anti-GBM disease, distinction from GPA would be important. Careful review of the clinical history, physical examination, and laboratory studies would be needed to correctly render the diagnosis.

Summary

Clinical Presentation

- A rare autoimmune disease characterized by renal involvement and sometimes with lung involvement.
- The non-collagenous domain-1 of the α3 chain of type IV collagen is the autoantigen.

Histologic Features

- Crescentic glomerulonephritis on kidney biopsy
- A linear IgG deposition along glomerular basement membrane on direct immunofluorescence
- Presence of circulating anti-GBM antibodies, specifically the anti-α3(IV) NC1 antibodies on solid-phase immunoassay

Differential Diagnosis

- Other conditions that cause pulmonary-renal syndromes such as systemic lupus erythematosus and ANCA-associated vasculitides
- Granulomatosis with polyangiitis in those with anti-GBM and MPO-ANCA

Takeaway Essentials

Clinical Relevant Pearls

- Without prompt diagnosis and treatment, the patient can develop alveolar hemorrhage, kidney failure, and subsequently death.
- The key to better prognosis is timely diagnosis.
- Since 20–35% have both anti-GBM and MPO-ANCA simultaneously, anti-GBM and ANCA should be tested in parallel in patients with renal disease.

Pathology Interpretation Pearls

- Kidney biopsy would provide a definitive diagnosis.
- Serologic studies for anti-GBM antibodies to confirm the diagnosis and to monitor therapeutic response.

Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides are rare systemic diseases which comprise of microscopic polyangiitis

(MPA), eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome), and granulomatosis with polyangiitis (GPA, Wegener's). They have few or no immune deposits and predominantly affect small vessels (such as capillaries, venules, arterioles, and small arteries). ANCA-associated vasculitides are systemic diseases, but limited forms confined to single organs may occur. Renal biopsy is still the best for rendering diagnosis, and it is an important predictor of renal outcome.

The ANCA antibodies can be specific for either myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). By using indirect immunofluorescence on ethanol-fixed neutrophils, C-ANCA is characterized by diffuse cytoplasmic granular fluorescence, and the antigen is generally PR3. P-ANCA is characterized by perinuclear neutrophil staining pattern, and the major target antigen is myeloperoxidase. A-ANCA or atypical ANCA exhibits both cytoplasmic and perinuclear/nuclear staining. PR3-ANCAs account for majority of ANCA with cytoplasmic immunofluorescence (cANCA) and are associated with GPA (Wegener's) in 60–80% of the cases. MPO-ANCAs account for perinuclear immunofluorescence pattern (pANCA) and are associated with MPA (80–90%) and EGPA (Churg-Strauss) (35–40%) [3]. Currently enzyme-linked immunosorbent assay (ELISA) is commonly used to detect these antibodies.

ANCA status is important since patients with C-ANCA and P-ANCA have different organ manifestations, likelihood of therapy response, and risk of relapse (Fig. 7.3). ANCA specificity predicts differences in long-term prognosis. Patients with PR3-ANCAs are at a higher risk of relapse than patients with MPO-ANCAs [44]. ANCA specificity has been suggested to be better than clinical diagnosis for defining homogeneous groups of patients, since PR3-ANCA and MPO-ANCA are associated with different genetic backgrounds and epidemiology [44]. Patients with PR3-AAV and MPO-AAV do not share the same genetic background and have only some pathophysiologic mechanisms in common. ANCA specificity predicts response to induction therapies; rituximab is more effective than cyclophosphamide in patients with PR3-AAV. On the contrary, both treatments are similarly effective in patients with MPO-AAV.

The pathogenesis of ANCA-associated vasculitis remains unclear, and it is likely due to a variety of factors such as genetic susceptibility, environmental agents, and innate and adaptive immune responses. In a genome-wide association study (GWAS) of 2687 Northern European Caucasian patients, GPA was reported to be associated with genetic variants within *HLA-DP*, *SERPINA1* (encoding alpha-1-antitrypsin), and *PRTN3* (encoding PR3), while MPA is associated with *HLA-DQ* [45]. Of interest, these genetic backgrounds were more closely associated with MPO- or PR3-ANCA specificity than with the clinical syndrome.

Proteomic analyses have identified TIMP1 as a marker of ANCA-associated vasculitis activity and TKT and CD93 as markers of renal involvement and outcome in ANCA-associated vasculitis [46]. A recent meta-analysis identified 33 genetic variants, supporting a role for alpha-1-antitrypsin, the major histocompatibility complex system, and inflammatory processes in the pathogenesis of ANCA-associated vasculitis [47].

Microscopic Polyangiitis

Initially reported as microscopic polyarteritis, microscopic polyangiitis (MPA) affects mainly small vessels (capillaries, venules, and arterioles), but can involve the medium arteries. It is with few or no immune deposits and lack of granulomatous inflammation. Necrotizing glomerulonephritis and pulmonary capillaritis are common symptoms. It is associated with P-ANCA due to antibodies against MPO in 50–75% of cases [48]. Although environmental factors such as silica exposure have been implicated, the etiology of MPA remains unknown.

Clinical Presentation

MPA is a systemic vasculitis that can affect multiple organs; however, it can be restricted to only the kidneys. Renal involvement often as rapidly progressive glomerulonephritis is invariably seen in all patients [48]. Renal symptoms seen in 80–100% of patients can range from an asymptomatic urinary sediment to end-stage renal disease necessitating dialysis. Glomerulonephritis is

the only symptoms in some cases. Pulmonary involvement can be seen in 25–55% with diffuse alveolar hemorrhage resulting in hemoptysis, dyspnea, cough, and pleuritic chest pain as the classic presentation [48]. Cutaneous involvement as palpable purpura, livedo reticularis, nodules, urticarial lesions, and skin ulcers on bilateral extremities can be seen in 30–60% of patients. Skin lesions can be the initial presenting sign in 15–30% of the patients [49]. Abdominal pain, the most common gastrointestinal symptom, can be seen in 30–58% of patients. Neurologic involvement can be seen in 37–72% of the patients and commonly comprises peripheral neuropathy including mononeuritis multiplex and distal symmetrical polyneuropathy [49].

Prognosis or Clinical Course

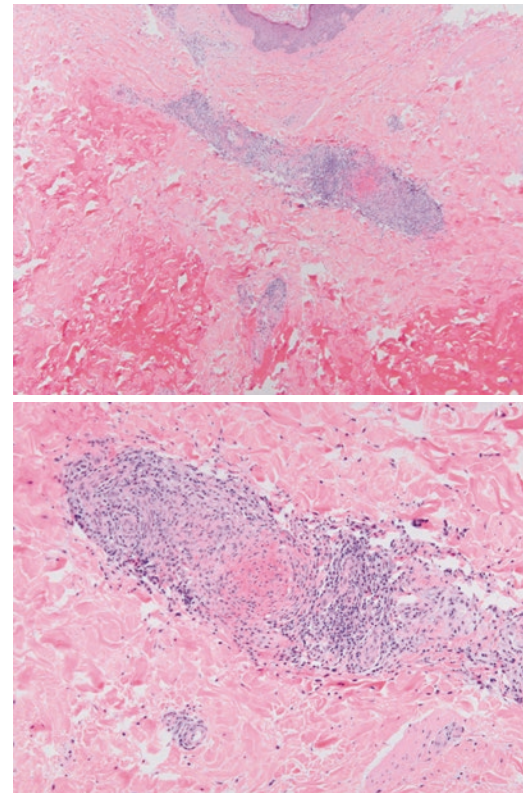
If untreated the prognosis is very poor due to pulmonary hemorrhage and rapidly progressive glomerulonephritis with a 10% 1-year survival. With aggressive immunosuppressive treatment, the 1-year and 5-year survival rates are 82% and 76%, respectively [50]. Serum creatinine level, African American ethnic background, and arterial sclerosis on kidney biopsy are predictors for end-stage renal failure [50]. Response to induction therapy in Japanese patients with MPA can be predicted by monitoring the altered gene expression of 16 candidates in the peripheral blood [51].

Histopathology

Skin biopsies often show only leukocytoclastic vasculitis (Figs. 7.11 and 7.12). Histologic confirmation of necrotizing vasculitis of small vessels including arterioles, capillaries, and venules, usually with either kidney or lung biopsy, is still the gold standard. Since P-ANCA due to antibodies against myeloperoxidase is seen in 50–75% of cases, a negative ANCA test does not exclude the diagnosis of MPA.

Differential Diagnosis

The presence or absence of small-vessel involvement rather than the presence of medium-sized arteries is the distinguishing feature between polyarteritis nodosa and MPA. In a comparison study in children, pulmonary manifestations were less frequent and less severe in patients with MPA versus those with GPA [52]. However, renal involvement with greater severity (nephrotic-range proteinuria, dialysis, and end-stage renal disease) was noted in patients with MPA versus GPA. Genome-wide association analyses of MPA and GPA cases have demonstrated correlation between the patients' genotypes and ANCA specificity [45].



Figs. 7.11 and 7.12 *Microscopic polyangiitis*. A perivascular infiltrate of lymphocytes, neutrophils, and fibrin is noted in addition to vascular thrombosis (×40, ×100)

Summary

Clinical Presentation

- A systemic vasculitis that affects small vessels of multiple organs, mainly the lungs and kidneys causing diffuse alveolar hemorrhage and rapidly progressive glomerulonephritis, respectively

Histologic Features
- Small-vessel vasculitis
- P-ANCA due to antibodies against myeloperoxidase seen in 50–75% of cases

Differential Diagnosis
- Polyarteritis nodosa
- Granulomatosis with polyangiitis (GPA)

Takeaway Essentials

Clinical Relevant Pearls
- Renal disease is the most frequent clinical presentation, followed by systemic features, musculoskeletal, cutaneous, lower respiratory tract, and gastrointestinal involvement.
- Diagnosis relies on clinical findings, ANCA antibody, kidney, and lung biopsies.

Pathology Interpretation Pearls
- In the setting of pulmonary-renal syndrome antineutrophil cytoplasmic antibodies (ANCA), testing is useful for the diagnosis of ANCA-associated vasculitis.
- ANCAs are predominantly directed against myeloperoxidase (MPO-ANCA), but against proteinase 3 (PR3-ANCA) in 20–30% of MPA cases.
- ANCA can be negative in a small subset of MPA patients.
- ANCA can be falsely positive in connective tissue diseases, infection, and malignancies.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Eosinophilic granulomatosis with polyangiitis (EPGA) (formerly Churg-Strauss syndrome) is a rare necrotizing vasculitis affecting small to medium vessels with eosinophil-rich and necrotizing granulomatous inflammation involving the respiratory tract, associated with asthma and peripheral blood eosinophilia [3]. The ACR criteria are most commonly used for diagnosis which can be based on clinical findings with or without histologic confirmation. The diagnosis can be made with a sensitivity of 85% and specificity of 99.7% [53] when four of the following six criteria are present: asthma, eosinophilia greater than 10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils on biopsy [1].

EGPA is considered a systemic disease; however, limited expressions of EGPA confined to the upper or lower respiratory tract may occur. ANCA with a perinuclear immunofluorescence staining pattern is positive in only about 40–60% of patients [48]. Those with ANCA were more likely to have definitive features or surrogates of small-vessel vasculitis, purpura, peripheral neuropathy, myalgia, arthralgia, and glomerulonephritis [54], whereas those without ANCA developed myocarditis, lung infiltrates, and gastrointestinal symptoms frequently. In addition, a recent study reported that not all EGPA patients had definite vasculitis features [54]. Hypereosinophilic asthma with (any) systemic (nonvasculitic) manifestations (HASM) has been proposed for patients with asthmas, blood hypereosinophilia, and systemic symptoms [54].

Tissue eosinophil proliferation and activation result in granule cytotoxic protein release contributing to tissue damage including eosinophilic pneumonitis and myocarditis. Production of IL-25 maintains the cycles of Th2-mediated disease.

Clinical Presentation

The clinical presentations appear to segregate into two subsets: vasculitic and eosinophilic manifestations. Asthma with or without allergic rhinitis is seen in 96–100% of patients in the initial *prodromal phase*. Other symptoms can be present in this phase including arthralgias, myalgias, malaise, fever, and weight loss which can last from months to years. The *eosinophilic phase* is characterized by peripheral eosinophilia and organ (lung, cardiac, and gastrointestinal)

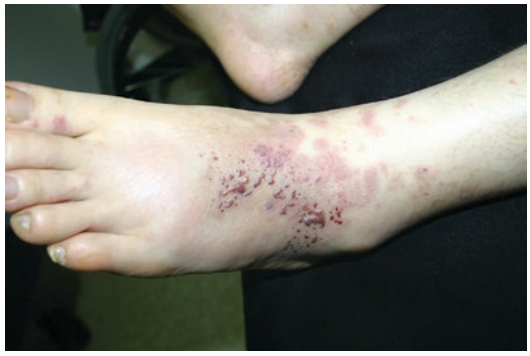


Fig. 7.13 *Eosinophilic granulomatosis with polyangiitis*. A vesiculopapular eruption on a background of purpura is seen on the lower extremities

involvement. Constitutional symptoms (fever, weight loss, fatigue) and skin lesions are common in the *vasculitic phase*.

Cutaneous involvement, seen in 40–50% of cases, can be papular and nodular, purpuric, erythematous, or vesiculopapular arising on a background of purpura on extremities, trunk, neck, and face. Purpura and petechiae on the lower extremities are the most common (Fig. 7.13). Other skin manifestations including urticarial, erythematous papule, cutaneous or subcutaneous nodules, livedo reticularis, digital gangrene, and bullous lesion can be seen [55].

Both vessel inflammation and eosinophilic proliferation are thought to contribute to organ damage, but the clinical presentations are heterogeneous. Neurologic symptoms can be present including peripheral neuropathy (polyneuropathy or multiple mononeuropathy) in 55% of cases, CNS such as ischemic lesions and intracerebral hemorrhages, cranial nerve palsies, and loss of visual acuity in 8% of cases [56]. CNS involvement was noted at diagnosis in 86%, before the diagnosis in 2%, and during follow-up in 12% of cases [57]. Cerebral infarction and subarachnoid hemorrhage, the main CNS manifestations, are thought to be induced by vasculitis and/or eosinophil-mediated injury [57].

Prognosis or Clinical Course

In general EGPA is considered a milder form of systemic vasculitis with lower mortality compared to other types of vasculitis. Long-term outcomes are generally good, and relapse was noted in 26–28% of patients in remission [58]. The overall 5-year and 10-year survival rates were 88.9% and 78.6%, respectively [48]. ANCA-positive patients more frequently had a "vasculitic" phenotype, ENT involvement, peripheral neuropathy, and/or renal involvement, whereas the ANCA-negative patients would have an eosinophilic "tissue" phenotype – more frequently cardiomyopathy [56]. The 5-year relapse-free survival was 58% and 68% for ANCA-positive and ANCA-negative patients, respectively [56]. Cardiomyopathy and older age at diagnosis were independent risk factors for death and lower eosinophil count at diagnosis as predictive of relapse in multivariate analyses [56]. Myocardial and gastrointestinal tract involvement are indicators of frequent relapses in a series of 121 Japanese patients with EGPA [59].

The French Vasculitis Study Group has proposed the five-factor score (FFS). These include (1) elevated serum creatine levels (>1.58 mg/dl), (2) proteinuria (>1 g per day), (3) gastrointestinal tract involvement, (4) cardiomyopathy, and (5) central nervous system involvement [60]. Those with FFS of 0 have better survival than those with FFS greater than 1.

Histopathology

Extravascular tissue eosinophils are seen in any organ during the early phase. Features of vasculitis (fibrinoid necrosis, neutrophils, and eosinophils infiltration of vessel walls) are seen in small- to medium-sized vessel walls in the vasculitic phase. The presence of numerous eosinophils is often a diagnostic clue (Fig. 7.14). Due to the widespread of glucocorticoid therapy and available small biopsy specimens, granulomatous inflammation is rarely observed histopathologically. Since the skin is most accessible, biopsy of a cutaneous lesion might result in early diagnosis of EPGA.

Differential Diagnosis

The presence of asthma and eosinophilia distinguishes EGPA from MPA and GPA. Although EGPA belongs to the ANCA-associated vasculitis group, ANCAs are detected in only 40% of the

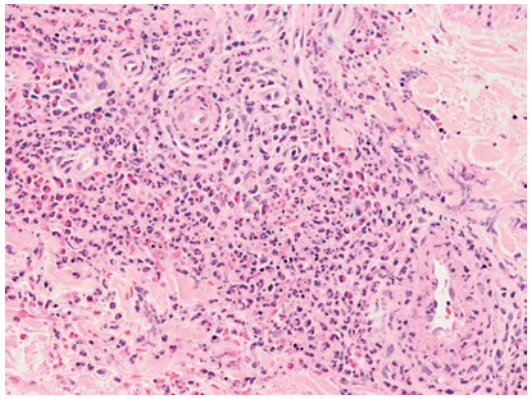


Fig. 7.14 *Eosinophilic granulomatosis with polyangiitis*. A small-vessel vasculitis with a prominent infiltrate of eosinophils (×400)

cases. In addition, its clinical presentation and pathophysiology are different from those of MPA and GPA. Eosinophils in EGPA are the main responsible inflammatory cells in contrast to neutrophils in MPA and GPA. Although idiopathic hypereosinophilic syndrome (HES) is characterized by tissue infiltration by eosinophils, there is absence of asthmas, vasculitis on biopsy, and serum ANCA. Venous thrombosis (75%) occurs more frequently than arterial thrombosis (39%) in EGPA, whereas arterial thrombosis (72%) is more frequent than venous thrombosis (28%) in hypereosinophilic syndrome [61].

Summary

Clinical Presentation

- EGPA is a necrotizing vasculitis affecting small to medium vessels and associated with asthma and eosinophilia.
- The features of the clinical phases of EGPA include asthma in prodromic phase, peripheral eosinophilia and organ involvement in eosinophilic phase, and symptoms due to small-vessel vasculitis in vasculitic phase.
- Vasculitis can be diagnosed as EGPA when four of the following six criteria are met: asthma, eosinophilia greater than 10%, neuropathy, migratory pulmonary infiltrates, paranasal sinus abnormality, and biopsy-proven extravascular eosinophils.
- Skin involvement can be seen in 40–50% of cases.

Histologic Features

- Vasculitis with prominent eosinophils
- Associated with myeloperoxidase ANCA (P-ANCA)

Differential Diagnosis

- Hypereosinophilic syndrome
- Microscopic polyangiitis (MPA)
- Granulomatosis with polyangiitis (GPA)

Takeaway Essentials

Clinical Relevant Pearls

- ANCA-positive patients more frequently had peripheral neuropathy or renal involvement, but less frequently had cardiomyopathy.
- Cardiomyopathy and older age at diagnosis were independent risk factors for death and lower eosinophil count at diagnosis as predictive of relapse in multivariate analyses.
- Pediatric cases more frequently have cardiomyopathy which can account for the higher mortality rates.

Pathology Interpretation Pearls

- ANCA can be falsely negative in patients with EGPA.

Granulomatosis with Polyangiitis (Wegener Granulomatosis)

The American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism have recommended to replace "Wegener granulomatosis"

with "granulomatosis with polyangiitis." Granulomatosis with polyangiitis (GPA) is necrotizing vasculitis affecting small to medium vessels (capillaries, venules, arterioles, arteries, and veins), necrotizing granulomatous inflammation involving the upper and lower respiratory tract [3]. Necrotizing glomerulonephritis is common.

Clinical Presentation

There are two phenotypes of GPA, the limited or localized form and the systemic form. The localized GPA is characterized by eye and ear, nose, and throat (ENT) involvement, small percentage of ANCA positivity, severe local damages, and frequent relapses. The age of the patients at presentation is often between 50 and 75 years. Nasal sinus involvement is reported in 70–100% of cases at the time of diagnosis and might be the only symptom in the localized form of the disease. Saddle nose deformity is due to the destruction of the nasal cartilage (Fig. 7.15). The lungs can be affected in 50–90% of patients resulting in alveolar hemorrhage and/or parenchymal nodules [48]. The kidney is often affected in 40–100%. Skin involvement is seen in 50% of patients and presents as polymorphic papules, nodules, vesicles, and blisters on a background of livedo reticularis. They most commonly occur on the lower extremities but also the face and scalp.

Cytoplasmic-pattern antineutrophil cytoplasmic autoantibodies (C-ANCA) with antigen specificity for proteinase 3 (PR3-ANCA) are sensitive serologic marker for GPA. *ETS1* (ETS proto-oncogene 1) polymorphism was suggested to be associated with GPA and C-ANCA in Japanese population [62]. However, MPO-ANCA can be seen in 10–20% of patients in Europe and greater than 50% in Asia. Patients with MPO-ANCA-positive GPA are predominantly females. They had limited disease, high incidence of subglottic stenosis, less need for immunosuppressive therapy, and lower relapse rates in comparison to patients with PR3-ANCA [63].

Prognosis or Clinical Course

Infections and renal failure are the main causes of mortality [48]. The prognosis of untreated patients is very poor with only 10% 1-year survival [48]. With the introduction of glucocorticoids and cyclophosphamide, the clinical course has become a chronic relapsing and remitting disease with remission noted in 90% of the patients. Increased risk for relapse is associated with PR3-ANCA positivity and lung or ENT involvement [63]. The ANCA titer often rises in active disease.

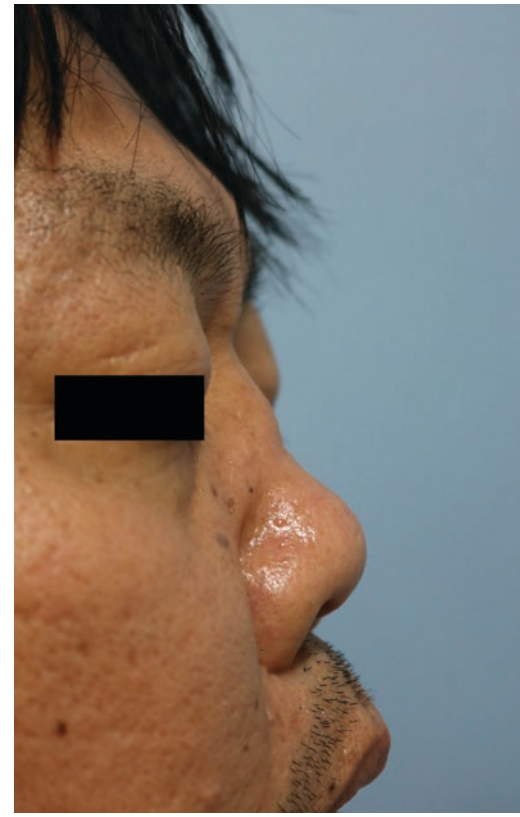


Fig. 7.15 *Granulomatosis with polyangiitis*. Destruction of the nasal cartilage results in a saddle nose deformity

Histopathology

Leukocytoclastic vasculitis is seen up to 50% of skin biopsies. Granulomatous inflammation around the vessels or palisading necrotizing granulomatous can be seen in biopsies of internal organ infiltrates, but rarely noted in the skin (Fig. 7.16). Neutrophilic dermatoses and pyoderma gangrenosum or Sweet's syndrome can be seen in association of ANCA-associated vasculitis, most commonly with GPA [64].

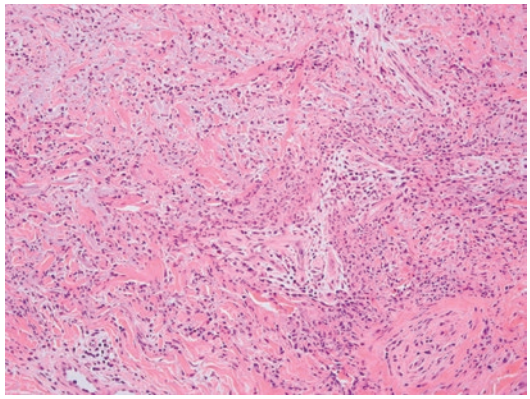


Fig. 7.16 *Granulomatosis with polyangiitis*. Granulomatous vasculitis affecting the small vessel is noted in the dermis (×200)

Differential Diagnosis

GPA can be distinguished from MPA by the involvement of the respiratory tract. However, it is difficult to distinguish GPA from microscopic polyangiitis (microscopic polyarteritis) with respiratory tract involvement. Drug exposure must be excluded in patients with localized GPA to rule out levamisole-induced/cocaine-associated vasculitis and midline destructive lesion due to cocaine use. In the setting of a solitary nodule, opportunistic infection such as blastomycosis, aspergillosis, and mycobacterial infection rather than localized GPA is the likely etiology. There can be overlap between GPA and IgG4-related disease. Chronic periaortitis, tubulointerstitial nephritis, and prevertebral fibrosis are characteristics of IgG4-related disease rather than of ANCA-associated vasculitis [65]. Rarely extranodal natural killer/T-cell lymphoma can present with midline destructive lesion.

Summary

Clinical Presentation

- Typically characterized by ear-nose-throat involvement followed by systemic symptoms, renal, lower respiratory tract, musculoskeletal, and cutaneous involvement
- Associated with proteinase 3 ANCA (C-ANCA)

Histologic Features

- Leukocytoclastic vasculitis is seen up to 50% of skin biopsies.
- Vascular granulomatous inflammation or palisading necrotizing granulomatous can be seen in biopsies of internal organ infiltrates.

Differential Diagnosis

- Microscopic polyangiitis
- Levamisole-induced/cocaine-associated vasculitis
- Opportunistic infection
- Extranodal natural killer/T-cell lymphoma

Takeaway Essentials

Clinical Relevant Pearls

- GPA can be distinguished from MPA by the involvement of respiratory tract.
- C-ANCA directed against proteinase 3 is a sensitive serologic marker for GPA.
- Patients with MPO-ANCA-positive GPA exhibit a different clinical course than those with PR3-ANCA-positive GPA.
- Increased risk for relapse is associated with PR3-ANCA positivity and lung or ENT involvement.

Pathology Interpretation Pearls

- Granulomatous inflammation is rarely noted in the skin.

Medium-Vessel Vasculitis

The types of vasculitis that affect the medium vessels include polyarteritis nodosa and Kawasaki disease.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) has been divided into two major subtypes, the systemic PAN and cutaneous PAN. The rare systemic form is a vasculitis that affects predominantly medium-sized arteries without glomerulonephritis and not associated with ANCA. Small arteries may be involved, but arterioles, capillaries, and venules are not. Cutaneous PAN is limited to the skin and rarely progressed to systemic PAN. Gastrointestinal PAN is a vasculitis that is limited to the gastrointestinal system and is associated with significant morbidity and mortality.

PAN can be idiopathic or triggered by viral infection including hepatitis B virus, hepatitis C virus, and human immunodeficiency virus. Approximately 36% of PAN cases are associated with hepatitis B infection prior to the availability of hepatitis B virus vaccine. Deficiency of adenosine deaminase type 2 (ADA2) has been reported in pediatric cutaneous PAN cases and is associated with various systemic symptoms [66]. A recent study proposed that cutaneous PAN and macular lymphocytic arteritis are related and not distinct entities [67].

Clinical Presentation

Systemic PAN

Based on the 1990 ACR classification criteria, systemic PAN is diagnosed if at least three of the following ten criteria are met: significant weight loss, livedo reticularis, testicular pain, myalgia or muscle weakness, neuropathy, elevated diastolic blood pressure, increased blood urea nitrogen or creatinine, hepatitis B infection, unexplained abnormal angiogram, and biopsy-proven neutrophilic vasculitis [1].

Based on the EULAR classification criteria, childhood systemic PAN is diagnosed by the presence of either a biopsy-proven medium-sized artery necrotizing vasculitis or angiographic abnormalities together with at least two of the following seven criteria: skin involvement, myalgia or muscle weakness, systemic hypertension, neuropathy, abnormal urine analysis and/or impaired renal function, testicular pain, and signs or symptoms suggesting vasculitis of other major organ systems [68].

Cutaneous PAN

After systemic manifestations have been excluded, both clinical and histologic criteria must be present to diagnose cutaneous PAN. Cutaneous PAN can occur at any age, ranging from childhood to the elderly, with a mean age of 40 years at presentation [69]. Cutaneous lesions such as livedo reticularis, painful subcutaneous nodules (Fig. 7.17), and large "punched-out" ulcers are present often over the lower extremities (knee, anterior lower leg, malleoli, and dorsal foot) in 20–50% of cases.

Although cutaneous PAN is uncommon in the pediatric population, group A beta-hemolytic streptococcus infections are the most frequent infections associated with cutaneous PAN in this population. In adults, hepatitis B and C, HIV, parvovirus B19, and *Mycobacterium tuberculosis*

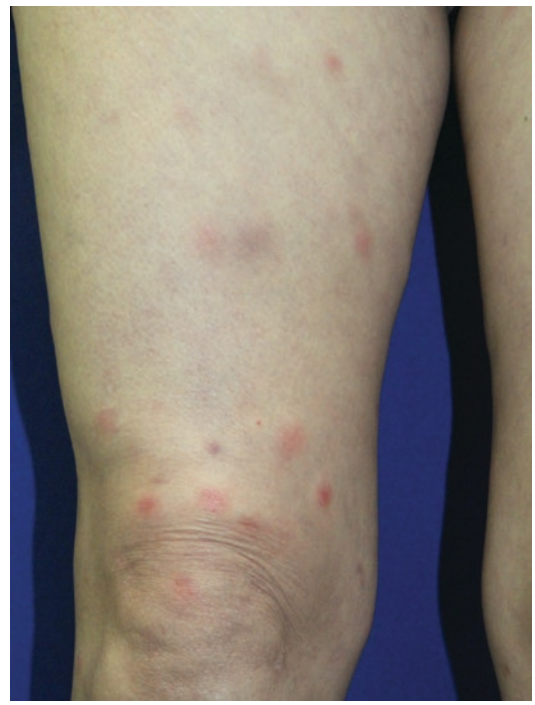
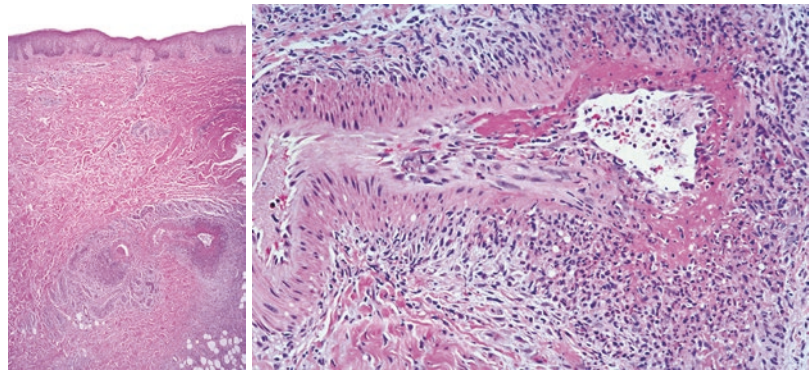


Fig. 7.17 *Polyarteritis nodosa*. Painful nodules are seen on the lower extremity. (Courtesy of Dr. Hyun Chang Ko, Department of Dermatology, Pusan National University, Pusan, South Korea)



Figs. 7.18 and 7.19 Polyarteritis nodosa is characterized by a medium-sized vessel vasculitis in the deep dermis and subcutaneous tissue junction (×40, ×100)

infections have been implicated. Association with systemic diseases such as inflammatory bowel diseases and rheumatoid arthritis has been reported [69].

Prognosis or Clinical Course

The following factors were significantly associated with poorer 5-year survival in systemic PAN: age greater than 65 years, cardiac manifestations, gastrointestinal involvement, and renal insufficiency [70]. The French Vasculitis Study Group has proposed the five-factor score (FFS). Those with FFS of 0 have better survival than those with FFS greater than 1 [Guillevin 2011] [70]. While systemic PAN is a potentially life-threatening disorder, cutaneous PAN is a chronic benign disease with frequent relapses [71]. Cutaneous PAN rarely progresses to the systemic form. Comorbidities may be present in 60% of cases of cutaneous PAN [72].

Histopathology

Both localized and systemic PAN are characterized by necrotizing vasculitis of arterioles or medium-sized arteries (Figs. 7.18 and 7.19). Fibrinoid necrosis of the muscular wall accompanied by an infiltrate rich in neutrophils is seen in the initial phase. Later on fibrous endarteritis can result in vascular occlusion.

Differential Diagnosis

Macular lymphocytic arteritis (MLA) is characterized clinically by erythematous or pigmented reticulated patch on the lower extremities and histopathologically by prominent lymphocytic infiltrate. It has been proposed that MLA represents the early stage of cutaneous PAN [67]. The absence of ANCA is a distinguishing clinical feature from microscopic polyangiitis. In addition, PAN does not involve the lungs, while microscopic polyangiitis can cause pulmonary hemorrhage. Kawasaki disease is associated with mucocutaneous lymph node syndrome in addition to arteritis.

Summary

Clinical Presentation

- The rare systemic form is a vasculitis that affects predominantly medium-sized arteries without glomerulonephritis and is not associated with ANCA.
- Cutaneous PAN is characterized by painful nodules and ulceration on the lower extremities.

Histologic Features

- Necrotizing vasculitis of arterioles or medium-sized arteries

Differential Diagnosis

- Microscopic polyangiitis
- Kawasaki disease

Takeaway Essentials

Clinical Relevant Pearls

- Systemic polyarteritis nodosa (PAN), cutaneous arteritis, and gastrointestinal (GI) vasculitis likely represent different diseases due to their different clinical courses.
- Cutaneous PAN rarely progresses to systemic PAN.
- Patients with cutaneous PAN have a higher relapse rate than those with systemic PAN, likely attributed to less use of immunosuppressive agents.
- Deficiency of adenosine deaminase type 2 (ADA2) has been reported in pediatric cutaneous PAN cases and is associated with systemic symptoms.
- PAN has become a rare disease with the decline of hepatitis B virus infection.

Kawasaki Disease

Kawasaki disease (KD) is an arteritis associated with the mucocutaneous lymph node syndrome and affecting predominantly medium and small arteries. KD is the most common medium-vessel vasculitis and second most common pediatric vasculitis after HSP. It affects mainly the pediatric population in children below the age of 5 and with predilection for the coronary artery. It is the leading cause of pediatric acquired heart disease in Asian countries such as Japan, Korea, China, and Taiwan but also North America and Europe [17].

The Kawasaki Disease Research Committee guidelines (Japanese Ministry of Health guidelines) were introduced in 2002 [73]. Five of the following six criteria must be met for diagnosis: fever persisting greater than 5 days, bilateral conjunctival congestion, changes of lips and oral cavity, polymorphous exanthema, changes of peripheral extremities, and acute non-purulent cervical lymphadenopathy [73]. The 2004 American Heart Association (AHA) guidelines are the widely used ones and have been revised in 2017 [74]. Fever is essential for the diagnosis per AHA criteria but not per the Japanese criteria. The diagnosis is a clinical one and relies on the presence of fever greater than 5 days and four or more of the following features: bilateral bulbar conjunctival injection, mucosal changes involving the lips and oral cavity, unilateral cervical lymphadenopathy, polymorphous exanthema, and extremity changes [74].

As there is seasonal variation, viral infections have been suspected as etiologic agents. Various organisms (*Streptococcus*, *Staphylococcus*, *Epstein-Barr virus*, *Coronavirus*, and *Parvovirus*), bacterial super antigens (staphylococcal and streptococcal), and genetic factors have been proposed as possible etiology; however, the cause remains unknown [Gupta 2016] [75]. Potential susceptibility genes include single nucleotide polymorphism in *ITPKC* (1,4,5-inositol trisphosphate 3-kinase C), *CASP3*, *FCGR2A* (Fc gamma receptor IIa), and *KCNN2* genes; B lymphoid tyrosine kinase; and the transforming growth factor-beta signaling pathway.

Clinical Presentation

The disease typically affects infants and young children less than 5 years of age. Coronary arteries are often involved. Aorta and large arteries may be involved. The disease appears to have three phases. An acute febrile phase lasts for 10–14 days and is characterized by fever, polymorphous rash (Fig. 7.20), mucosal changes, extremity changes, and cervical lymphadenopathy. The eruption can be macular to maculopapular or morbilliform. There can be vertically cracked lips, "strawberry" tongue, and exanthema of oral and pharyngeal mucosa. The subacute phase from week 2 to 4 is characterized by periungual desquamation and at the tips of fingers and toes. Coronary artery abnormalities are most commonly detected by echocardiography during the subacute phase. The patients become asymptomatic during convalescent phase.

When there is fever yet with less than four principal clinical features, the patient would be diagnosed to have "incomplete KD." Risk of coronary abnormalities is increased in this group due to delayed diagnosis. When a child exhibits

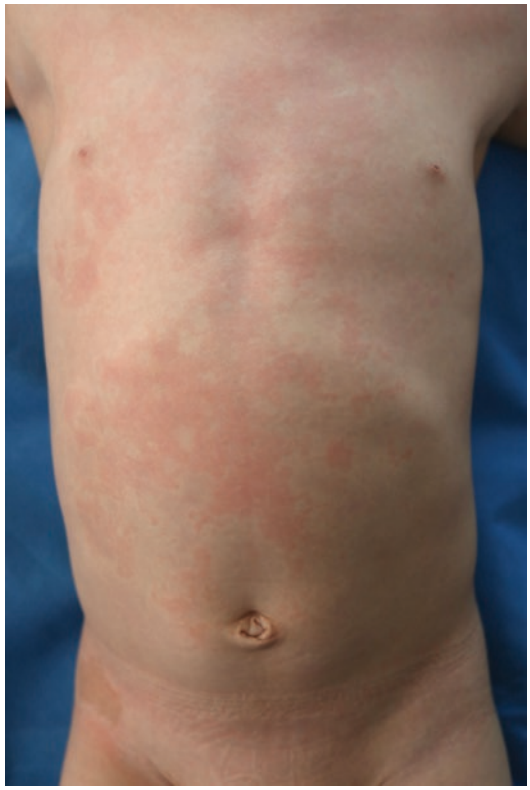


Fig. 7.20 A polymorphous rash is noted on the trunk of a child with Kawasaki disease

seizures, stroke, pneumonia, myositis, nephritis, and acute hepatitis in addition to features of KD, he/she would be diagnosed with "atypical KD." [75] Although rare, adult-onset KD has a high incidence of cardiovascular complication.

Prognosis or Clinical Course

Although it is a self-limiting disease in the majority of cases, coronary dilatations and aneurysms can be developed in a quarter of untreated patients. Timely diagnosis and implementation of intravenous immunoglobulin are important to decrease the risk of coronary artery complications. Even those with treatment coronary artery abnormalities can develop down the road; therefore, long-term follow-up is important [75].

Histopathology

The diagnosis remains a clinical one, and there is no laboratory test to confirm the clinical diagnosis. The absence of involvement of vessels smaller than arteries distinguishes Kawasaki disease from microscopic polyangiitis. Two-dimensional transthoracic echocardiography has long been the traditional diagnostic tool. Dual-source computed tomography coronary angiography is increasingly employed to assess the coronary arteries [76].

Differential Diagnosis

Since the disease occurs mainly in children under 5 years of age and fever more than 5 days is a required diagnostic criteria, viral infection is a main clinical differential diagnosis. The various infections can include adenovirus, measles, parvovirus, human herpes viruses, Rocky Mountain spotted fever, and *Leptospira*, streptococci, and staphylococci. Although scarlet fever is in the differential diagnosis, the lip involvement and conjunctival injection are features seen only in KD. The differential diagnosis also includes immune system reactions (toxic shock syndrome, serum sickness) and rheumatic diseases (systemic juvenile idiopathic arthritis, polyarteritis nodosa).

Summary

Clinical Presentation

- An arteritis associated with the mucocutaneous lymph node syndrome and affecting predominantly medium and small arteries.
- Kawasaki disease is the most common vasculitic disorder in children and affects patients less than 5 years of age.
- The diagnosis is clinical and includes the presence of fever greater than 5 days and four or more of the following features:
  - Bilateral bulbar conjunctival injection
  - Mucosal changes involving the lips and oral cavity
  - Unilateral cervical lymphadenopathy
  - Polymorphous exanthema
  - Extremity changes

Histologic Features
- The diagnosis can only be made based on clinical findings.

Differential Diagnosis
- Various infections include adenovirus, measles, parvovirus, human herpes viruses, Rocky Mountain spotted fever, and *Leptospira*, streptococci, and staphylococci.
- Immune system reactions.
- Rheumatic diseases.

Takeaway Essentials

Clinical Relevant Pearls
- Currently the diagnosis remains a clinical one and there is no laboratory test to confirm the clinical diagnosis.
- Children with incomplete and atypical Kawasaki disease may have higher rate of coronary complications since the diagnosis often is delayed.
- Timely diagnosis and appropriate treatment will decrease the risk of coronary artery complications.

Large-Vessel Vasculitis

Giant Cell Arteritis

Giant cell arteritis (GCA) is a systemic, often granulomatous vasculitis affecting large vessels branching from the aorta, with a predilection for branches of the external carotid and vertebral arteries. Giant cell arteritis is the most common vasculitis in the elderly in Western countries, while it is uncommon in Asia, Africa, and South America. Association with HLA-DRB1∗04 alleles has been implicated in disease susceptibility and risk of visual complications [77].

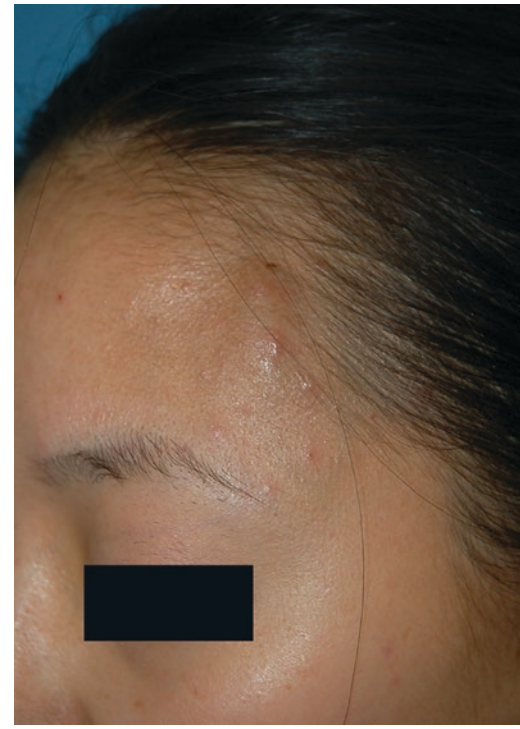


Fig. 7.21 *Giant cell arteritis*. Palpable and tender nodules are seen over the temporal artery. (Courtesy of Dr. Hyun Chang Ko, Department of Dermatology, Pusan National University, Pusan, South Korea)

Clinical Presentation

GCA involves large- and medium-sized vessels with predilection for branches of the external carotid and vertebral arteries [69]. It frequently involves the temporal artery of patients older than 50 years of age, women more than men, and has associated polymyalgia rheumatica. Symptoms include headaches in the temporal and occipital areas, temporal artery tenderness, jaw claudication, malaise, and fever [69]. Red and tender nodules may be palpable over the temporal arteries with diminished pulse (Fig. 7.21). A minority of patients experienced partial or complete loss of vision. Cutaneous manifestations of giant cell arteritis are rare as the result of arterial occlusions. They include scalp induration, erythema, or necrosis; tongue necrosis; purpura; periorbital ecchymosis; edema of the face and neck; and nodules of the head or limbs [69].

Prognosis or Clinical Course

A risk of partial or complete loss of vision can be seen in 13–19% of patients. Visual complications were seen in 35–60% of patients prior to the introduction of corticosteroids [Gonzalez-Gay 2000] [77]; however, their frequency has significantly diminished with this therapy.

Histopathology

It is characterized by granulomatous inflammation of the internal elastic lamina of the aorta and major branches best diagnosed on a temporal artery biopsy (Figs. 7.22 and 7.23). The histologic features of giant cell arteritis can be identical to those of Takayasu's disease.

Differential Diagnosis

The serum IgG4 level is elevated in patients with polymyalgia rheumatica in comparison to patients with giant cell arteritis [78]. Although it has been suggested that both diseases represent ends of the same disease spectrum [79], giant cell arteritis and Takayasu disease are classified as two diseases based on differences in genetics, age, ethnicity, signs, symptoms, and vascular distribution. Giant cell arteritis is associated with HLA-DR4, while Takayasu arteritis is associated with HLA-Bw52 [80]. While Takayasu arteritis affects patients younger than 50 years, giant cell arteritis affects patients older than 50 years. Takayasu arteritis is more common in Asian populations; on the contrary, giant cell arteritis would be more common in Caucasians. Although both have contiguous aortic involvement and symmetric in paired branch vessels, left carotid and mesenteric arteries have more significant disease in Takayasu arteritis and more left and right axillary artery disease in GCA [79]. The shape of the stenotic lesions in the subclavian and carotid arteries can be a useful discriminator [79].

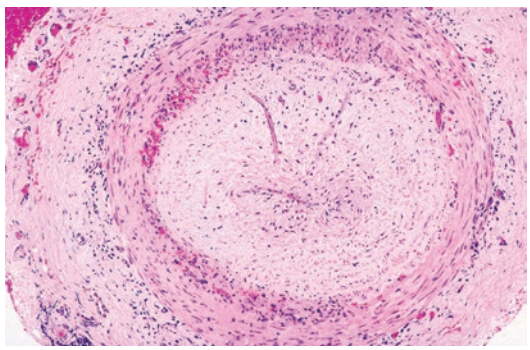


Fig. 7.22 *Giant cell arteritis*. Granulomatous inflammation of the internal elastic lamina of the temporal artery is seen (×100)

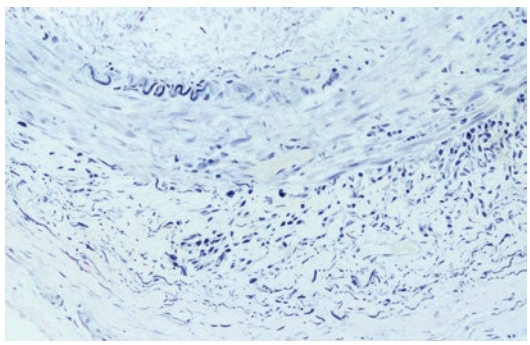


Fig. 7.23 *Giant cell arteritis*. Fragmentation of the internal elastic lamina (arrow) is seen on elastic stain (×100)

Summary

Clinical Presentation

- A vasculitis of large- and medium-sized vessels with predilection for branches of the external carotid and vertebral arteries.
- Frequently involves the temporal artery of patients older than 50 years of age.
- Symptoms include headaches in the temporal and occipital areas and partial or complete loss of vision.

Histologic Features

- Granulomatous inflammation of the internal elastic lamina

Differential Diagnosis

- Takayasu arteritis

Takeaway Essentials

Clinical Relevant Pearls

- While Takayasu arteritis affects patients younger than 50 years in Asian populations, giant cell arteritis affects patients older than 50 years in Caucasians.
- A minority of patients experienced partial or complete loss of vision.

Takayasu Arteritis

Takayasu arteritis is a rare chronic large-vessel vasculitis affecting predominantly the aorta, its major branches, and the pulmonary arteries. Large arteries including the ascending or descending aorta and subclavian and carotid arteries are involved in 60–90% of cases [81]. This disease is common in Southeast Asia, India, Mexico, or Africa and rare in European countries. This could be due to underlying genetic differences. Patients with HLA-B52 have susceptibility to Takayasu arteritis, and those with leukocyte antigen Bw52 have a higher rate of complications than those without [80].

Doppler ultrasound (US), magnetic resonance angiograph (MRA), computed tomography angiograph (CTA), and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) have the potential to replace conventional X-ray angiography as noninvasive diagnostic method [Barra 2018] [82]. ^{18}F-FDG-PET is helpful in the setting of absent vascular symptoms, fever of unknown origin, or unexplained acute-phase response.

Clinical Presentation

There is a predilection for women during the second and third decades of life. Onset is typically in patients younger than 50 years of age. Nonspecific symptoms such as fever, malaise, and weight loss are noted in the initial inflammatory stage. It is followed by an occlusive stage characterized by inflammation of the medial and adventitial layers of large-vessel walls resulting in stenosis and/or aneurysm formation (Figs. 7.24 and 7.25).

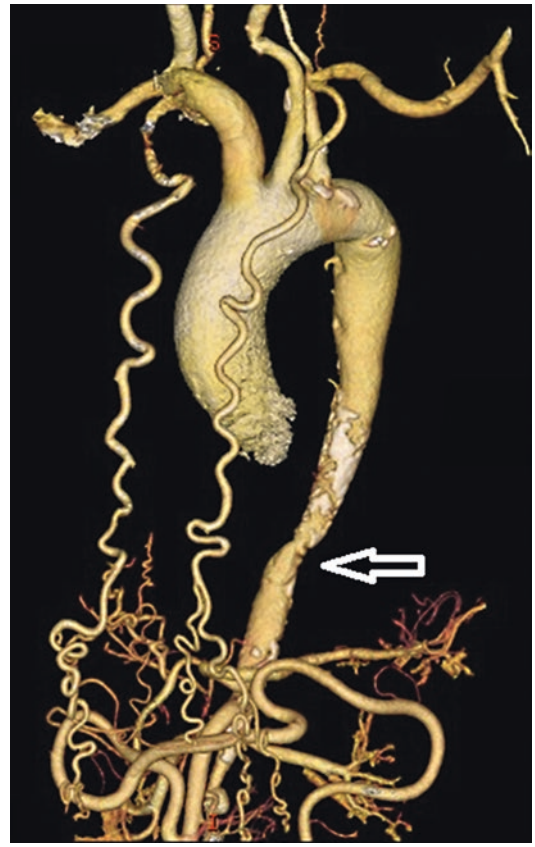


Fig. 7.24 *Takayasu arteritis*. Narrowing of the descending aorta is noted on computed tomography

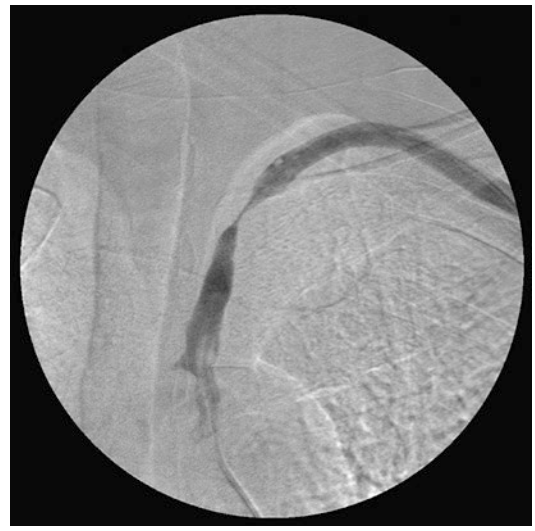


Fig. 7.25 A stenosis of the subclavian artery is noted in a patient with Takayasu arteritis

Symptoms related to ischemia of involved vessels are extremity pain, claudication, absent or diminish pulse, and/or asymmetric blood pressure. While most Japanese patients present with pulselessness, Indian patients would be hypertensive [83].

A subclassification was created based on angiographic findings: type I, branches of the aortic arch; type IIa, ascending aorta, aortic arch, and its branches; type IIb, ascending aorta, aortic arch its branches, and thoracic descending aorta; type III, descending thoracic aorta, abdominal aorta, and/or renal arteries; type IV, abdominal aorta and/or renal arteries; and type V, combined features of types 2b and 4 [83].

Cutaneous manifestations vary according to geographical locations. Erythema nodosum-like and acute inflammatory lesions are most commonly seen in Europe and North America, whereas pyoderma gangrenosum is frequently observed in Japan. Livedo reticularis, papular or papulonecrotic lesions, and superficial phlebitis may also be observed [69].

Prognosis or Clinical Course

It follows an indolent course. Acute visual loss and stroke are rare events in Takayasu arteritis [81]. The HLA-B52 allele has been implicated in disease severity of Takayasu arteritis [84]. The presence of aortic regurgitation, renal arterial stenosis, aortic coarctation and aneurysms are significant prognostic factors.

Histopathology

It is often a granulomatous arteritis. Rendering the diagnosis is a clinical challenge since there is a lack of a tissue biopsy or a "gold standard." Diagnostic criteria were outlined by the American College of Rheumatology in 1990 [1].

Differential Diagnosis

Since the histopathologic features of Takayasu arteritis and giant cell arteritis are similar and aortic involvement can be seen in giant cell arteritis, it has been suggested that both diseases represent ends of the same disease spectrum [79].

Summary

Clinical Presentation

- A chronic large-vessel vasculitis affecting predominantly the aorta, its major branches, and the pulmonary arteries.
- The disease is common in Southeast Asia, India, Mexico, or Africa and rare in European countries.
- It has a predilection for women during the second and third decades of life.

Histologic Features

- An initial inflammatory stage is followed by an occlusive stage.

Differential Diagnosis

- Giant cell arteritis

Takeaway Essentials

Clinical Relevant Pearls

- While Takayasu arteritis affects patients younger than 50 years in Asian populations, giant cell arteritis affects patients older than 50 years in Caucasians.

Variable-Vessel Vasculitis

Behcet disease and Cogan syndrome can affect either small vessel or medium vessel; thus, the category of variable-vessel vasculitis has been proposed.

Behcet Disease

Described in 1937 by Hulusi Behcet as a clinical triad of oral ulcers, genital ulcers, and uveitis, Behcet disease is now recognized to be a systemic condition having clinical features of

both autoinflammatory disease and vasculitis [85]. There is an increased incidence in individuals from Japan and the Middle East with the highest prevalence in Turkey [85]; therefore, Behcet disease is known as Silk Road disease. In 1990, the International Study Group for Behcet disease evaluated 914 patients from 7 different countries and proposed the following diagnostic criteria: presence of oral ulceration that recur at least 3 times in a 12-month period plus 2 of the following which are recurrent genital ulcers, uveitis, cutaneous lesions, and positive pathergy test. A minimum of three out of six outlined categories was defined as having pediatric Behcet disease [86].

Although its pathogenesis remains currently unclear, a combination of hormonal factors, genetic background (predisposing genes), and environmental factors (especially infection) plays a role. Infectious factors can trigger the disease in genetically predisposed patients. Genetic studies have identified HLA-B∗51 to be the important risk factor. Genome-wide association studies (GWAS) have cited an association between Behcet disease and the following loci: *IL23R-IL12RB2*, *IL10*, *STAT4*, *CCR1-CCR3*, *KLRC4*, *ERAP1*, *TNFAIP3*, and *FUT2*. Rare nonsynonymous variants of IL23R, TLR4, NOD2, and MEFV have been implicated in pathogenesis by targeted next-generation sequencing [87].

Clinical Presentation

The mean age of onset was 27 years with the most common clinical presentations being oral aphthous lesions (Fig. 7.26), genital ulcers (Fig. 7.27), and skin lesions. In a recent prospective cohort of 230 pediatric patients from 42 centers from 12 countries, the male-to-female ratio was 1:1. Although men and women are equally affected worldwide, women are more frequently affected in Europe and the USA. Papulopustular lesions, pathergy positivity, and vascular, eye, and renal involvement were commonly seen in men, whereas genital ulcers, arthritis, and arthralgia were more commonly seen in women [88].

Oral aphthosis invariably presents in most patients, up to 98%, and can precede other manifestations in an average of 7–8 years. Genital ulcers (57–93%) commonly affect the scrotum in males and vulva, vagina, and cervix in females [89]. Ocular disease (30–70%) is the main cause of blindness in a quarter of the patients. It is characterized by anterior and posterior uveitis, iridocyclitis, keratitis, episcleritis, vitritis, retinal vasculitis, and optic neuritis [89]. Cutaneous

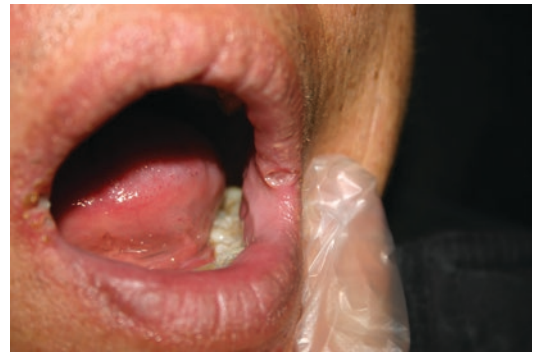


Fig. 7.26 *Behcet disease*. Ulceration is noted on oral mucosa

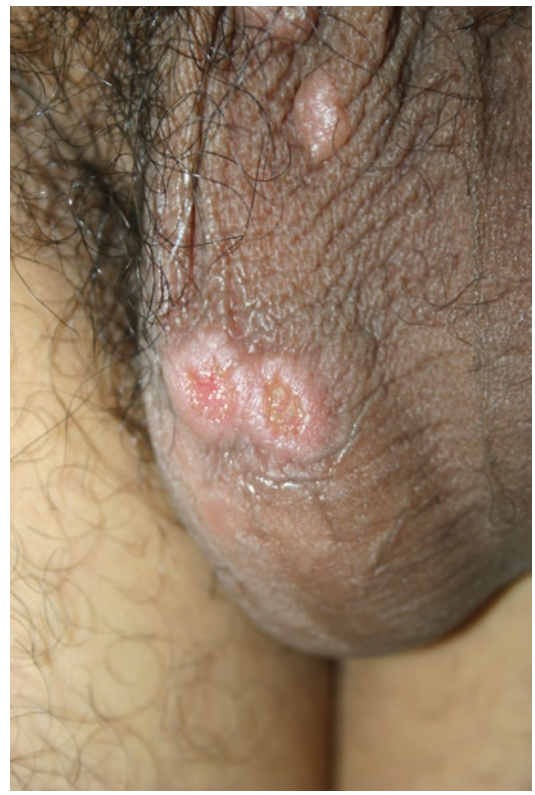


Fig. 7.27 *Behcet disease*. Ulceration on scrotal skin

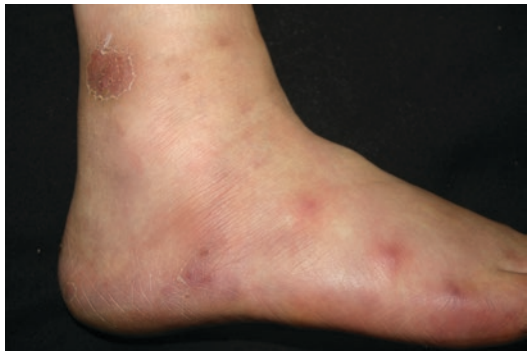


Fig. 7.28 *Behcet disease*. Vasculitic lesions are noted on the patient's foot

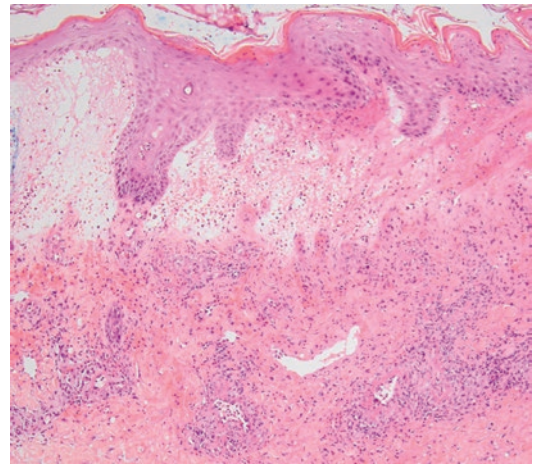


Fig. 7.29 *Behcet disease*. Small-vessel vasculitis is seen below a markedly edematous papillary dermis (×100)

lesions (38–99%) include papulopustular and acne-like lesions. Neurological manifestations (5–10%) affect the central nervous system more frequently than the peripheral nervous system. Vascular manifestations include vasculitis (Fig. 7.28) deep vein thromboses and recurrent superficial venous thrombosis.

Prognosis or Clinical Course

The prognosis of severe forms of the disease has significantly improved in recent years due to the use of aggressive immunosuppressant therapy and new treatment modalities. However, when ocular, cardiovascular, neurological, and gastrointestinal systems are involved, the prognosis remains unfavorable.

Histopathology

Vasculitis in Behcet disease can affect arteries or veins. Small-vessel vasculitis, thromboangiitis, thrombosis, arteritis, and arterial aneurysms may occur. The cutaneous histologic features of Behcet disease are often nonspecific. Approximately 50% of biopsies show vasculitis, either lymphocytic or leukocytoclastic (Fig. 7.29). The following histopathologic features can be seen: leukocytoclastic vasculitis, lymphocytic vasculitis, superficial and/or deep perivascular inflammation, and folliculitis and/or perifolliculitis.

Differential Diagnosis

Although papulopustular lesions are common cutaneous lesions in Behcet disease, they can also be seen in acne vulgaris. In a comparative study by Kalkan et al., [90] papulopustular lesions from 42 patients with Behcet disease were compared to those of 21 patients with acne vulgaris; vasculitis was seen significantly more frequent in the Behcet disease patients. In another study by Ilknur et al., [91] the histologic features of papulopustular lesions of 18 Behcet disease patients were compared to those of 16 control lesions (11 bacterial folliculitis and 5 acne vulgaris), and lymphocytic vasculitis was more frequently noted in Behcet disease group ($p = 0.046$) and folliculitis or perifolliculitis more frequently in the control group ($p = 0.038$). In a series of 26 cases of erythema nodosum-like lesions in Behcet disease, Misago et al. [92] reported the presence of vasculitis in 73% of cases. Thus, although the histology of Behcet disease is nonspecific, the finding of vasculitis appears to be very helpful to render the diagnosis.

Summary

Clinical Presentation

- Described initially as a clinical triad of oral ulcers, genital ulcers, and uveitis, Behcet disease is now recognized to be a systemic condition.

- Diagnostic criteria include the presence of oral ulceration that recurs at least three times in a 12-month period plus two of the following: recurrent genital ulcers, uveitis, cutaneous lesions, and positive pathergy test.

Histologic Features
- Approximately 50% of biopsies show vasculitis, either lymphocytic or leukocytoclastic.

Differential Diagnosis
- Cogan disease
- Crohn's disease

Takeaway Essentials

Clinical Relevant Pearls
- Vascular manifestations can include venous claudication, bronchial arterial collaterals, and "silent" Budd-Chiari syndrome.
- Eye disease or vascular involvement might be more specific than other organ manifestations.

Pathology Interpretation Pearls
- There are no unique histologic or laboratory criteria; therefore, the diagnosis relies mainly on clinical features.
- Although the histology of Behcet disease is nonspecific, the finding of vasculitis can be helpful to render the diagnosis.

Cogan Syndrome

Cogan syndrome is a rare autoimmune systemic disease which is characterized by a triad of inflammatory eye disease, vestibuloauditory dysfunction, and vasculitis. It was first described by Morgan and Baumgartner as a non-syphilitic interstitial keratitis associated with vestibuloauditory dysfunction in 1934. An ophthalmologist, David Cogan, was the one who defined the entity in his 1945 report of five cases [93]. Haynes et al. in 1980 proposed to classify the syndrome as "typical" and "atypical" which is characterized by Grasland and colleagues in 2004 [94]. Although the pathogenesis of Cogan syndrome is currently unknown, there is mounting evidence toward autoimmunity. In 27% of cases, there is preceding upper respiratory tract infection [94].

Clinical Presentation

The disease affects individuals in early adulthood; however, it can occur in children and older patients, characterized by ocular inflammatory lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction (tinnitus and vertigo). Vasculitic manifestations may include arteritis (affecting small, medium, or larger arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis. Approximately 70% of the patients have systemic disease likely attributed to vasculitis. Either the eye (41%) or the ear (43%) alone is the first affected site.

The most common eye disease is interstitial keratitis which can result in photophobia, pain, redness, tearing, and blurring of vision. The autoimmune inner ear diseases can result in deafness in 30–50% of patients.

The symptoms of typical Cogan syndrome include (1) ocular involvement (interstitial keratitis, iritis, conjunctivitis, subconjunctival hemorrhage), (2) audiovestibular involvement similar to Meniere's disease, and (3) less than a 2-year interval between the onset of ocular and audiovestibular manifestations [95]. Those of atypical Cogan syndrome include (1) chronic and recurrent conjunctivitis, scleritis, uveitis, optic disk edema, and retinal vasculitis and audiovestibular symptoms not resembling Meniere's disease [95].

Prognosis or Clinical Course

Delay in diagnosis can result in debilitating outcome.

Histopathology

Histologic sections of corneal tissue show nonspecific lymphocytic and plasma cell infiltrate, suggesting a cell-mediated reaction. Vasculitis involving the dura, brain, gastrointestinal system, kidneys, spleen, aorta, and the coronary arteries was observed at autopsies [96].

Differential Diagnosis

The systemic features can resemble PAN.

Summary

Clinical Presentation

- A triad of inflammatory eye disease, vestibuloauditory dysfunction, and vasculitis.
- The diagnosis is a clinical one since there are no confirmatory laboratory or imaging tests.

Histologic Features

- Nonspecific lymphocytic and plasma cell infiltrate of corneal tissue

Differential Diagnosis

- Behcet disease
- Polyarteritis nodosa

Takeaway Essentials

Clinical Relevant Pearls

- The possibility of large-vessel involvement must be considered in all patients.

Systemic Disease-Associated Vasculitis

Rheumatoid Vasculitis

Rheumatoid arthritis (RA) is a chronic, inflammatory, and debilitating disease that can present with articular as well as extra-articular symptoms. The disease preferentially affects females prior to 50 years of age. The cutaneous manifestations of RA include neutrophilic dermatosis, palisading granuloma, and vascular lesions. Rheumatoid vasculitis, a rare yet serious complication, can affect 2–5% of patients with at least 10 years of severe disease [97, 98]. Male gender, multiple rheumatoid nodules, joint erosions, higher rheumatoid factor titer, and treatment with biological agents are risk factors of developing rheumatoid vasculitis [97, 98]. Rheumatoid vasculitis likely represents a type III hypersensitivity reaction due to immune complex deposition [98].

Clinical Presentation

Rheumatoid vasculitis can affect small, medium, and large vessels of any organ. A peri- and/or epineural arteritis causing mononeuritis multiplex or sensory symmetric neuropathy can be seen in half of the cases [99]. In less than 1% of the patients, systemic vasculitis involving the heart, lungs, central nervous system, eyes, kidneys, and gastrointestinal tracts can be observed [99]. Clinical presentation of a small-vessel involvement includes petechiae, palpable purpura, and hemorrhagic vesicles. Bywaters' lesions are small, 0.5–1 mm, painless, purpuric papules on the pulp or nail fold of the distal finger due to small-vessel vasculitis. Urticarial vasculitis can be seen which is characterized by wheals lasting greater than 24 hours. Subcutaneous nodules, livedo reticularis, atrophie blanche, and ulceration would be the clinical presentation of an involvement of medium-sized vessels.

Other vasculopathic lesions observed in RA include pauci-inflammatory vascular thrombosis, reactive angioendotheliomatosis with glomeruloid neovascularization, perifollicular vasculitis, and granulomatous vasculitis [100].

Prognosis or Clinical Course

Vasculitis is associated with an increase in morbidity and mortality. Prognosis is determined by the size of involved blood vessels and severity of systemic diseases [98]. Isolated cutaneous rheumatoid vasculitis has a better clinical course, whereas a poorer prognosis would be observed when cutaneous lesions are followed by peripheral

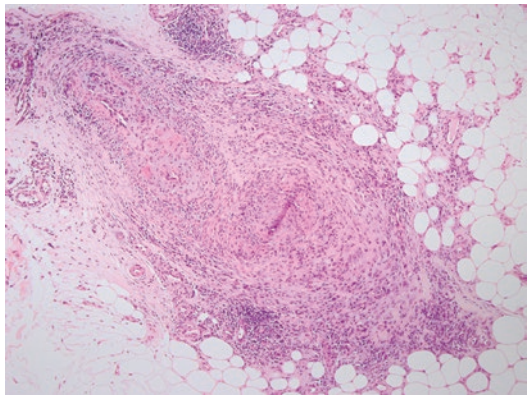


Fig. 7.30 Involvement of a medium vessel in rheumatoid vasculitis is indistinguishable from polyarteritis nodosa (×100)

nerve (mononeuritis multiplex), digital gangrene, bowel, or cardiac involvement [101].

Histopathology

Involvement of the small vessel would show a leukocytoclastic vasculitis on skin biopsy. Direct immunofluorescence studies would show IgM as well as C3 deposition within vascular walls of small- and medium-sized vessels [100].

Differential Diagnosis

Involvement of medium-sized vessels by rheumatoid vasculitis resembles polyarteritis nodosa histopathologically (Fig. 7.30).

Summary

Clinical Presentation

- Petechiae, palpable purpura, and hemorrhagic vesicles for small-vessel vasculitis
- Subcutaneous nodules, livedo reticularis, atrophie blanche, and ulceration for medium-vessel vasculitis

Histologic Features

- Leukocytoclastic vasculitis for small-vessel involvement
- Neutrophilic vasculitis of medium vessel

Differential Diagnosis

- Polyarteritis nodosa

Takeaway Essentials

Clinical Relevant Pearls

- Prognosis is determined by the size of involved blood vessels and severity of systemic diseases.

Vasculitis in Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can affect any organ (see Chap. 11). Affecting any vessel sizes in 11–36% of SLE patients, vasculitis has been considered one of the leading causes of death in SLE patients due to mesenteric vasculitis, pulmonary hemorrhage, or mononeuritis multiplex [102]. Deposition of immune complexes within the vascular wall has thought to trigger the vascular inflammatory process.

Clinical Presentation

Vasculitis was documented in 11% of SLE patients [102]. 89% of the patients presented with cutaneous vasculitis, while 11% presented with visceral vasculitis. In another cohort of 540 SLE patients with 10 years of follow-up, 82% had cutaneous involvement, 12% with visceral involvement, and 5% with both [103]. The patients with vasculitis experienced longer disease duration, presented at younger age, and were frequently males [103]. Vasculitis would occur in association with fever, fatigue, weight loss, anemia, elevated erythrocyte sedimentation rate, and autoantibodies [104].

The clinical presentation would depend on the size of the involved vessels and affected organs. Small-vessel vasculitis (86%) is more frequently seen in cutaneous lesions, whereas medium- and large-vessel vasculitis (14%) would affect internal organs [102]. Cutaneous vasculitic

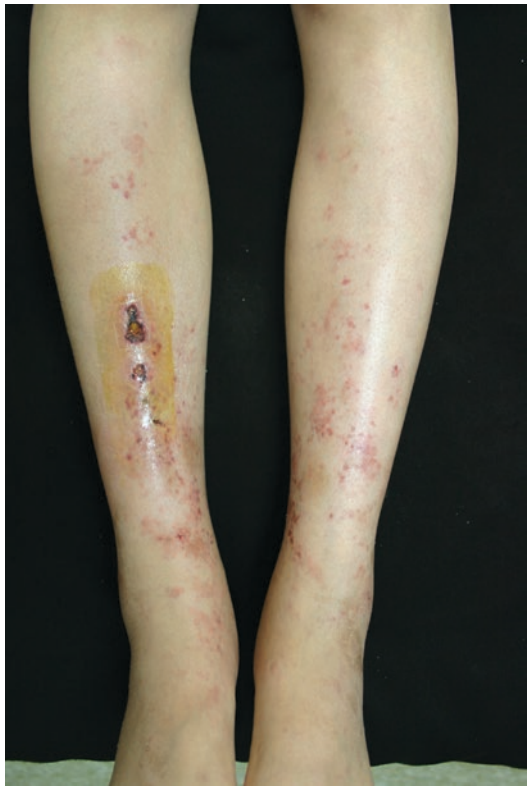


Fig. 7.31 *SLE vasculitis*. Purpuric papules with associated ulceration seen on bilateral lower extremities

lesions in SLE can present as palpable purpura, petechiae, papulonodular lesions, livedo reticularis, panniculitis, and ulcerations (Fig. 7.31). Some presented with non-blanching erythematous or violaceous punctate lesions on the fingertips and/or palms (Fig. 7.32). Urticarial vasculitis is a nonspecific finding. Hypocomplementemia can be seen in one-fifth of patients.

Prognosis or Clinical Course

Patients with medium-sized arterial involvement have a greater risk for thrombotic events and higher mortality than those without. Vasculitis was found to be associated with antiphospholipid syndrome, myocarditis, Raynaud's phenomenon, serositis, pleuritis, lymphopenia, and leukopenia [103].

Histopathology

Small-vessel vasculitis characterized by neutrophilic infiltrate, fibrinoid necrosis of vessel wall, and leukocytoclasis is seen affecting the entire

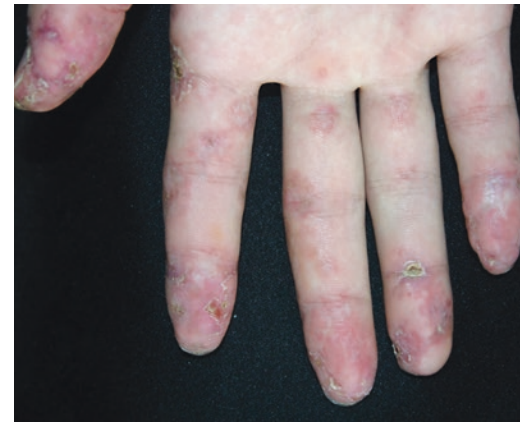


Fig. 7.32 *Chilblain-like SLE vasculitis*. Retiform purpura and digital infarcts

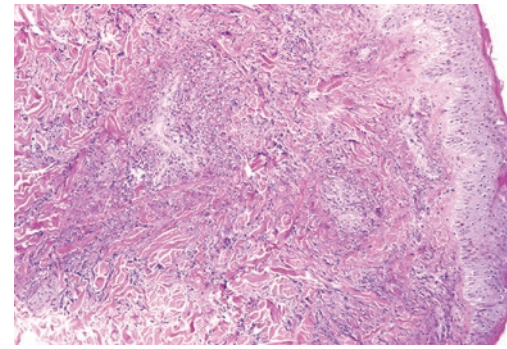


Fig. 7.33 Features of a leukocytoclastic vasculitis are seen in lupus vasculitis (×100)

dermis with associated epidermal necrosis (Fig. 7.33). Lymphocytic vasculitis can be seen.

Differential Diagnosis

The differential diagnosis includes other forms of small-vessel vasculitides.

Summary

Clinical Presentation

- Vasculitis in systemic lupus erythematosus can involve vessels of any sizes; small vessels are most commonly affected.

- The clinical presentation would depend on the size of the involved vessels and affected organs.

Histologic Features
- Small-vessel vasculitis is more frequently seen in cutaneous lesions, whereas medium- and large-vessel vasculitis would affect internal organs.

Differential Diagnosis
- Other small-vessel vasculitides

Takeaway Essentials

Clinical Relevant Pearls
- Visceral vasculitis is associated with increased mortality.
- There appears to be a correlation between the presence of vasculitis and lupus activity.

Sarcoid Vasculitis

Sarcoidosis is a granulomatous disease of unknown etiology that can affect multiple organs including the lymph nodes, lungs, skin, and eyes. Sarcoid vasculitis was defined in the 2012 Chapel Hill Consensus Conference (CHCC) as vasculitis that is associated or secondary to sarcoidosis [3]. As with sarcoidosis, the associated vasculitis can be a single-organ or systemic process. The presence of vasculitis in patients with sarcoidosis is exceedingly rare with few cases with Takayasu-like large-vessel vasculitis, and cases of sarcoidosis associated with giant cell arteritis or granulomatosis with polyangiitis have been reported in the literature [105].

Clinical Presentation

The onset of cutaneous vasculitis was simultaneous with sarcoidosis in majority of the patients, preceded (12.5%), or subsequent to (25%) sarcoidosis [106]. Lower extremities were the most commonly involved site. The clinical presentation would reflect the size of affected vessels. African American and Asian patients are more common than Caucasians to have large-vessel involvement.

In a French series of seven cases of both sarcoidosis and Takayasu vasculitis, these patients represented 0.7% of the sarcoidosis cases and 4% of the Takayasu cohort [105]. Less than 15 cases of concurrent sarcoidosis and Takayasu have been reported, and majority of the patients were females with the mean age at diagnosis of 36 and 37 years for sarcoidosis and Takayasu vasculitis, respectively. The diagnosis of sarcoidosis often precedes the diagnosis of Takayasu vasculitis; however, Takayasu vasculitis is diagnosed before sarcoidosis supportive of their association [105, 107]. There is often a significant time lapse between the two diagnoses.

Prognosis or Clinical Course

The patients with leukocytoclastic vasculitis would more likely have a complete resolution in comparison to those with granulomatous vasculitis.

Histopathology

The vasculitis can be either leukocytoclastic vasculitis or granulomatous vasculitis in the setting of acute or chronic sarcoidosis, respectively. Sarcoidal granulomas were observed at postmortem in cases of sarcoidosis affecting the aorta and its branches.

Differential Diagnosis

Although granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis are in the clinical differential diagnosis, neutrophils and eosinophils would be seen, respectively, in contrast to granulomas in sarcoid vasculitis.

Summary

Clinical Presentation

- Vasculitis that is associated or secondary to sarcoidosis which can affect small to large vessels

Histologic Features

- Can be either leukocytoclastic vasculitis or granulomatous vasculitis

Differential Diagnosis

- Hypersensitivity vasculitis
- Takayasu arteritis
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis

Takeaway Essentials

Clinical Relevant Pearls

- As with sarcoidosis, the associated vasculitis can be a single-organ or systemic process.

Case Studies

Case 1

Clinical History

A 60-year-old woman presented with recurrent erythematous plaques on her face especially the cheek (Fig. 7.34).

Microscopic Description

A skin biopsy of the cheek lesion was performed. A dense dermal infiltrate with overlying grenz zone is noted (Fig. 7.35). The dermal infiltrate is comprised of neutrophils, lymphocytes, and eosinophils. Plump endothelial cells, fibrinoid necrosis of small-vessel walls, and leukocytoclasis are characteristic features of a small-vessel vasculitis (Fig. 7.36).

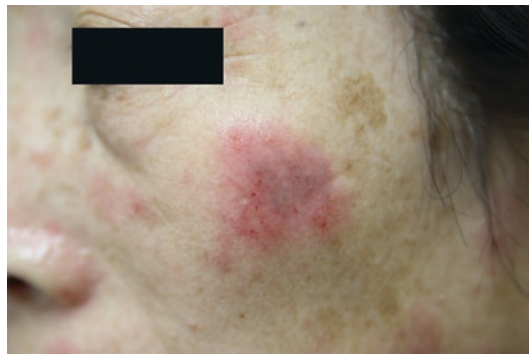


Fig. 7.34 Erythematous plaque is noted over the patient's cheek

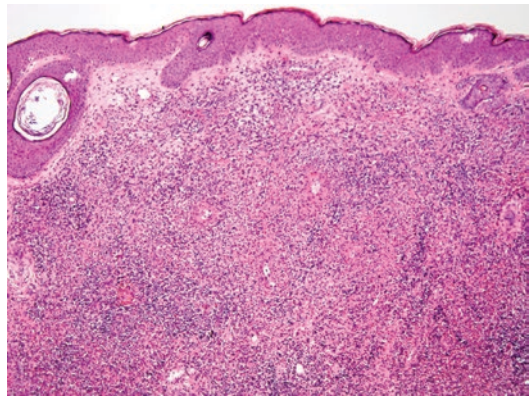


Fig. 7.35 A dense dermal infiltrate with overlying grenz zone is noted (×100)

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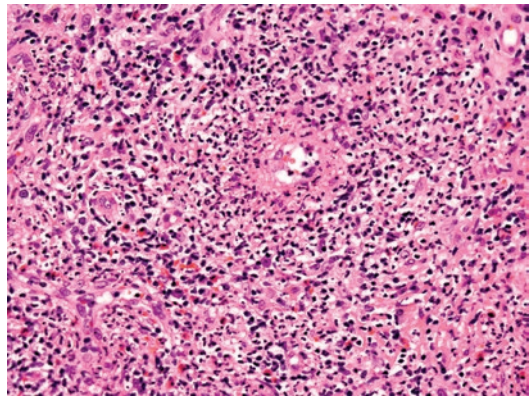

Fig. 7.36 Plump endothelial cells, fibrinoid necrosis of small-vessel walls, and leukocytoclasis are seen (×400)

Diagnosis

Granuloma faciale

Discussion

Granuloma faciale is most often seen in middle-aged men [108]. The lesions present clinically as recurrent erythematous plaques on the forehead, ears, nose, and cheeks. The majority, up to 92%, of the patients has only facial lesions. However, the presence of extrafacial lesions do not exclude the possibility of granuloma faciale. Although the etiology remains unknown, ultraviolet light exposure, radiation, trauma, and allergy have been implicated as predisposing factors. It is currently thought by many to be a chronic form of cutaneous vasculitis. The documentation of perivascular IgG, IgA, IgM, and C3 deposition on direct immunofluorescence studies is supportive of the speculation that classical pathway activation of complement is causative of vasculitis in granuloma faciale [109].

The clinical differential diagnosis of granuloma faciale includes sarcoidosis, lupus erythematosus, and cutaneous lymphoma. The reddish-brown color of the clinical lesion and the presence of dilated follicular ostia are helpful features to distinguish granuloma faciale from sarcoidosis and lymphoma [108]. The histologic differential diagnosis includes erythema elevatum diutinum (EED), angiolymphoid hyperplasia with eosinophilia, and Kimura's disease.

Granuloma faciale has been suggested to represent a localized form of EED to the face. EED, another distinctive form of chronic recurrent form of cutaneous leukocytoclastic vasculitis, often presents as symmetrical, firm, tender, reddish-brown papules and nodules on the extensor aspects of the extremities of middle-aged and older adults. There is no gender predilection. They are located on the fingers, hands, elbows, ankles, and knees. EED often follows a chronic clinical course. Although the etiology is unknown, the thought is that it is likely secondary to vascular immune complex deposition due to its association with rheumatoid arthritis, ulcerative colitis, Crohn's disease, and diabetes mellitus. Associated infections include tuberculosis, syphilis, hepatitis B virus, and human immunodeficiency virus [110]. Early histopathologic changes of EED include leukocytoclastic vasculitis and a mixed dermal infiltrate containing neutrophils, histiocytes, lymphocytes, and eosinophils.

(continued)

As the lesion ages, histiocytes become more prominent. These early histologic changes can mimic granuloma faciale and Sweet's syndrome. On the other hand, angiocentric fibrosis ranging from perivascular to storiform would be seen in older lesions [111]. The changes of the late-stage lesion can resemble a fibrous neoplasm such as sclerotic fibroma or inflammatory pseudotumor [111].

Case 2

Clinical History

A 9-year-old girl presented to the emergency room with left hip pain and a skin rash. She had a history of sore throat, fever, and lethargy several days ago with multiple subcutaneous, erythematous, and indurated nodules.

Microscopic Description

Fibrinoid necrosis and neutrophilic infiltrate affect a medium vessel at the deep dermis and subcutaneous tissue junction (Figs. 7.37 and 7.38).

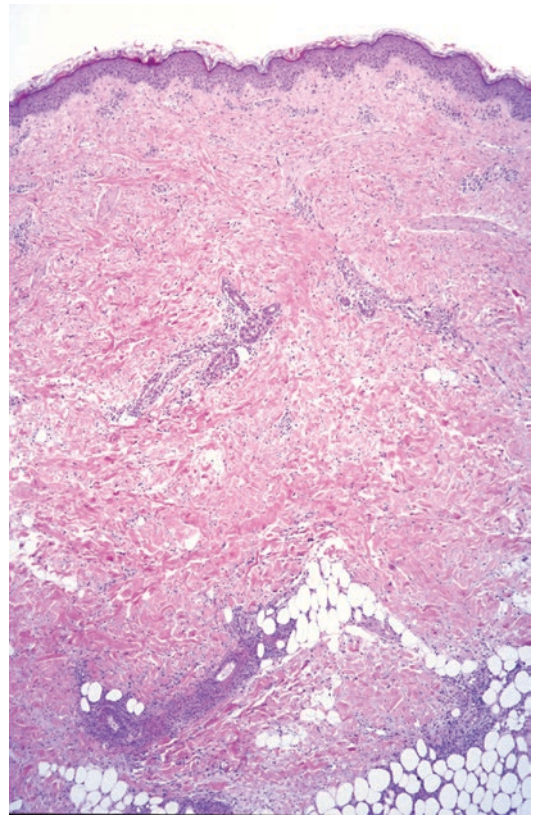

Fig. 7.37 A medium-vessel vasculitis is noted at the deep dermis and subcutaneous tissue junction (×40)

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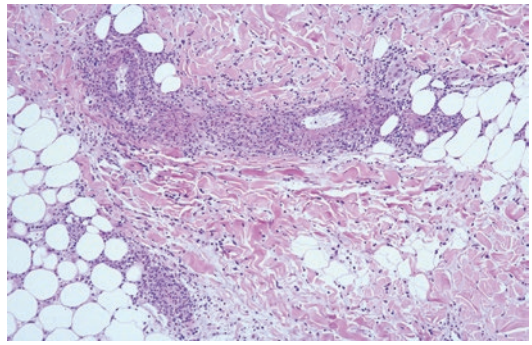

Fig. 7.38 Fibrinoid necrosis of the vascular wall and accompanied neutrophilic infiltrate (×100)

Diagnosis

Poststreptococcal polyarteritis nodosa

Discussion

Although PAN is a disease of adults, this form of medium-sized vasculitis can be seen in children after an episode of streptococcal infection, implicated by positive throat swab or a significant titer of either antistreptolysin O or antihyaluronidase. The relationship between streptococcal infection and a medium-sized vasculitis was initially proposed by Fink in a series of seven children with PAN [112].

Poststreptococcal PAN can be limited to the skin or exhibits widespread systemic involvement. The clinical findings can comprise fever, arthralgias, myalgias, arthritis, cutaneous eruption, abdominal pain, hematuria, hypertension, and peripheral neuropathy. The cutaneous presentation includes tender erythematous subcutaneous nodules on the lower extremities [112]. The palms and soles can be involved. Although mild systemic symptoms were present in the majority of patients, the clinical course was typically benign. Poststreptococcal PAN follows a relapsing and remitting clinical course [113]. Recognition of this form of PAN is important for prompt antibiotic therapy and prophylaxis. The main differential diagnosis would be PAN associated with hepatitis B and a systemic form of PAN in childhood [114]. Laboratory testings to detect streptococcal infection should be performed routinely in children presenting with fever, painful subcutaneous nodules, and arthralgias.

Case 3

Clinical History

A 42-year-old woman presented with multiple pin-sized purpura on both of her lower extremities (Fig. 7.39).

Microscopic Description

A skin biopsy demonstrated a perivascular infiltrate of lymphocytes and erythrocytes in the superficial dermis (Fig. 7.40). An iron stain highlighted the prominent hemosiderin deposition in the dermis (Fig. 7.41).

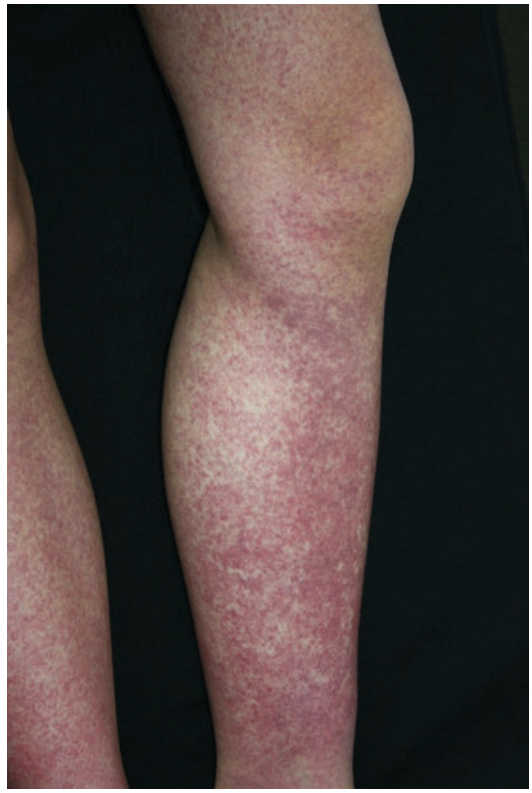

Fig. 7.39 "Cayenne pepper" purpura is noted on both lower extremities

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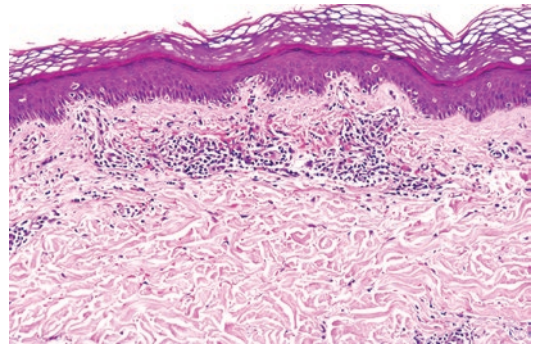

Fig. 7.40 A superficial perivascular infiltrate of lymphocytes and erythrocytes is noted in the dermis (×100)

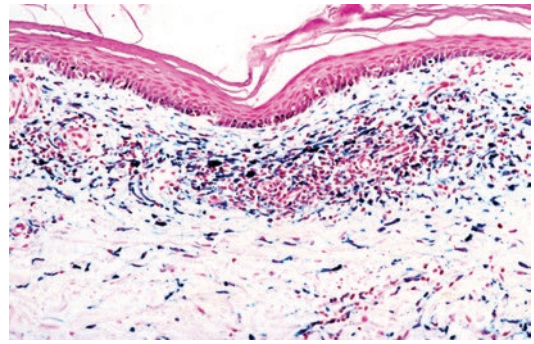

Fig. 7.41 An iron stain highlights the hemosiderin deposition within the dermis (×200)

Diagnosis

Schamberg variant of pigmented purpuric dermatosis

Discussion

Pigmented purpuric dermatoses (PPD) comprise a spectrum of chronic and relapsing purpuric rash. There are six groups including Schamberg's disease, purpura annularis telangiectodes, lichen aureus, Lichenoid purpura of Gougerot and Blum, itching purpura, and eczematoid purpura of Doucas and Kapetanakis [115]. The clinical presentation varies with the different types of PPD. Schamberg's disease would present with asymptomatic punctate purpura on lower extremities, whereas bluish-red annular macules would be seen in purpura annularis telangiectodes. A golden-brown eruption is typically seen in lichen aureus. The eruption is intensely pruritic and affects more sites in eczematoid purpura of Doucas and Kapetanakis [115]. Although the etiology remains unknown, medications, chronic venous hypertension, thyroid dysfunction, and diabetes mellitus have been implicated [115].

In a recent retrospective review of 107 Asian cases, five histopathologic patterns were observed: lichenoid (42%), perivascular (37%), interface (10%), spongiotic (7%), and granulomatous (4%). Of interest, lymphocytic vasculitis was noted in 16% of cases [116]. Schamberg, eczematoid, and lichen aureus clinical variants correlate with perivascular, spongiotic, and lichenoid histopathologic patterns [116].

Case 4

Clinical History

A 35-year-old woman presented with a 3-year history of painful nodules on her lower extremity (Fig. 7.42).

Microscopic Description

A skin biopsy showed a necrotizing and granulomatous vasculitis of medium-sized vessels (Figs. 7.43 and 7.44).

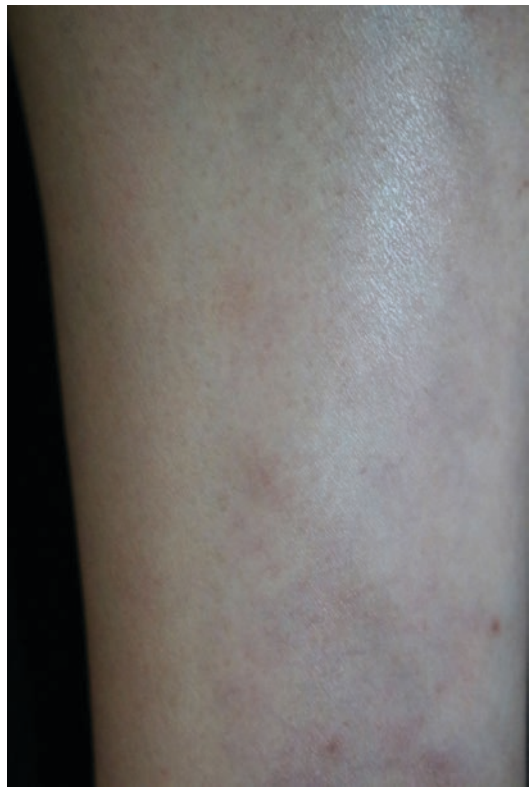

Fig. 7.42 Painful nodules are noted on the lower extremity

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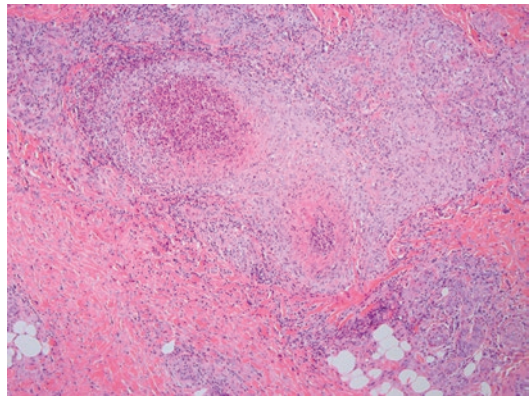

Fig. 7.43 A lobular panniculitis is noted at low magnification (×40)

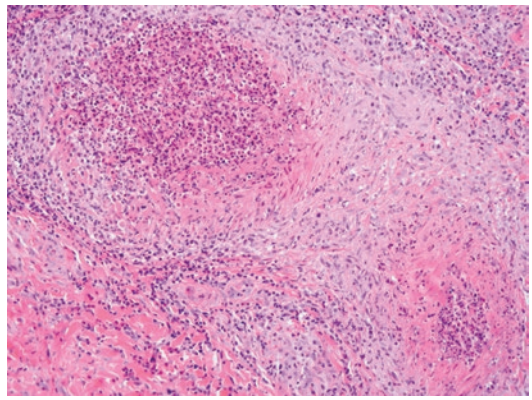

Fig. 7.44 Large zone of caseous necrosis is noted in addition to the granulomatous vasculitis (×200)

Diagnosis

Nodular vasculitis or erythema induratum of Bazin

Discussion

Nodular vasculitis is most commonly associated with a lobular panniculitis with medium-vessel vasculitis. It is known as erythema induratum of Bazin in the presence of tuberculosis [117]. Tuberculosis is the most frequently identified causative agent, and *Mycobacterium tuberculosis* DNA was detected by polymerase chain reaction in 77% of 74 skin biopsies from 65 patients [118]. In countries with low prevalence of tuberculosis, nodular vasculitis could represent a reactive process to cold, chronic venous insufficiency, or thrombophlebitis.

In a retrospective series of 101 skin biopsies from 86 patients with the diagnosis of nodular vasculitis, vasculitis affecting the small vessels as well as the medium vessels was evident in 90% of the cases [117]. A lobular granulomatous panniculitis with associated vasculitis was seen in 12% and mainly lobular panniculitis without associated vasculitis in 10%. The vasculitis can be neutrophilic, granulomatous, or lymphocytic depending on the stage of the

(continued)

disease. Neutrophils are prominent in the early stage, whereas histiocytes and multinucleated giant cells impart a granulomatous pattern in the established lesion. Large zones of caseous necrosis would be seen when there is much vascular damage. The accompanied lobular panniculitis distinguishes nodular vasculitis from cutaneous PAN. The primary location of the vasculitis in the panniculus separates nodular vasculitis from GPA and EGPA.

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