Systemic Polyarteritis Nodosa

14

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Abstract

Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis predominantly affecting the medium-sized arteries with widely variable presenting features, disease course, and outcomes. Recent updates regarding the nomenclature of PAN have resulted in the description of several PAN sub-phenotypes. Herein discussed are idiopathic PAN, Hepatitis B-associated PAN and monogenic disorders such as adenosine deaminase-2 deficiency. The current understanding of the pathogenesis, histopathological features, and treatment of these conditions are reviewed.

Keywords

Autoimmunity · Vasculitis · Polyarteritis nodosa · Hepatitis B · Adenosine deaminase 2 deficiency

14.1 Introduction

The terminology associated with polyarteritis nodosa (PAN) has undergone significant changes over the last century, particularly in the last four decades. Therefore, a review of the evolving nomenclature is integral to understanding this condition and its associated subgroups. The term "periarteritis nodosa" was first used by Kussmaul and Maier in 1866 during their description of a 27-year-old male with multiple nodules along the length of medium and small arteries in the thorax and abdomen [1].

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Further histologic evaluation by Ferrari in 1903 revealed that the inflammatory process was not relegated to the adventitia, but rather was transmural, so use of "polyarteritis nodosa" was proposed [2]. Historically, the presence of necrotizing vasculitis on any biopsy was attributed to PAN. Little further distinction was made during the first half of the twentieth century until granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) was initially described [3] and then subsequently considered as a separate vasculitic entity [4].

Discovery of anti-neutrophil cytoplasmic antibodies (ANCA) allowed for further distinguishing polyarteritis nodosa from the ANCA-associated vasculitides [GPA, microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss)] [5, 6]. A definitive distinction between PAN and MPA was outlined through the 1994 [7] and the revised 2012 International Chapel Hill Consensus Conference (CHCC) nomenclature of vasculitides [8] where PAN was defined as a necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis of the small vessels (i.e., arterioles, capillaries, and venules) and not associated with ANCA. MPA was defined as a necrotizing vasculitis with few or no immune deposits, predominantly affecting the small vessels and associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA.

Further distinction between PAN and PAN-like conditions has reduced the number of patients classified as having systemic idiopathic PAN. These subgroups now include vasculitis associated with probable etiology (i.e., drug, viral) and monogenic disease-related PAN-like conditions. Given the presentation of hepatitis B virus (HBV)-associated PAN and systemic idiopathic PAN have the same clinical features, the chapter herein will focus on both systemic idiopathic PAN and HBV-associated PAN but will additionally note distinguishing characteristics of the presentation and treatment of other less common PAN-like variants.

14.2 Epidemiology

PAN can affect any age but more commonly affects adults between their fourth and sixth decades of life. There is a slight male to female predominance (1.5:1), but ethnic predilection has not been observed [9]. Annual incidence of systemic idiopathic PAN has been estimated to be 1–5 per 1,000,000 with a prevalence of approximately 30 per 1,000,000 [9–11]. Incidence of HBV-associated PAN has been reported as high as 77 per 1,000,000 in endemic areas [12]. Following the institution of safer transfusion practices, hospital hygiene, and HBV vaccination, the rates of HBV-associated PAN have dramatically reduced from 35% to less than 5% of PAN cases [10].

14.3 Etiopathogenesis

According to more recent understanding, necrotizing vasculitis likely represents a range of diseases with varying etiopathogenesis [13]. In systemic idiopathic PAN, the underlying mechanisms are not well understood, but the predominance of

dendritic cells and CD4+ lymphocytes in vascular lesions suggest the possibility of an antigen-specific T-cell-mediated response [14]. Several infections have been identified as potential triggers. Hepatitis B virus is the most well-documented but hepatitis C [15], human immunodeficiency virus [16], parvovirus B19 [17], Epstein–Barr virus [18], and cytomegalovirus [19] have also been observed. In contrast to systemic idiopathic PAN, viral replication [20] and circulating immune-complex deposition [21, 22] have been noted to result in direct vascular inflammation among patients with HBV-associated PAN. Drug-induced causes are uncommon; however, systemic PAN-like disease in the context of chronic use of minocycline for treatment of acne vulgaris has been reported [23, 24].

Limited information is known regarding genetic abnormalities and risk of PAN. However, a monogenic polyarteritis with similar clinical and histological characteristics to systemic idiopathic PAN has been recently observed. This predominantly childhood-onset PAN-like variant called deficiency of adenosine deaminase 2 (DADA2) is caused by an autosomal recessive mutation in the Adenosine Deaminase 2 (*ADA2*) gene [formerly known as the Cat Eye Syndrome Chromosome Region 1 (*CECR1*) gene] [25], which encodes for the adenosine deaminase 2 enzyme (ADA2). ADA2 has been hypothesized to be a key growth factor for endothelial cells and a regulator in the differentiation of monocytes. Deficiency of ADA2 results in endothelial damages and skewing of monocytes to a pro-inflammatory macrophage subset [26]. Preliminary findings from evaluation of 117 adult-onset, HBV-negative systemic idiopathic PAN patients have also shown the presence of heterozygous or biallelic missense variants in *ADA2* among 8 (7%) patients resulting in reduced ADA2 activity. These findings suggest a potential genetic basis among a subset of systemic idiopathic PAN patients [27].

14.4 Clinical Manifestations and Laboratory Markers

14.4.1 Clinical Manifestations

Because medium- and small-sized arteries are involved in PAN, a wide spectrum of clinical manifestations has been reported (Table 14.1). Constitutional symptoms of fever, weight loss, myalgia, and arthralgia are common and are present in 30–70% [28–30]. Cutaneous findings are lower extremity predominant and occur in up to 50–60% of patients as demonstrated by purpura, livedo reticularis/racemosa, nodules, and ulcers [28]. Digital infarction resulting in gangrene can also occur (6%) but limb ischemia is rare [29, 31] (Fig. 14.1). Peripheral nerve involvement results from arteriolar occlusion of the vasa nervosum [32]. Mononeuritis multiplex, typically presenting as wrist drop or foot drop, is the most common neurologic feature. Patients will often note pain or change in sensation (hypo/hyper/dysesthesia) prior to the onset of a motor deficit, but palsy can develop suddenly without sensory prodrome. Symmetric sensorimotor peripheral neuropathy and pure sensory neuropathy are also seen; among which, the sciatic, peroneal, tibial, ulnar, median, and radial nerves appear to have a higher likelihood of involvement [33]. Cranial nerve palsies have been reported but are infrequent and affect less than 2% of patients

Table 14.1 Clinical features of polyarteritis nodosa [28–30, 36]

Symptoms	Frequency
Constitutional	**71–93%**
Fever	25–69%
Weight loss	46–70%
Myalgia	34–69%
Arthralgia	32–59%
Neurologic	**38–79%**
Peripheral neuropathy	27–74%
Mononeuritis multiplex	17–70%
Central nervous system	5–13%
Cutaneous	**28–58%**
Purpura	22–27%
Nodules	17–23%
Livedo	17–27%
Ulcers	13%
Digital gangrene	6–7%
Gastrointestinal	**14–53%**
Abdominal pain	36–38%
Bleeding	3–10%
GI manifestation requiring surgery	13–14%
Cardiac manifestations	**10–30%**
Cardiomyopathy	8%
Pericarditis	6%
Genitourinary	**37–51%**
Hematuria	2–15%
Proteinuria (>0.4 g/day)	11–21%
Hypertension	10–35%
Orchitis	17–38%

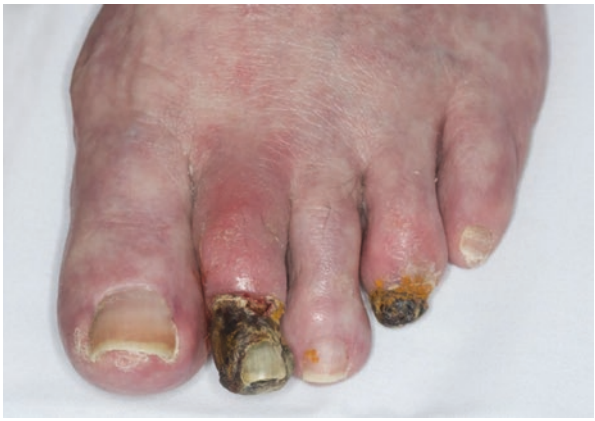

Fig. 14.1 Dry gangrene of the distal second and fourth phalanx on a background of livedo reticularis and acrocyanosis

[33]. Stroke can occur in systemic idiopathic PAN but is rare. If present, particularly in a child or young adult, DADA2 variant should be considered.

Abdominal pain is the most frequent gastrointestinal feature but is nonspecific. If associated with or exacerbated by meals, this raises concern for intestinal angina secondary to mesenteric arteritis. Ischemia appears to be more common in the small intestine compared to the colon and can result in nausea, vomiting, diarrhea, melena, or hematochezia. Vasculitic involvement of visceral organs such as the gallbladder and appendix can be seen and mimic cholecystitis and appendicitis, respectively. Upon surgical removal, histologic evaluation confirms arteritic involvement if present. Both ischemic bowel perforation and rupture of a visceral artery aneurysm can manifest as a surgical abdomen; a presentation which carries high morbidity and mortality [34].

Renal abnormalities in PAN differ from ANCA-associated vasculitis as the former does not cause glomerulonephritis [8]. Renal infarcts (Fig. 14.2), resulting from either occlusion of intrarenal arteries or rupture of microaneurysms (Fig. 14.3), can produce micro- or macroscopic hematuria, but dysmorphia is generally absent. Proteinuria, if detected, is typically sub-nephrotic [28]. Renal insufficiency is uncommon but may develop as a consequence of significant renal parenchymal loss due to infarction or as a result of severe renovascular hypertension from renal artery stenosis. Urologic involvement has been noted in 17% of cases and is rarely the initial manifestation; nevertheless, non-infectious orchitis secondary to testicular arteritis is a characteristic feature of PAN [28, 29].

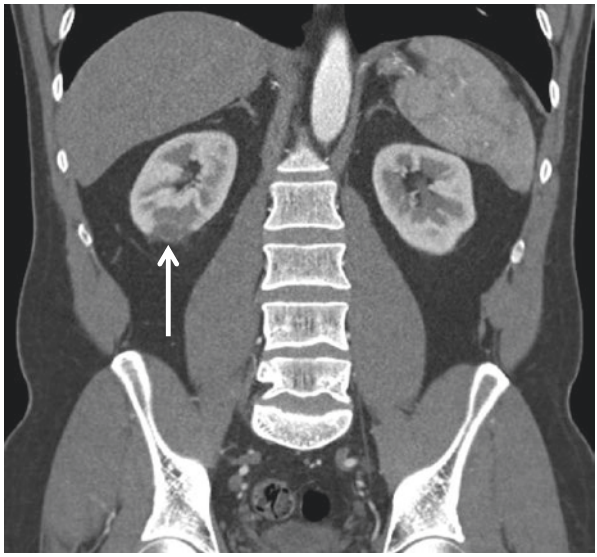

Fig. 14.2 Renal infarct, right inferior pole (CT, coronal view)

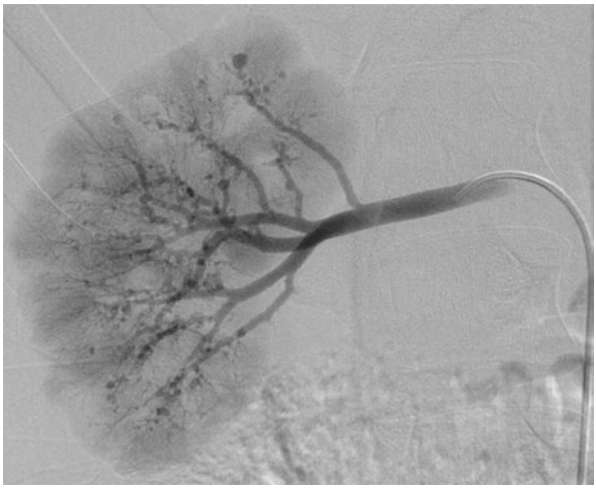

Fig. 14.3 Selective conventional right renal angiogram demonstrating multiple segmental microaneurysms

Cardiac involvement has been noted since the index description of PAN in 1866 but is an underreported finding as many patients may be asymptomatic. Indeed, only 2–10% of patients have clinically diagnosed cardiac findings [28, 29], whereas histologic evidence has been reported in up to 78% of patients in autopsy studies [35]. Left ventricular heart failure is the most frequently observed abnormality, and the etiology is likely multifactorial with coronary arteritis, myocardial infarction, and renovascular hypertension as potential contributors [36]. Coronary arteritis has been described in 50% of autopsy cases [35] but clinically symptomatic coronary angina (2–18%) and myocardial infarctions (1–12%) are less often reported [36]. Giant coronary aneurysms (Fig. 14.4) have been observed but are considered rare [37, 38]. These are likely sequelae of untreated disease and angiographically may be challenging to distinguish from patients with history of Kawasaki's Disease.

Myalgias occur in 60–70% [28, 29] of patients but inflammatory myopathy is rare [39]. Creatine kinase levels may be elevated but are generally less than 2000 IU/L. Pain can be present due to arterial insufficiency of the medium-sized muscular vessels. Thigh and calf muscle involvement is typical. Magnetic resonance imaging of the musculature can demonstrate diffuse or patchy hyperintensity of the affected muscle on T2-weighted imaging and contrast-enhanced images may demonstrate small fluffy enhancing lesions centered on the vessels ("cotton wool appearance") [40].

Overall, the clinical features of patients with classical PAN and HBV-associated PAN are similar. However, a few noted differences have been observed with HBV-associated PAN demonstrating a higher frequency of myalgia, neurologic manifestations, abdominal pain, and vasculitis-related cardiomyopathy but a lower frequency of livedo and nodular skin lesions [28].

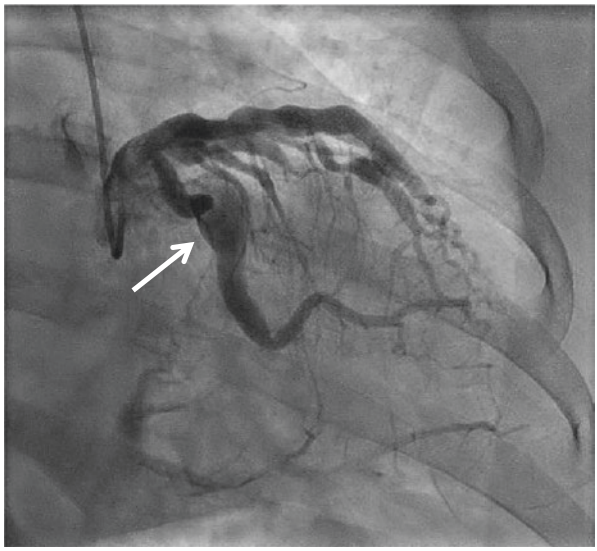

Fig. 14.4 Conventional coronary angiogram with alternating stenotic and aneurysmal segments of the left anterior descending (top) and giant aneurysm of the left circumflex (arrow)

14.4.2 Laboratory Markers

There are no specific laboratory markers for PAN. An inflammatory state with normocytic anemia, thrombocytosis, and elevated erythrocyte sedimentation rate and/or C-reactive protein is common. Leukocytosis may be seen. If peripheral eosinophilia is noted, particularly if >10%, then the possibility of eosinophilic granulomatosis with polyangiitis should be assessed. Renal insufficiency can be present, but is not typically severe. Urinalysis may show sub-nephrotic proteinuria and non-dysmorphic microscopic hematuria. ANCA serologies (cANCA/PR3, pANCA/MPO) should be negative. Cryoglobulins, complements (C3, C4), and rheumatoid factor should be evaluated to assess for possibility of cryoglobulinemia. The presence of HIV, hepatitis B, and hepatitis C should be investigated. Lactate levels may be of assistance in patients presenting with severe abdominal pain or surgical abdomen to assess for tissue ischemia.

14.5 Histopathology

Cutaneous findings observed in classical systemic PAN are indistinguishable from the isolated cutaneous variant (see histopathology 13.4). The vascular abnormalities in PAN demonstrate a segmental pattern with a predilection for arterial branch points of muscular arteries [41]. The cause for predisposition of branch points is unknown but an increase in expression of adhesion molecules and intimal macrophages at these locations has been proposed [42]. The vascular infiltrates observed vary

depending on the stage of the inflammatory process. In the early, active phase a transmural inflammatory infiltrate composed of an admixture of lymphocytes, macrophages, neutrophils and eosinophils are seen along with findings of fibrinoid necrosis of the vessel wall [41]. Subsequently, vascular remodeling occurs with dense vessel wall fibrosis as well as intimal hyperplasia. Thrombosis can lead to vascular occlusion whereas disruption of the elastic lamina results in aneurysmal dilation.

14.6 Diagnosis and Differential Diagnosis

There are no validated or approved diagnostic criteria for PAN. The American College of Rheumatology has developed classification criteria for PAN (Table 14.2) [43]. Unfortunately, these criteria are of limited utility for two reasons. First, these criteria are intended for research purposes to distinguish what subtype of vasculitis a patient has once they have a confirmed vasculitis diagnosis. As such they should not be used in the clinical setting to determine if a patient does or does not have vasculitis. Second, these criteria are not useful in differentiating patients with PAN from microscopic polyangiitis, given the latter was not considered a separate entity at the time of drafting. Because of these noted limitations, an ongoing international

Table 14.2 1990 American College of Rheumatology Classification criteria for polyarteritis nodosa [43][a]

Criterion	Description
1. Weight loss ≥4 kg	Loss of 4 kg or more since illness began, not due to dieting or other factors
2. Livedo reticularis	Mottled reticular pattern over the skin or portions of the extremities or torso
3. Testicular pain or tenderness	Pain or tenderness of the testicles, not due to infection, trauma, or other causes
4. Myalgias, weakness, or leg tenderness	Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles
5. Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy
6. Diastolic blood pressure >90 mmHg	Development of hypertension with diastolic blood pressure higher than 90 mmHg
7. Elevated blood urea nitrogen (BUN) or creatinine	Elevation of BUN >40 mg/dL or creatinine >1.5 mg/dL, not due to dehydration or obstruction
8. Hepatitis B virus	Presence of hepatitis B surface antigen or antibody in serum
9. Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes
10. Biopsy of small- or medium-sized artery containing polymorphonuclear cells	Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

[a]For classification purposes, a patient shall be said to have polyarteritis nodosa if at least 3 of these 10 criteria are present. The presence of ≥3 criteria yields a sensitivity of 82.2% and a specificity of 86.8%

collaborative effort is currently underway to develop diagnostic and classification criteria for PAN [44].

Consequently, the diagnosis of PAN requires the combination of characteristic clinical manifestations, laboratory parameters, angiographic features, and histopathology in a suspected individual. Biopsy of an affected organ confirming the presence of focal, segmental, transmural, necrotizing inflammation of the medium- or small-sized arteries is considered the gold standard for diagnosis. If affected, the highest yield is typically observed in skin, nerve, muscle, and testicle [45]. Combined nerve and muscle biopsy appears to be superior to muscle biopsy alone for diagnosis. In a large series of patients with suspected PAN, vasculitis confirmation from dual nerve/muscle biopsy was obtained in 83% (90/108) of patients with peripheral neuropathy and 81% (17/21) of patients without peripheral neuropathy; compared with 68% (41/60) positive biopsy specimens in patients with peripheral neuropathy and 60% (24/40) without peripheral neuropathy among those with isolated muscle biopsy performed [28]. While this study highlights the potential utility of blind nerve and/or muscle biopsy even in asymptomatic patients, it is suggested that evaluation with electromyogram and/or muscle MRI be performed to identify if pathologic findings are present in order to guide biopsy location. Although confirmatory findings of PAN can be observed on kidney and liver biopsy specimens, these locations carry a high risk of post-procedure hemorrhage and therefore should not be considered as first-line targets.

Angiography provides additional diagnostic utility in patients with suspected PAN, particularly among those with abdominal or renal symptoms for which biopsy was not able to be obtained or was non-diagnostic. The typical angiographic features of PAN include saccular or fusiform microaneurysms (1–5 mm diameter) usually coinciding with stenotic lesions [46] (Fig. 14.5). Larger aneurysm may also be present within which dissections may occur (Figs. 14.6, 14.7, and 14.8). The most frequent arterial territories affected include the celiac, hepatic, renal, and mesenteric branches. Visceral organ infarcts, bowel wall thickening, and perinephric hematoma are commonly seen but are less specific for PAN and must be differentiated from

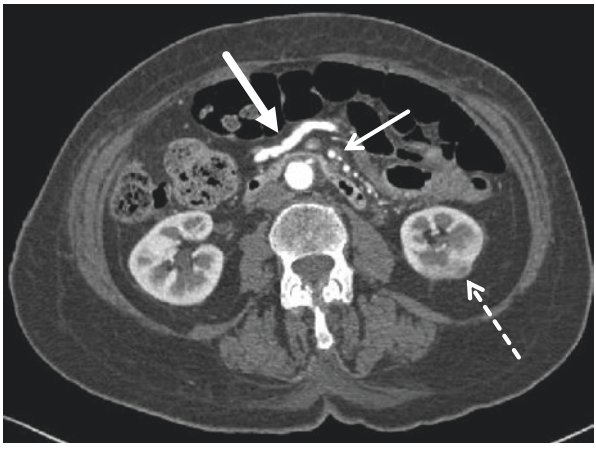

Fig. 14.5 Computed tomography angiography (axial view) demonstrating superior mesenteric artery branch with alternating stenotic and aneurysmal segments (thick arrow), mesenteric artery branches with arterial thickening (thin arrow), and mid-pole left renal infarct (dashed arrow)

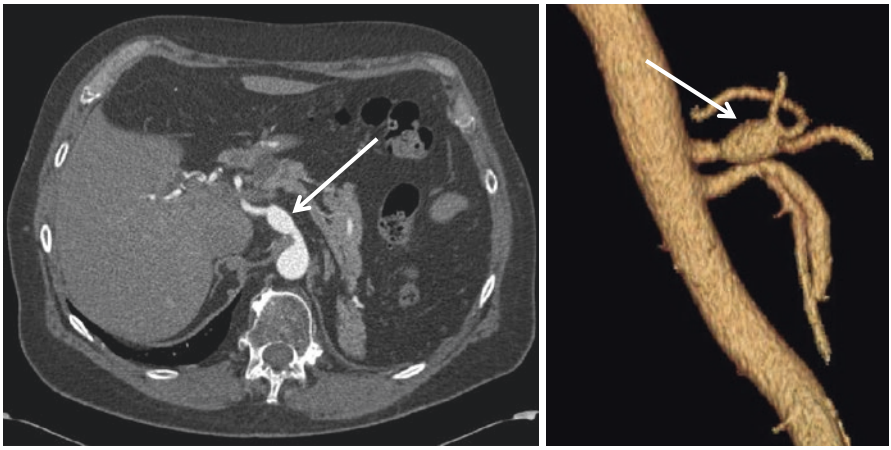

Fig. 14.6 Computed tomography angiography highlighting proximal celiac artery aneurysm (arrow) [Axial view, left pane; 3D formatted, right pane]

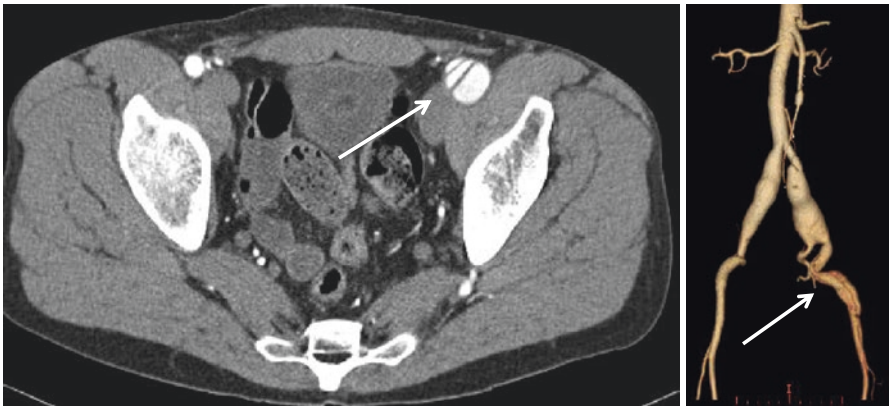

Fig. 14.7 Multiple aneurysms in the superior mesenteric artery, bilateral common iliac arteries, and common femoral arteries [computed tomography 3D formatted, right pane] with complex dissection of the left femoral artery (arrow) [axial view, left pane]

diseases causing in situ thrombosis or thromboembolism [47]. With the advancements in noninvasive imaging, computed tomography angiography (CTA) is a reasonable initial screening modality given it has spatial resolution detail that is sufficient to evaluate for the majority of findings suggestive of PAN including stenosis/occlusion, infarcts, and aneurysms >2 mm diameter. However, if CTA is negative or equivocal and suspicion remains, then conventional angiography is required. If characteristic angiographic findings are identified by an experienced radiologist the diagnosis may be confirmed, even without biopsy, provided there is appropriate clinical context and mimicking conditions (Table 14.3) have been ruled out.

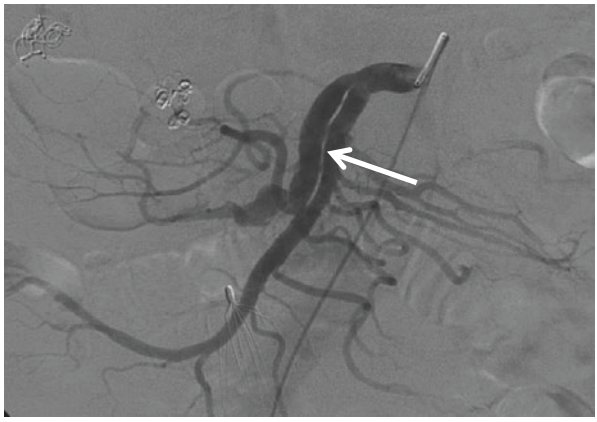

Fig. 14.8 Selective superior mesenteric artery conventional angiogram with long segment proximal dissection (arrow)

Table 14.3 Conditions to consider during evaluation of polyarteritis nodosa

Disease	Common clinical features	Common lab/imaging features
Rheumatic disease		
Granulomatosis with polyangiitis (Wegener's)	Sinusitis, upper airway inflammation, pulmonary nodules, glomerulonephritis	cANCA/PR3 > pANCA/MPO
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)	Asthma, nasal polyposis, upper airway inflammation, neuropathy	Eosinophilia (>10% peripheral) pANCA/MPO (40–60%)
Microscopic polyangiitis	Alveolar hemorrhage, glomerulonephritis	pANCA/MPO > cANCA/PR3
Behcet's Disease	Oral/genital/gastrointestinal ulcers	–
Infectious disease		
Infective endocarditis	Multifocal infarcts, splinter hemorrhages, subcutaneous nodules, fever	Echocardiography with vegetation +/− positive blood cultures
Mycotic aneurysm	Fever. Painful, pulsatile, enlarging aneurysm (if superficial). Gastrointestinal bleeding (if visceral)	CT angiography: saccular, eccentric aneurysm or multilobulated aneurysm. Perivascular fluid collection Intramural or perivascular air
Viral infection (HIV, HepB, HepC)	Fever, weight loss, arthralgia, myalgia	Positive viral studies
Vascular disease		
Antiphospholipid syndrome	Recurrent thromboses (arterial or venous)	Positive lupus anticoagulant and/or anticardiolipin ab (IgG/IgM) and/or Beta2 glycoprotein ab (IgG/IgM) times two draws separated by ≥12 weeks

(continued)

Table 14.3 (continued)

Disease	Common clinical features	Common lab/imaging features
Cholesterol emboli	Livedo, blue toe syndrome, renal insufficiency/infarct, gastrointestinal infarct typically following an endovascular procedure	Eosinophiluria Biopsy with cholesterol clefts within arterioles
Fibromuscular dysplasia (FMD)	Medium artery stenosis, spontaneous dissection, aneurysm. Female > Male Renal ≫ carotids > vertebrals > iliac > mesenteric	Normal inflammatory markers Multifocal FMD: vessel stenosis with intervening dilations causing "string of beads" pattern where diameter of beading is larger than the diameter of the artery
Segmental arterial mediolysis	Spontaneous intra-abdominal hemorrhage, more common at 50–80 years of age	Normal inflammatory markers Dissecting aneurysm

14.7 Prognosis

If left untreated, systemic PAN carries a high mortality with a 5-year survival of 13% [48]. Conversely, those receiving treatment have a notably improved outcome with 5-year survival nearing 80–90% [28, 49]. The overall outcome is largely dependent on the severity of disease at time of diagnosis. A prognostic scoring system called the Five-Factor Score (FFS) was devised by the French Vasculitis Study Group from evaluation of a prospective study of 342 patients with polyarteritis nodosa, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Table 14.4) [50]. For patients with an FFS = 0, 5-year mortality was 12%, whereas the mortality rate for FFS = 1 was 26% and FFS ≥ 2 was 46% [50]. The same group re-evaluated this scoring system evaluating 1108 total patients with systemic necrotizing vasculitis, this time including granulomatosis with polyangiitis [51]. The updated 2009 FFS (Table 14.4) added age > 65 year at diagnosis as a poor prognostic factor but no longer includes CNS involvement among these parameters. Given patients with ANCA-vasculitis were included, ENT symptoms were evaluated and the absence of such findings were considered to carry a poorer prognosis; however, this is not applicable to patients with PAN. The updated rates are similar to the original FFS prediction model, demonstrating reliability of this prognostic tool [51]. Death in the first year is more commonly due to poorly controlled vasculitis, whereas subsequent mortality is more often attributable to complications resulting from sequelae of vasculitis-associated organ damage, cardiovascular disease, or consequences of immunosuppressive treatments, particularly infection [52, 53].

PAN has been noted to have a more frequent monophasic pattern when compared to other systemic necrotizing vasculitides; nevertheless, a proportion of patients will undergo a relapsing course. Among a cohort of 348 patients with PAN, 76 (22%) relapsed within 5 years of follow-up [28]. Patients with HBV-associated PAN have

Table 14.4 Prognostic scoring systems for polyarteritis nodosa

1996 Five-factor score [50]			2009 Revised five-factor score [51]		
Factor	Description	Score	Factor	Description	Score
Creatinine >1.58 mg/dL	At time of diagnosis	+1	Age > 65 years	Age at time of diagnosis	+1
Proteinuria >1 g/24 h	At time of diagnosis	+1	Renal insufficiency	Creatinine ≥150 μmol/L (1.70 mg/dL) measured at its stabilized peak level	+1
Cardiac insufficiency	Based on the presence of clinical symptoms (e.g., heart failure, pulmonary edema) and not on laboratory parameters (i.e., brain natriuretic peptide) or asymptomatic echocardiography abnormalities	+1	Cardiac insufficiency	Same as 1996 FFS	+1
Gastrointestinal involvement	Bowel perforation, bleeding, pancreatitis	+1	Gastrointestinal involvement	Same as 1996 FFS	+1
Central nervous system involvement	Not further defined	+1	*Absence* of ENT symptoms[a]	Clinical symptoms confirmed by examination of ENT specialist	+1
Five-year mortality rate FFS = 0—12% FFS = 1—26% FFS ≥ 2—46%			**Five-year mortality rate** FFS = 0—9% FFS = 1—21% FFS ≥ 2—40%		

[a]Pertinent only for patients with granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis; *ENT* ear/nose/throat, *FFS* Five-factor score

been observed to have less frequent relapse than those with non-HBV-associated disease with 5-year relapse-free survival rates being seen in 59.4% of patients with non-HBV-associated PAN, compared to 67% in those with HBV-associated disease [28]. Childhood-onset PAN has been reported to have a more benign course when compared to adults with less renal and neurologic involvement noted and shorter duration of induction treatment required [54].

Patients with PAN require long-term follow-up with specialists that are familiar with the disease process and its multi-system clinical manifestations, as well as clinicians that are comfortable with the immunosuppressive therapies required for induction and maintenance. During the active phase, patients should be closely observed with visits every 2–4 weeks for the first 3–6 months. Once stabilized, visits can occur at less frequent intervals of every 2–6 months for the 2 years following diagnosis. Because of possible late-stage relapse as well as potential development

of comorbidities due to sequelae from vascular damage or immunosuppressive therapy, patients should be followed life-long at intervals of every 6–12 months, even during remission. At each visit, patients should (at a minimum) have a blood pressure evaluation, comprehensive multi-system physical examination, creatinine and urinalysis with microscopy. Additional labs may be needed for immunosuppressive drug monitoring. In asymptomatic patients, routine repeat angiography is not requisite but should be considered if there are new or progressive symptoms of abdominal or cardiac pain or if there are known arterial dilatations/aneurysms that require routine monitoring.

14.8 Treatment

The level of clinical trial evidence guiding the therapeutic decisions in the management of PAN is low [55]. In addition, trials evaluating this condition must be interpreted carefully as they commonly include an admixture of other systemic necrotizing vasculitides such as EGPA and MPA [49, 56–59]. In general, treatment for systemic PAN is determined based on the severity of disease at time of presentation as well as the presence or absence of HBV. Patients with systemic idiopathic PAN with mild disease (FFS = 0) may be treated with glucocorticoid monotherapy with initial doses of 1 mg/kg/day (up to 60 mg) with subsequent tapering over 6–8 months [28, 49]. For patients with glucocorticoid-resistant disease and in those that develop major relapse despite the use of adequate glucocorticoid doses, the addition of an adjunct disease-modifying agent may be required. Among patients with mild PAN, cyclophosphamide is generally avoided and medications such as azathioprine (up to 2 mg/kg/day) have shown similar efficacy to pulse dose cyclophosphamide but with lower risk of side effects [49]. While often used, the overall long-term benefit of azathioprine is debated. In a recent study evaluating 95 systemic necrotizing vasculitis patients (51, EGPA, 25 MPA, 19 PAN) with FFS = 0, the addition of azathioprine to a glucocorticoid remission-induction regimen did not significantly improve the rates of remission and failed to reduce the risk of relapse or overall steroid exposure [57]. Methotrexate (up to 25 mg/week) and mycophenolate (up to 1500 mg twice daily) have also been used in the management of glucocorticoid-resistant disease, but supportive data for these agents is limited to observational studies [29, 60] and largely extrapolated from their use in the treatment of other systemic necrotizing vasculitidies such as ANCA-associated vasculitis.

The treatment of patients with poor prognostic factors (FFS $\geq$1) requires more aggressive management. In such circumstances, cyclophosphamide is advocated in addition to high-dose glucocorticoids. Both oral (target 2 mg/kg/day) and intravenous pulse (600 mg/m^2 monthly) regimens have shown efficacy, but the latter has demonstrated a more tolerable side effect profile [59]. The duration of cyclophosphamide treatment is less well understood and has only been evaluated in the context of a single clinical trial evaluating 47 patients with MPA and 18 patients with PAN [58]. The results of this study suggest that 6 months of cyclophosphamide was less effective than 12 months of therapy; however, remission maintenance therapies

were not utilized. Conventionally, patients with severe PAN are treated with cyclophosphamide for a minimum of 6 months, after which if they are in remission are transitioned to a lower level immunosuppression agent such as azathioprine, methotrexate, or mycophenolate for ongoing remission maintenance. The therapeutics options for patients with severe systemic idiopathic PAN failing to respond to cyclophosphamide are limited. Rituximab [61, 62] and tocilizumab [63] have been used with reported success, but results are limited to case reports and small case series and are considered currently experimental. Inhibitors of tumor necrosis factor alpha (infliximab, adalimumab, etanercept) have also shown preliminary benefit in systemic PAN [64–67] and appear to have a greater observed role in managing patients with the PAN-like DADA2 variant [68].

In patients with a potential precipitant for the development of PAN or PAN-like illness control or removal of the offending agent is imperative. For example, in patients with minocycline-induced PAN-like illness, cessation of minocycline may be sufficient to result in disease remission. However, in severe cases additional immunosuppressive therapy may be required [24].

Management of patients with HBV-associated PAN is focused on initial control of severe life-threatening manifestations (if present) followed by removal of immune complexes and subsequent clearance of viremia. Although prolonged use of glucocorticoids is contraindicated due to an increased risk of viral replication, short-term use of glucocorticoids (1 mg/kg/day for 1 week then tapered off over 1 additional week) has been safely utilized [69, 70]. Plasma exchange has not demonstrated improvement in outcomes among patients with systemic idiopathic PAN [71] but is considered integral in the treatment of HBV-associated PAN because clearance of immune complexes attenuates vessel inflammation [69, 70]. Suggestions for plasma exchange frequency are 3/week for 3 weeks, 2/week for 2 weeks, then weekly until hepatitis B e antigen to hepatitis B e antibody seroconversion is observed, or until 2–3 months of sustained clinical recovery has been obtained [69]. Antiviral therapy should be initiated at the time of diagnosis. Selection of the antiviral agent and determination of duration should be guided through coordination with hepatology. Interferon alpha2b and lamivudine have shown efficacy in prospective open-label trials [69, 72]. While newer nucleos(t)ide analogs (entecavir and tenofovir) have not been formally evaluated in patients with HBV-associated PAN their efficacy in patients with chronic hepatitis B viral infections is well established [73] and may be considered for assistance with viral clearance. Prolonged vasculitis control occurs in 90–100% of patients for which viral replication has ceased and seroconversion has occurred [69, 70].

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