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Cutaneous Manifestations of Medium- and Large-Vessel Vasculitis

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Abstract Dermatologic manifestations are observed in almost all systemic vasculitides, even in large-and medium-vessel vasculitides, although such vessels are not found in the skin. Cutaneous manifestations may be related to a direct skin localization of the systemic vasculitis or a non-specific process associated with the vasculitis. According to the 2012 International Chapel Hill consensus, the two major variants of large-vessel vasculitides are Takayasu arteritis and giant-cell arteritis. In Europe and North America, acute inflammatory nodules or erythema nodosum-like lesions are the most commonly observed skin lesions with Takayasu arteritis. Medium-sized arteriole vasculitis of the dermis or subcutis but also septal or lobular panniculitis may be found during pathological examination. In Japan, widespread pyoderma gangrenosum-like lesions are more frequent. Cutaneous manifestations of giant-cell arteritis are rare; they are ischemic, linked to arterial occlusions, or non-ischemic, with various mechanisms. The two major medium-vessel vasculitides are Kawasaki disease and polyarteritis nodosa. Kawasaki disease is characterized by a mucocutaneous lymph node syndrome without skin vasculitis. Two subsets of polyarteritis nodosa with different skin manifestations are described, without transition from one to the other. In the systemic subset, the most frequent skin lesions are in the order of frequency purpura, livedo, and nodules. Cutaneous polyarteritis nodosa mainly features nodules, livedo racemosa, and ulcerations. Genetic screening and measurement of plasma levels of adenosine deaminase 2 should be considered for patients with uncommon systemic polyarteritis nodosa or early-onset cutaneous polyarteritis nodosa.

Keywords Takayasu arteritis · Giant-cell arteritis · Polyarteritis nodosa · Kawasaki disease

Abbreviations

ACR	American College of Rheumatology
ADA2	Adenosine deaminase 2
ANCA	Anti-neutrophil cytoplasmic antibodies
CECR1	Cat eye syndrome chromosome region candidate 1 gene
CHCC	Chapel Hill Consensus Conference
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
FFS	Five-factor score
GCA	Giant-cell arteritis
G6PD	Glucose-6-phosphate dehydrogenase
HBV	Human hepatitis B virus
KD	Kawasaki disease
LVV	Large-vessel vasculitis
LVVs	Large-vessel vasculitides
MLA	Macular lymphocytic arteritis
MVV	Medium-vessel vasculitis
MVVs	Medium-vessel vasculitides
PAN	Polyarteritis nodosa
SoJIA	Systemic onset juvenile idiopathic arthritis
SOV	Single-organ vasculitis
TAK	Takayasu arteritis
TSS	Toxic shock syndrome

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Introduction

According to the 2012 revised International Chapel Hill Consensus Conference (CHCC) on the nomenclature of vasculitides [1], as compared with other vasculitides, large-vessel vasculitides (LVVs) more often affect large arteries, including the aorta and its major branches. Of note, in a specific patient, large arteries are not always the predominant type of vessel affected and smaller branches may be involved [1]. Takayasu arteritis (TAK) and giant-cell arteritis (GCA) are the two major LVV variants. Their histopathologic features are indistinguishable and are often granulomatous [2].

Medium-vessel vasculitides (MVVs) predominantly affect medium-sized arteries, defined as the main visceral arteries and their branches. Inflammatory aneurysms and stenosis are commonly observed. Polyarteritis nodosa (PAN) and Kawasaki disease (KD) are the two major MVV variants.

Large- or medium-sized vessels are not found in the dermis or subcutaneous tissues; however, cutaneous manifestation of vasculitides may be related to direct involvement of smaller vessels in the skin such as arterioles or post-capillary venules. Other dermatologic lesions observed in these vasculitides may be secondary to the obstruction of larger vessels or not directly related to the vascular damages.

Large-Vessels Vasculitis

Takayasu Arteritis

TAK is a rare chronic inflammatory arteriopathy of unknown origin that predominantly affects the aorta, its main branches and the pulmonary arteries [1]. Most cases are in females; the age of onset is mostly in the second and third decades. Two stages of this disease have been distinguished and may overlap: a first systemic inflammatory stage, followed by an occlusive stage characterized by inflammation of the media and adventitial layers of large-vessel walls resulting in vascular stenosis and/or aneurysm formation [3]. The first inflammatory stage is characterized by non-specific symptoms such as fever, malaise, anorexia, and weight loss associated with an increase of erythrocyte sedimentation rate or C-reactive protein rate. During the occlusive stage, symptoms are related to regional ischaemia from stenosis and thrombosis. Constitutional features are extremity pain, claudication, bruits, absent or diminished pulse, and/or asymmetry of blood pressure according to the vessel involvement.

The disease is ubiquitous, rare in European countries, and more common in Southeast Asia, India, Mexico, or Africa, with clinical differences depending on the country [3, 4]. Indeed, the systemic phase is frequent in Europe, whereas retinal damage, resulting mainly from ischemia due to large vessels involvement, is frequent in Japan and the ectasitic forms in India. Moreover, lesions confined to branches of the aortic arch dominate in northern Europeans, with lesions in the abdominal aorta and/or renal arteries predominating in Asian/African populations [4]. A genetic predisposition could explain these clinical differences. Indeed, rates of complications seem higher in patients with than without human leukocyte antigen Bw52 [5]. The roles of environmental conditions and certain infections such as tuberculosis have been discussed without confirmation [6]. Associations with Crohn's disease and ankylosing spondylitis have been described [4, 7].

Cutaneous manifestations have been reported in 2.8 to 28% of patients [7–11]. They are reported in Table 1. Some are directly related to large-vessel occlusions such as unilateral Raynaud's phenomenon, digital gangrene, or unilateral digital clubbing [11, 12]. Other skin manifestations were frequently thought to be related to the systemic vasculitis. In Europe and North America, acute inflammatory nodules or erythema nodosum-like lesions (Fig. 1) are the most commonly observed skin lesions [11, 13]. Erythema induratum corresponds to ulcerated subacute nodular lesions. The pathological features of these nodules are variable, including granulomatous or necrotizing vasculitis of medium-sized arterioles of the

Table 1 Clinical and pathological features of cutaneous manifestations observed in patients with Takayasu arteritis

Clinical features	Pathological features	Commentary	References
Raynaud phenomenon, digital gangrene	Not available	–	[7–12]
Erythema nodosum-like lesions	Necrotizing or granulomatous vasculitis or non-specific infiltrate	Frequent in Europe and North America	[11, 13]
Purpuric and necrotic lesions	Small vessels necrotizing vasculitis	–	[9, 13–15]
Livedo reticularis	Not available		
Superficial phlebitis	Venous thrombosis with tuberculoid infiltration	Rarely described	[9]
Pyoderma gangrenosum-like lesions	Dermal edema, neutrophilic abscesses ± vasculitis	Frequent in Japan	[16–18]
Sweet disease	Neutrophils infiltration Edema of the superficial dermis	–	[19]
Urticaria, angioedema, erythema multiforme, erythematous eruptions	Non-specific perivascular infiltrate	Probable not directly related to Takayasu arteritis	[9, 11, 15, 20]

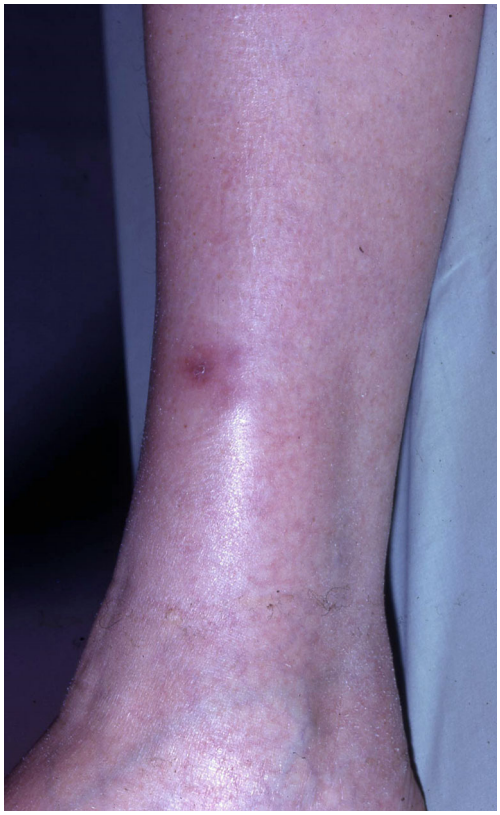


Fig. 1 Nodular lesions of the legs in a woman with Takayasu arteritis

dermis or subcutis, extravascular necrotizing granuloma (Churg-Strauss granuloma), and septal or lobular panniculitis [9, 11]. Usually, no relationship is found between the location of the nodules and vessel involvement [11]. Furthermore, these nodules can occur at any stage of the disease. Purpuric and necrotic lesions are also observed and correspond to necrotizing vasculitis of small vessels in the dermis [13–15]. Because the inflammatory process of the large arteries affects regions of the wall supplied by the vasa vasorum, similar to the cutaneous vessel system, the involvement of small vessels may contribute to the development of the LVV [14].

Livedo reticularis, papular or papulonecrotic lesions, and superficial phlebitis may also be observed [9]. Tuberculoid infiltration has been reported in biopsies of papular or papulonecrotic lesions, which suggests an infectious origin of the disease [6].

In Japan, pyoderma gangrenosum-like lesions are frequently observed in TAK [16]. This type of lesion (Fig. 2) has rarely been reported in patients from northern Africa, North America, and Europe [9, 11, 16–18]. A retrospective study comparing 35 well-documented pyoderma gangrenosum cases associated with TAK with 106 pyoderma gangrenosum cases without TAK showed that the former were more widespread and were localized more frequently on upper arms (74.3 vs 9.4%) [16]. Additionally, the lower limbs, the trunk, the buttock, and the pubic region were frequently involved.

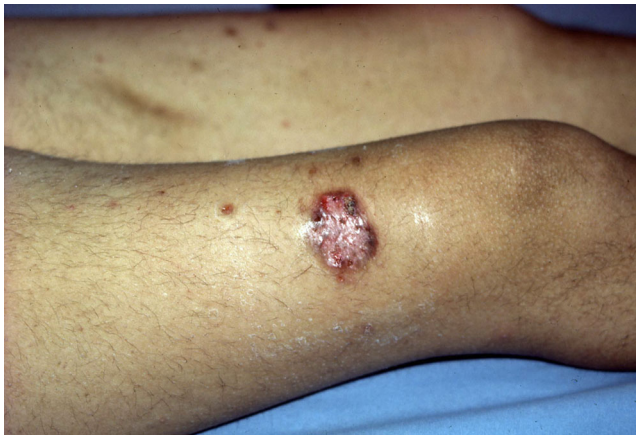


Fig. 2 Pyoderma gangrenosum-like ulceration in a woman with Takayasu arteritis

Pyoderma gangrenosum occurred before the diagnosis of TAK in 21 cases (60%) (median interval, 3 years) [16].

A few cases of Sweet's syndrome with postinflammatory elastolysis and TAK have been reported, mainly in children [19]. Aneurysmal dilatation of the thoracic aorta was always present, which is unusual for TAK. In the three cases with available aortic pathology, the histologic features were similar to those observed in the skin, with prominent neutrophil infiltration and elastolysis. Features of granulomatous inflammation or concurrent large-vessel stenoses were also noted, consistent with TAK. Therefore, in these cases, a true association between TAK with Sweet's syndrome or Sweet's syndrome with aortic localization remains debated [19].

The association between the dermatologic manifestations and TAK is established by excluding all other etiologies of this type of skin lesion and are suggested according to the course of the LVV. Indeed, whatever the disease stage, the reccurrence of skin lesions strongly suggests TAK activity [8].

Finally, other manifestations, such as urticaria, angioedema, erythema multiforme, erythematous eruptions, and "dermatitis," are occasionally related, without a causal relationship with TAK [9, 11, 15, 20].

TAK has rarely been described in children [21]. In a retrospective study of 11 patients followed in the UK, the median age at diagnosis was 11.8 (range 1.3 to 17.0). Cutaneous findings were found in two cases including one case of purpura of the legs and one case of Raynaud's phenomenon.

Systemic corticosteroids are the mainstay of treatment for TAK [22]. Prednisone is usually started at a dose of 1 mg/kg/day during 4 weeks to achieve disease remission. Then the dose may be gradually tapered and treatment can be discontinued within 1 year. Although most patients achieve disease remission with corticosteroids alone, relapses or corticosteroids dependance are observed in about two-thirds of patients [23]. Classical immunosuppressive agents such as methotrexate, azathioprine, and less commonly cyclophosphamide or mycophenolate mofetil are used as steroid-

sparing agents [3, 22]. Biologics agents are increasingly being used for refractory TAK. Among them, TNF-α antagonists particularly infliximab 3–10 mg/kg every 4–8 weeks and anti-IL-6 receptors (tocilizumab) have shown promising results with global improvement in about 60–80% of cases [23, 24]. In a recent randomized double-blind placebo-controlled trial, the addition od CTLA4-Ig (abatacept) 10 mg/kg intravenously on days 1, 15, and 29 and week 8 to treatment regimen with prednisone did not reduce the risk of relapse (median duration of remission of 5.5 months for abatacept versus 5.7 months for placebo, $p = 0.853$) [25].

Giant-Cell Arteritis

GCA is a systemic, often granulomatous vasculitis primarily affecting large vessels branching from the aorta, with a predilection for branches of the external carotid and vertebral arteries [1]. It occurs almost exclusively in patients older than 50 years, with incidence ranging from 5.8 to 31.3/100,000 and prevalence of 30.4/100,000 [26, 27]. Characteristic symptoms are headaches in the temporal and occipital areas, tenderness of the temporal artery, jaw claudication, malaise, and fever. Polymyalgia rheumatica is associated with GCA in about half of the patients. There is a risk of partial or complete loss of vision, with 13% to 19% of patients experiencing ischemic injuries related to occlusion of ophthalmologic artery branches or, less frequently, posterior occipital artery strokes [28, 29]. Cutaneous manifestations are rare [30] and are reported in Table 2. It is not possible to make a clinicopathological correlation because of the rarity of skin biopsies.

Classically, the scalp and temples are tender and red, and tender nodules may be palpable over the temporal (Fig. 3), occipital or facial arteries. Pulsations in these arteries are diminished or absent [30].

Table 2 Clinical and pathological features of cutaneous manifestations observed in patients with giant-cell arteritis

Clinical features	Commentary	References
Induration, erythema, and bullae of scalp and temples	–	[30, 32]
Glossitis, necrosis of the tongue	Usually occurs in the anterior two-thirds of the tongue	[31]
Scalp necrosis	Associated with increased incidence of vision loss and mortality	[32–35, 38, 39]
Purpura, distal gangrene of the limb	Rare	[31, 36]
Periorbital ecchymosis, edema of the face and neck, and nodules of the head	Edema of the face was reported in 8% cases in a case series of 250 cases	[37]
Granuloma annulare	Probably not associated with giant-cell arteritis	[40]

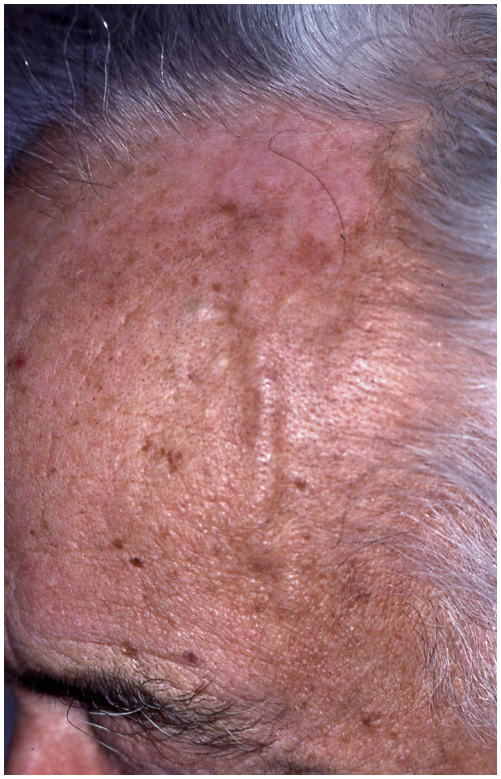


Fig. 3 Indurated and inflammatory temporal artery in a patient with giant-cell arteritis

Two other types of lesions may be observed: ischemic lesions linked to arterial occlusions and non-necrotic lesions of various mechanisms, often misunderstood. Ischemic lesions are localized especially on the tongue and the scalp. Glossitis occurred in 10% of an older retrospective series and may sometimes reveal the disease [31]. The tongue has a red, "raw-beef" color and becomes blistered, desquamated, or gangrenous [31]. Necrosis usually occurs in the anterior two-thirds of the tongue (Fig. 4). Bullae, ulcers, or massive necrosis may occur on the scalp (Fig. 5). Pathogenetically, the formation of scalp necrosis is considered related to the occlusion of most of the four arteries supplying the temporal region of the scalp (temporal, frontal, retro-auricular, and occipital arteries). Patients with scalp necrosis belong to a subgroup of severe GCA with older age at onset and frequent serious complications such as visual loss, gangrene of the tongue, or nasal septum necrosis [32]. An analysis of 78 cases of scalp necrosis associated with GCA reported between 1946 and 2007 showed GCA with scalp necrosis associated with increased incidence of vision loss (32%) and other visual defects (37.3%) as compared with GCA without scalp necrosis (visual disturbance in up to 20%) and with an increased mortality [33]. In this series, the mean interval between onset of GCA symptoms and scalp necrosis was 2.9 months. Under corticosteroid therapy or immunosuppressive treatment, scalp healing was complete or satisfactory in 75% of cases [32, 33]. With refractory ulceration, skin grafts were a good

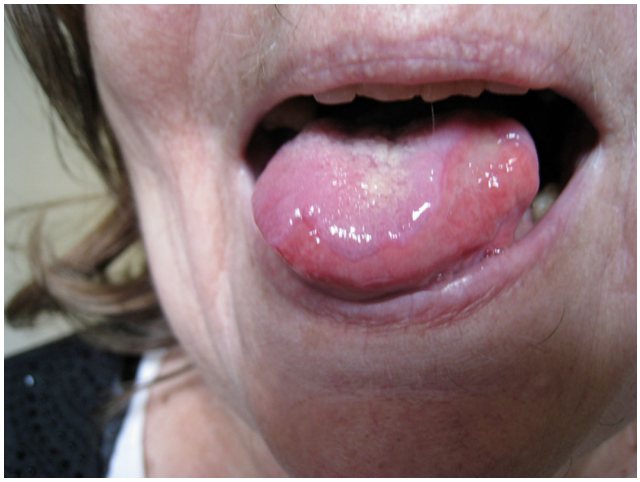


Fig. 4 Post-necrotic ulceration of the tongue in a woman with giant-cell arteritis

alternative therapy [34]. Less severe chronic ischemia of the scalp may lead to thinning or loss of hair. Ischemic skin lesions of the neck or cheeks have been reported [35]. Rarely, vessels of the lower limbs are involved by the vasculitis, leading to ischemic ulcerations or distal gangrene [36]. Skin biopsies of the borders of ulcerations or necrotic tissues are rarely contributive because granulomatous vasculitis was revealed in only 2 of 24 biopsies from patients with scalp necrosis [32].

Other dermatologic manifestations have rarely been reported: periorbital ecchymosis, erythema, bullae in the temporal artery area, edema of the face and neck, and nodules of the head or limbs [31, 32]. Edema of the head is usually painful, prominent on the cheeks and periorbital areas. It was noted in 8% of cases in a large French series of 250 cases, occurring often early during the course of the disease but rarely isolated, disappearing spontaneously or with corticosteroid therapy [37]. Nodules of the lower limbs or the head may be related to a specific necrotizing or granulomatous vasculitis of medium-sized arterioles of the dermis or subcutis [38]; in other cases, lesions were non-specific and only a septal panniculitis was observed [39]. A few cases of granuloma annulare during GCA have been reported, the link with the vasculitis remaining doubtful [40].

Senile purpura is frequent on exposed skin areas in older patients, especially those under corticosteroid therapy, but palpable purpura of the lower limbs due to vasculitis of post-capillary venules remains exceptional in GCA [31].

Systemic corticosteroids are the first-line treatment of GCA with an initial dose of 40–60 mg/day of prednisone during 2–4 weeks [41]. Then, the dose can be gradually tapered and treatment can be discontinued within 1–2 years in most cases [41]. Classical immunosuppressive agents mostly methotrexate are used as steroids-sparing agents in case of refractory disease or corticosteroids dependance [42]. Recently, a phase 2, randomized, double-blind, placebo-controlled trial showed the superiority of the addition of tocilizumab (8 mg/kg) every 4 weeks compared with placebo to standard corticosteroids therapy to reach complete remission by 12 weeks (85 versus 40%, $p = 0.03$) and showed higher relapse free survival by week 52 (85 versus 20%, $p = 0.001$) [43].

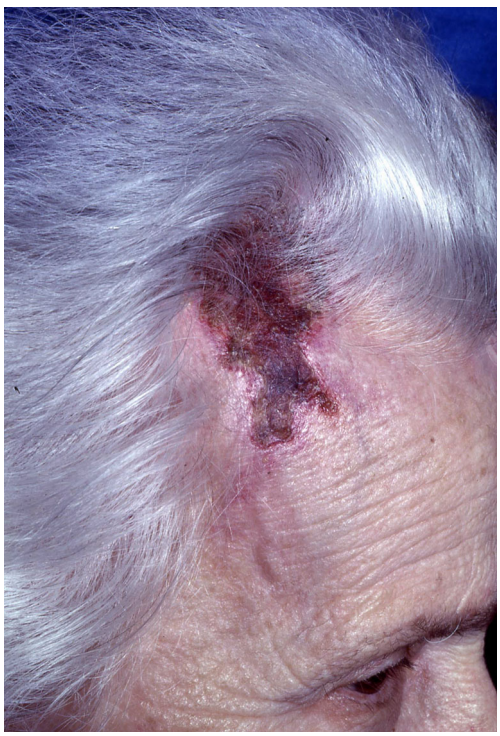


Fig. 5 Scalp necrosis in a man with giant-cell arteritis

Medium-Vessel Vasculitis

Kawasaki Disease

KD is an acute, self-limited vasculitis of unknown etiology that occurs classically in children younger than 5 years [44, 45]. KD is the most common vasculitic disorder affecting children of different races worldwide, although the risk is highest among Asians, particularly in Japan, with an annual incidence 264.8 cases per 100,000 children <5 years old in 2012 as compared with 9.1 cases per 100,000 white children in the USA [45, 46].

KD was originally named mucocutaneous lymph node syndrome, and KD vasculitis predominantly affects medium and small arteries of the heart. Coronary artery ectasia or aneurysms occur in 15 to 25% of patients with KD [44]. The classic clinical criteria for KD diagnosis requires ≥5 days of fever and ≥4/5 of the following features: polymorphous exanthema, extremity changes, lips and oral cavity lesions, bilateral bulbar conjunctival injection, and unilateral cervical lymphadenopathy [44]. The dermatological manifestations are essential for the diagnosis but are not predictive of the existence of a coronary vasculitis. An exanthema appears during the first

days of fever onset. It is polymorphous, varying from macular to maculopapular or morbilliform, beginning usually on the trunk and spreading, over the next few days, to involve the extremities. Bullous or vesicular eruption has not been described in KD, and an alternative diagnosis should be considered with such lesions [47]. Erythema of the palms and foot soles is frequently associated with edema of the dorsum of hands and feet. Perineal exanthema frequently undergoes desquamation during the first week of illness, whereas desquamation at the tips of fingers and toes (Fig. 6) usually occurs later, in the subacute phase of the disease (weeks 2–4). Involvement of mucosa appears in the acute febrile phase of the disease (1–14 days). Lips are vertically cracked dry and reddened, with a "strawberry" tongue (Fig. 7), and enanthema of oral and pharyngeal mucosa. Bilateral, non-exudative, bulbar conjunctival injection is seen. Transversal lines (Beau lines) or ridges over the nails may appear during the convalescent phase (after week 4) as a result of arrested nail growth during the initial phase of KD. Histologically, vasculitis is generally limited to the coronary arteries; non-specific features were classically found on skin biopsy [48]. Peripheral gangrene and/or small-vessel cutaneous vasculitis were reported in only 15 cases [48].

The diagnosis of KD may be challenging; indeed, characteristic clinical features are typically not present all at the same time. Moreover, the differential diagnoses for patients presenting similar features of KD are vast [47]. The differential diagnosis may be very difficult with viral infection, particularly adenovirus infection. Indeed, in a retrospective study of 31 children with adenovirus infection, 5 (16%) fulfilled fever and more than 4/5 KD diagnosis criteria [49]. In this series, extremity changes and unilateral neck swelling were significantly more common in patients with criteria for complete KD [49]. However, adenovirus infection was incidentally detected by PCR in a patient with complete KD and coronary artery

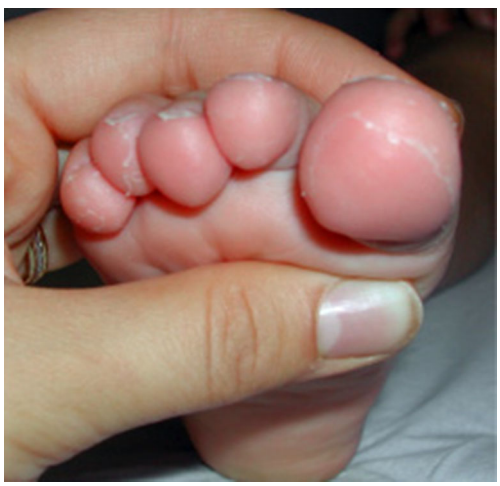


Fig. 6 Desquamation of toes in Kawasaki disease (collection of Doctor Maryam PIRAM, Department of Pediatric Rheumatology, Hospital Paris Sud, France)

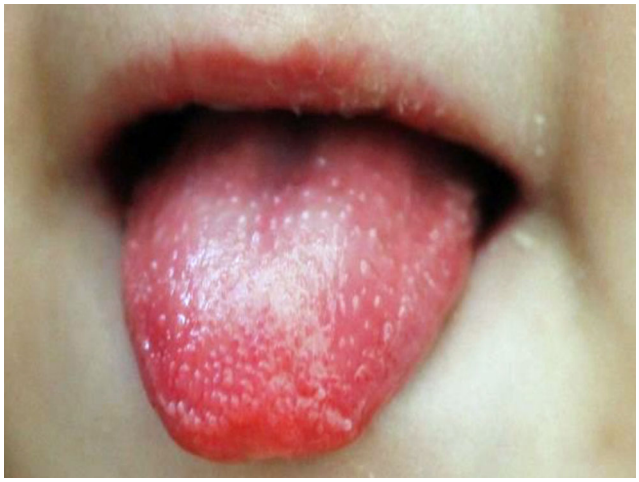


Fig. 7 Strawberry tongue in Kawasaki disease (collection of Doctor Maryam PIRAM, Department of Pediatric Rheumatology, Hospital Paris Sud, France)

abnormalities [47]. Therefore, one must differentiate incidental detection of adenovirus in patients with KD and primary adenoviral infection so as to avoid complications associated with undiagnosed KD [49]. Moreover, KD, toxic shock syndrome (TSS) and scarlet fever may present as hypotension, skin rash and desquamation, and differentiating between these diagnoses in the early stages may be challenging; microbiological samples are useful [50, 51].

A retrospective study compared 17 patients with KD and 16 with confirmed diagnosis of TSS. KD patients were significantly younger and had lower hemoglobin levels, higher median platelet count, and more echocardiographic abnormalities than TSS patients [51]. The clinical features of systemic onset juvenile idiopathic arthritis (SoJIA) may be similar to those of KD [52]. Classically, the rash with SoJIA is intermittent and coincides with fever spikes. Moreover, mucocutaneous findings are usually absent in SoJIA [52]. Finally, the node-first presentation of KD may be misdiagnosed as bacterial cervical adenitis or retropharyngeal abscess [53].

KD occurs rarely in adults [54, 55]. Recently, a French retrospective multicenter study of 43 KD in adults included 34 complete KD and 9 incomplete KD. Overall, 35% of patients showed coronary vasculitis and/or coronary aneurysm.

The use of intravenous immune globulin (IVIG) at a dose of 2 mg/kg in a single infusion is recommended in the acute phase of KD [44]. Treatment with IVIG should be administered within the first 10 days and have been shown to reduce coronary artery abnormalities from 25 to 5% [47]. High dosage of aspirin (30–50 or 80–100 mg/kg/day) should be administered in association with IVIG at least 48–72 h after the resolution of fever. Once high-dose aspirin is discontinued, low-dose aspirin 3–5 mg/kg/day should be started in order to prevent possible complications from coronary artery abnormalities at least until 6–8 weeks after the onset of KD depending of the results of coronary evaluation [44, 56].

Polyarteritis Nodosa

Since its first description in 1866 by Kussmaul and Maier [57], polyarteritis nodosa (PAN) has been divided in two major subtypes, the systemic PAN and cutaneous PAN. In each subtypes, different forms may be individualized according to whether a cause has been highlighted. More recently, deficiency of adenosine deaminase type 2 (ADA2), a genetic cause, has been identified in cutaneous PAN mostly in pediatric cases. ADA2 deficiency is frequently associated with various systemic manifestations [58]. According to the 2012 CHCC definition [1], systemic PAN is a necrotizing arteritis of medium- or small-sized arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules and not associated with anti-neutrophil cytoplasmic antibodies (ANCA). Medium-sized arteries are defined as the main visceral arteries and their branches [1]. In the skin, only arterioles are present in the deep dermis or hypodermis. Thus, according to this definition, vascular cutaneous involvement should be absent in systemic PAN, which is not the experience of dermatologists. According to the 2012 CHCC definition, cutaneous PAN should be included in the group of single-organ vasculitis (SOV) as a cutaneous arteritis [1]. However non-cutaneous involvement of nerves and muscles were observed in all the large series of the literature [59–62]. The dermatological lesions differ according to whether the PAN is systemic or mainly cutaneous. Systemic PAN is a potentially life-threatening disease, whereas cutaneous PAN is a chronic benign disease with relapsing course [63]. The progression of cutaneous PAN to a systemic form is exceptional.

Histologically, all clinical variants of PAN are characterized by a segmental necrotizing vasculitis of medium-sized arteries or arterioles. In the acute phase, fibrinoid necrosis of the media is observed with infiltration by polymorphic cells (Fig. 8). The infiltrate is composed predominantly of polymorphonuclear neutrophils with often pycnotic nuclei, associated with a variable number of lymphocytes and eosinophils. Aneurysms and thromboses may complicate inflammatory vascular lesions. Cicatricial repair is characterized by fibrous endarteritis which can lead to vascular occlusion. The coexistence of lesions of different ages with both active and cicatricial lesions within the same biopsy may be observed. Moreover, the involvement is segmental; therefore, vasculitis lesions or healthy tissue may be found along the same vessel.

Systemic Polyateritis Nodosa

Systemic PAN is the less common type of systemic vasculitides. It affects patients of any gender, age, or ethnic background. The peak of incidences occurs in the 5th–6th decades of life. Systemic PAN rarely occurs in childhood; clinical manifestations are similar to those observed in adults [64]. Reported prevalence and annual incidence estimates ranged, respectively from 2 to 33 and 0 to 16 per million [65, 66]. The 1990 American College of Rheumatology (ACR) classification criteria for PAN [67] and European League Against Rheumatism (EULAR) classification criteria for childhood PAN [68] are reported in Tables 3 and 4. Considering cutaneous manifestations, only livedo reticularis is taken into account in ACR criteria while all skin vasculitic lesions are included in the skin criterion of the EULAR classification. Of note, the 1990 ACR criteria have being developed prior to the distinction between microscopic polyangiitis and PAN [67]. Another set of diagnostic criteria suggested the use of positive and negative criteria, such as the absence of ANCA or cryoglobulinemia which enhances the sensitivity and the specificity of the ACR criteria [69]. The "European Medicines Agency (EMA) classification algorithm" in which several sets of ACR criteria and CHCC definitions are applied in a structured order, probably represents the most comprehensive approach to classify systemic PAN [70]. This classification is based on the prior exclusion of other vasculitides and a positive histology compatible with the CHCC definition of PAN or typical angiographic features (Table 5).

In the 1970s, a substantial percentage of patients with systemic PAN has been tested positive for active human hepatitis B virus (HBV) infection [71]. Before vaccination against HBV was available, more than one third of adults with PAN were infected with HBV. Currently less than 5% of patients

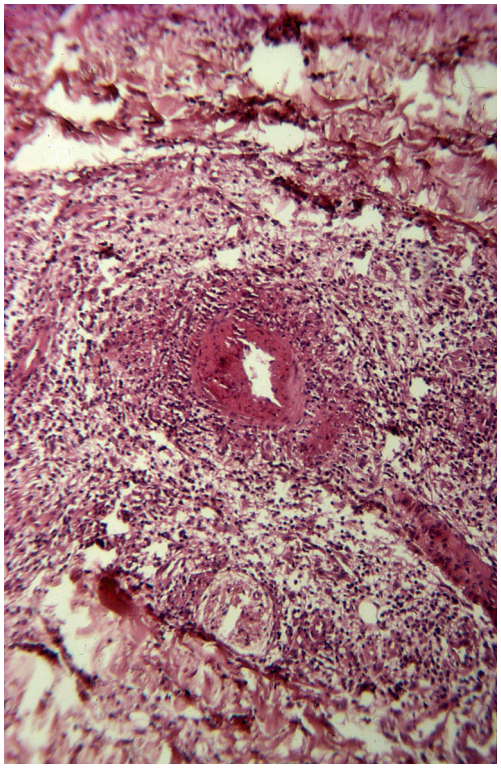


Fig. 8 Pathological findings of skin biopsy of PAN showing necrotizing vasculitis in a small artery of the lower dermis (staining with hematoxylin-eosin-saffron, ×100)

Table 3 1990 American College of Rheumatology (ACR) classification criteria for systemic polyarteritis nodosa [67]

1. Weight loss >4 kg
2. Livedo reticularis
3. Testicular pain or tenderness
4. Myalgias, weakness, or leg tenderness
5. Mononeuropathy or polyneuropathy
6. Diastolic BP >90 mmHg
7. Elevated BUN >40 mg/dl or creatinine >1.5 mg/dl, not due to dehydration, or obstruction
8. Presence of hepatitis B surface antigen or antibody in serum
9. Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other non-inflammatory causes
10. Biopsy of small or medium-sized artery containing PMN

Polyarteritis nodosa is diagnosed if at least 3 of these 10 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 82.2% and a specificity of 86.6%

BP blood pressure, *BUN* blood urea nitrogen, *PMN* polymorphonuclear neutrophils

with PAN are HBV infected in developed countries and fewer than 10 new cases per year are diagnosed in France [72]. Other viruses have rarely been reported in association with systemic PAN, such as human hepatitis C virus, human immunodeficiency virus, parvovirus B19, cytomegalovirus [73]. Minocycline have been reported to induce exceptionaly systemic PAN-like syndrome with positive ANCA [74].

The main clinical manifestations and biological abnormalities are reported in Table 6 [66, 72].

At the initial stage with only myalgias, weight loss, and fever, muscle biopsy can lead to diagnosis. Myalgias, present in half of the cases, are intense, diffuse, spontaneous or triggered by pressure, and sometimes associated with secondary muscle wasting contrasting with normal creatine phosphokinase.

Table 4 European League Against Rheumatism (EULAR) classification criteria for childhood polyarteritis nodosa [68]

A systemic illness characterized by the presence of either a biopsy showing small and mid-size artery necrotizing vasculitis OR angiographic abnormalities[a] (aneurysms or occlusions) (mandatory criteria), plus at least two of the following 7 criteria:
l. Skin involvement (livedo reticularis, tender subcutaneous nodules, other vasculitic lesions)
2. Myalgia or muscle tenderness
3. Systemic hypertension, relative to childhood normative data
4. Mononeuropathy or polyneuropathy
5. Abnormal urine analysis and/or impaired renal function[b]
6. Testicular pain or tenderness
7. Signs or symptoms suggesting vasculitis of any other major organ system (gastrointestinal, cardiac, pulmonary, or central nervous system)

[a] Should include conventional angiography if magnetic resonance angiography is negative

[b] Glomerular filtration rate of less than 50% normal for age

Arthralgias affect mainly the large joints (knees, ankles, elbows, and wrists), without erosions on x-rays.

The main neurological manifestation is mononeuritis multiplex. Neurological recovery is slow (12–18 months) in relation to the axonal lesional mechanism. The clinical presentation of central nervous system involvement varies according to cerebral localization and mechanism of vascular involvement: cerebral vasculitis, rupture of aneurysm, and hematoma.

Vascular nephropathy can lead to chronic renal failure and arterial hypertension. Radiological examinations highlight renal infarction and vascular abnormalities (stenosis and microaneurysms). PAN is diagnosed when typical angiographic changes are detected, even in the absence of histological confirmation. Renal biopsy is performed only if required for diagnosis, given the associated risk of rupture of microaneurysm.

Orchitis, included in the ACR classification criteria (Table 3), is often unilateral, secondary to testicular artery vasculitis, requiring emergency treatment because of the risk of irreversible ischemia [67].

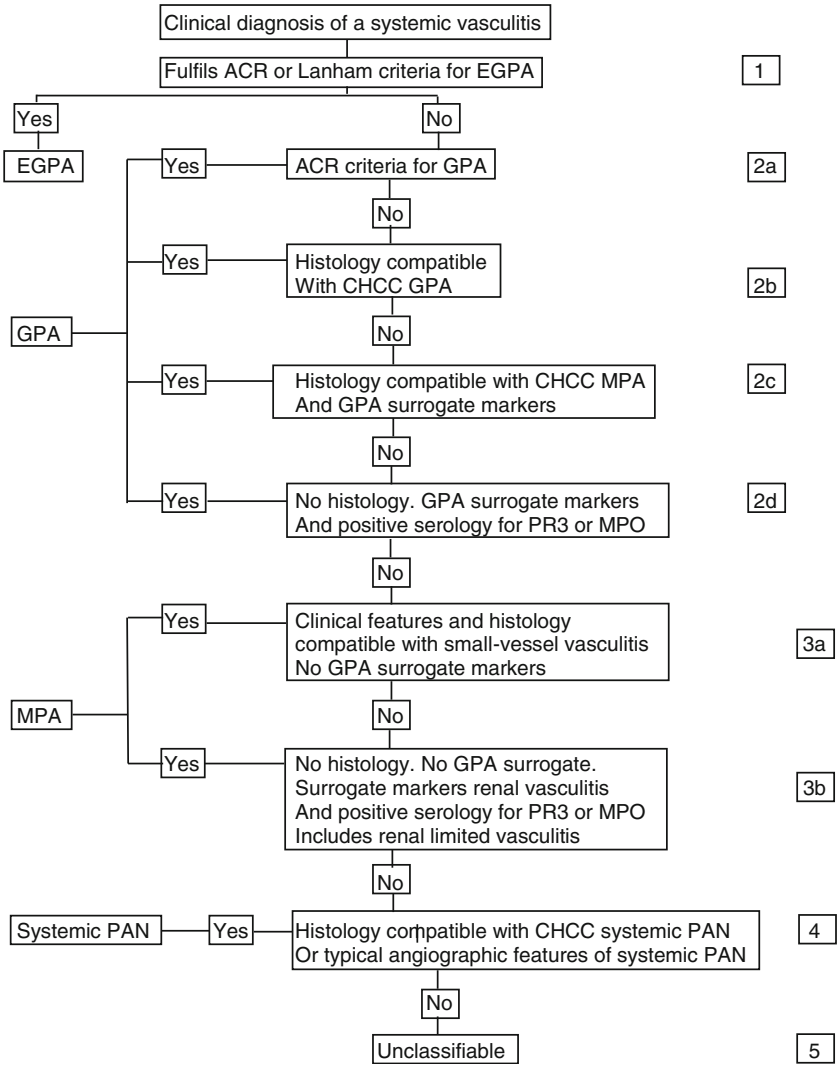
Cardiac involvement is mainly myocardial involvement secondary to vasculitis of the coronary arteries or their branches or secondary to uncontrolled hypertension. Heart failure is the most frequent clinical manifestation. Despite vasculitis of the coronary arteries, acute myocardial infarction is rare and coronary angiography is usually normal [75].

The digestive manifestations may be severe. Abdominal pain occurs in one third of patients. There is a risk of hemorrhage or perforation, mainly localized in small intestine and disease often manifests as an acute surgical abdomen. Digestive malabsorption and acute or chronic pancreatitis, with pseudocysts, have also been described [76, 77].

Ophthalmologic manifestations are mostly bilateral retinal detachment or retinal vasculitis [78]. Dysoric nodules, choroiditis, anterior uveitis, or scleritis have also been described [79].

The description of skin lesions in large series of systemic PAN are rarely been performed by dermatologists in the literature [80]. Skin manifestations are found in 28 to 60% of systemic PAN cases, 44% in our experience of a large series of 248 patients [80]. Cutaneous manifestations were the first manifestations in 33% of the cases and were statistically more frequent without than with HBV-positive PAN (78/144 [54%] vs 32/104 [30%]; $p = 0.0002$). The most common skin lesions were palpable purpura (19%) (Fig. 9), livedo (17%), and nodules (15%). Less common manifestations were urticarial lesions (6%), transient erythema, superficial phlebitis, distal necrosis (4%), and splinter hemorrhage (Fig. 10). Peripheral embolization of thrombi may cause infarction of the extremities (toes, fingers) or skin areas. Segmental edema indicates

Table 5 The European Medicines Agency classification algorithm for diagnosis of systemic polyarteritis nodosa modified from Watts et al. [70]



the underlying muscular involvement. Histologically, purpura or urticarial lesions corresponded to involvement of post-capillary venules. Patients with these cutaneous lesions may constitute a subgroup of systemic PAN that is an exception to the CHCC strict definition of PAN with vasculitis confined to medium- and small-sized arteries [1]. Nodules or livedo corresponded to an involvement of arterioles of the deep dermis or hypodermis. Leukocytoclastic infiltrates were always prominent. Direct cutaneous immunofluorescence was inconspicuously positive with deposits of C3 or immunoglobulins in the vessels [80].

The main objectives of treatment of systemic PAN are to prevent death, to achieve sustained disease remission and to minimize treatment-related side effects. The choice of treatment depends on the severity of the disease and comorbidities, especially associated HBV infection. The revisited five-factor score (FFS) [81] is a reliable simple tool, developed for the assessment of prognoses of systemic necrotizing vasculitides and may be used to assess severity of systemic PAN (Table 7). In the absence of HBV infection, therapy is initiated by high-dose corticosteroid therapy (1 mg/kg/day, preceded by one or more bolus of methylprednisolone at a dose of 15 mg/kg/day). The dose of corticosteroid may be tapered when remission is achieved. The decrease is progressive, in order to obtain a daily dose of prednisone in the range of 20 mg/day at 3 months, 10 mg/day at 6 months, and 5 mg/day at 12 months until corticosteroids withdrawal between 12 to 24 months. Corticosteroids may be prescribed alone when the FFS is equal to zero and should always being associated with immunosuppressive therapy in severe (FFS $\geq$1) or relapsing form. In the EULAR recommendations published in 2009 [82], the group of experts recommended a combination of glucocorticoids and cyclophosphamide. Cyclophosphamide could be given intravenously (600 mg/m^2, every 2–4 weeks) or taken orally daily (2 mg/kg/day). The intravenous route is usually preferred because of comparable efficacy and fewer rates of

Table 6 Main clinical and biological manifestations of systemic polyarteritis nodosa [66, 72]

Clinical or biological manifestations	Frequency (%)
Systemic manifestations	
Fever	31–69
Weight loss	16–69
Myalgias	30–59
Arthralgias	44–58
Cutaneous manifestations	28–60
Neurologic manifestations	40–79
Mononeuritis multiplex	38–72
Peripheral neuropathy	74
Central nervous manifestations	2–28
Cranial nerve palsy	<2
Gastrointestinal manifestations	14–44
Abdominal pain	36–97
Surgical abdomen/peritonitis	14–32
Urologic and renal involvement	8–66
Recent onset arterial hypertension	10–63
Hematuria	15
Proteinuria	22
Orchitis/epididymitis	22
Ophthalmologic manifestations	3–44
Cardiac manifestations	4–30
Laboratory features	
Biological abnormalities related to inflammation	78
Polynuclear leukocytosis	45–75
500/mm^3< eosinophilia <1500/mm^3	<10
ANCA (exclusion criterion)	<5%

side effects [83]. The dosage of cyclophosphamide and corticosteroids must be reduced in subjects older than 65 years or with renal insufficiency (creatinine >300 μmol/l or glomerular

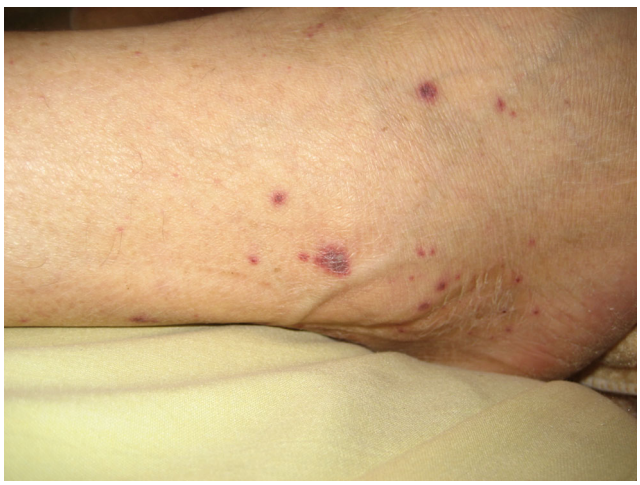


Fig. 9 Infiltrated purpura of the ankles in a patient with systemic polyarteritis nodosa

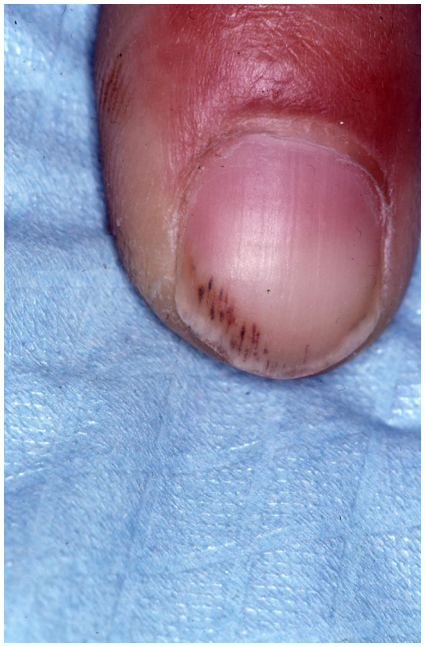


Fig. 10 Multiple splinter hemorrhages in the distal part of the nail

filtration rate <25 ml/min) [82, 84]. Rituximab is currently an alternative to treatment with cyclophosphamide for initial therapy. Maintenance therapy is essential in severe forms (FFS greater than or equal to one) for a minimum of 18 months (azathioprine or methotrexate or leflunomide), due to the frequency of relapses (32%) [82].

In HBV-associated PAN, the corticosteroid/immunosuppressive combination may stimulate viral replication and worsen the chronic hepatitis. A combination of corticosteroids, plasma exchanges and anti-viral therapy is currently recommended [82].

Cutaneous Polyarteritis Nodosa

The true incidence and prevalence of cutaneous PAN are still unknown. It is a rare disease with large variations of

Table 7 The revisited five-factor score for all systemic necrotizing vasculitides [81]

The following factors were significantly associated with higher 5 years mortality:
• Age >65 years
• Cardiac manifestations
• Gastrointestinal involvement
• Renal insufficiency (stabilized peak creatinine ≥150 μmol/l)
Only for granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis
• Absence of ear, nose, and throat manifestations

FFS = 0 in the absence of all these factors, FFS = 1 if presence of 1 of these factors, FFS = 2 if presence of 2 of these factors, FFS = 3 if presence of all these factors

male/female ratio according to the published series ranging from 1:1.7 to 1:6 [59, 61, 85]. Cutaneous PAN can occur worldwide; however, it has been more frequently reported in Caucasian or Japanese patients. The disease may occur at any age from 7 months to 81 years with a mean age at the time of diagnosis near 40 years. Cutaneous PAN is uncommon in the pediatric population with less than 200 cases reported in the literature [86].

In the childhood, group A beta-hemolytic streptococcus infections are the most frequent infections (>80% cases) associated with cutaneous PAN [86]. In adults, many other infections have been reported in small series or case reports such as hepatitis B and C, HIV, parvovirus B19, and *Mycobacterium tuberculosis* infections [61, 87, 88]. In addition to infectious causes, observations of cutaneous PAN have been described in the context of other systemic diseases such as inflammatory bowel diseases and rheumatoid arthritis [89]. These secondary cutaneous PAN did not have a distinctive course. In rare cases, patients with PAN associated with bacterial infections achieved remission after a long-term anti-biotherapy [59]. Cutaneous PAN may also be induced by drugs such as penicillin and minocycline [90]. In these cases, withdrawal of medications is usually followed by improvement of the skin lesions.

Cutaneous PAN is defined by clinical and histological criteria. It is a necrotizing vasculitis of the arterioles of the deep dermis and/or the hypodermis [60, 61]. Nakamura et al. established diagnostic criteria for cutaneous PAN (Table 8). Both clinical and histological criteria must be present to confirm the diagnosis of cutaneous PAN after systemic manifestations are ruled out [85].

Table 8 Diagnostic criteria for cutaneous polyarteritis nodosa [85]

Compatible clinical findings	Subcutaneous nodules, livedo, purpura, ulcers
Histopathological findings	Fibrinoid necrotizing vasculitis of small and medium-sized arteries
Exclusion manifestations	Fever (≥38 °C, ≥2 weeks), weight loss (6 kg or more in 6 months) Hypertension Rapidly progressive renal failure, renal infarction Cerebral hemorrhage, cerebral infarction Myocardial infarction, ischemic heart disease Pericarditis, heart failure Pleuritis Intestinal hemorrhage, intestinal infarction Peripheral neuropathy out of the affected skin lesion Arthralgia (arthritis) or myalgia (myositis) out of the skin lesion Abnormal arteriography (multiple microaneurysm, stenosis, and obliteration)

Both clinical and histological criteria must be present to confirm the diagnosis of cutaneous polyarteritis nodosa

The main cutaneous findings are nodules (74–80%), livedo reticularis (56–74%), and ulcerations (8–51%). The cutaneous lesions are mainly located on the legs (97%) and less frequently on the arms (11–33%) or on the trunk (3–8%) [60, 61]. Nodules are between 5 and 15 mm in diameter (Fig. 11) and are often multiple, red-dark reddish-purple, accompanied by spontaneous pain and tenderness and mainly located around the knees and on the feet. Livedo reticularis may precede or follow the onset of nodules; sometimes both livedo and nodules occur together. Livedo reticularis is typically suspended, located on the lower limbs, the dorsal face of the upper limbs and rarely the trunk (Fig. 12). The "fishnet" reticular pattern is irregular, with broken circles, which explains the term "livedo racemosa" used in some European countries. Some infiltrated areas on or between the fishnet reticular patterns are usually detected by careful examination and should be preferred for skin biopsy. Painful ulcerations (Fig. 13) are frequently associated with tender indurated plaques resulting from the coalescence of nodules. Purpura, papules, and "atrophie blanche" have also been reported [60, 61]. The term "atrophie blanche" or livedoid vasculitis is a descriptive term denoting atrophic ivory-white stellate scars surrounded by telangiectasias (Fig. 14). Histologically, depositions of fibrin are found within the small vessels of the superficial dermis. These lesions may be observed not only in association with venous insufficiency and various pro-thrombotic abnormalities but also in rare cases with cutaneous PAN, diagnosed on a deep cutaneous biopsy [91]. Macular lymphocytic arteritis (MLA) is clinically

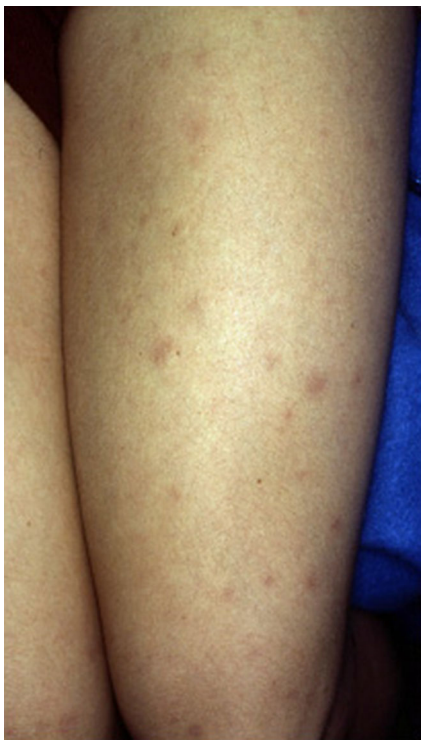


Fig. 11 Nodules on the lower limbs in a patient with cutaneous polyarteritis nodosa

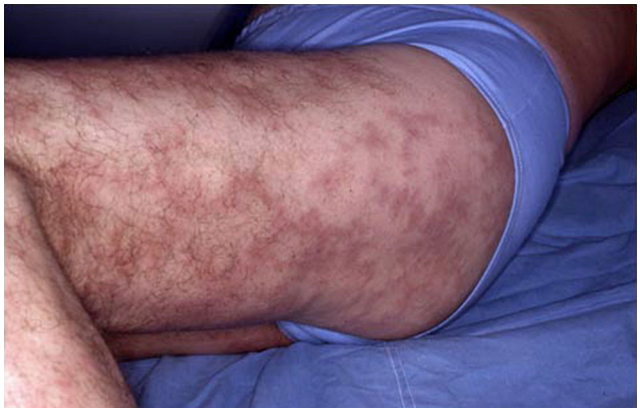


Fig. 12 Infiltrated livedo racemosa of the lower limbs in a man with cutaneous polyarteritis nodosa

characterized by erythematous or pigmented reticulated patches, mainly on the lower limbs (Fig. 15). Histologically, MLA is characterized by a prominent lymphocytic vessel wall infiltrate without polymorphonuclear cells, a hyalinized fibrin ring in the vessel lumen and the absence of internal elastic lamina disruption. The relationship between cutaneous PAN and MLA remains unclear. Ulcerations and sensitive neuropathy have also been reported in MLA [62]. MLA may be an evolutionary stage of cutaneous PAN with lymphocytic infiltrates [62].

When cutaneous PAN is suspected, a deep incisional skin biopsy and not a punch biopsy is required to obtain an adequate sample including the subcutaneous tissue. Indeed, vasculitis affects only small- and medium-sized arteries of the deep dermis and hypodermis, with fibrinoid necrosis and mainly neutrophilic infiltrates in the acute inflammatory stage [92]. Direct immunofluorescence may show vascular deposits, essentially C3 and IgM, without etiological significance [60].

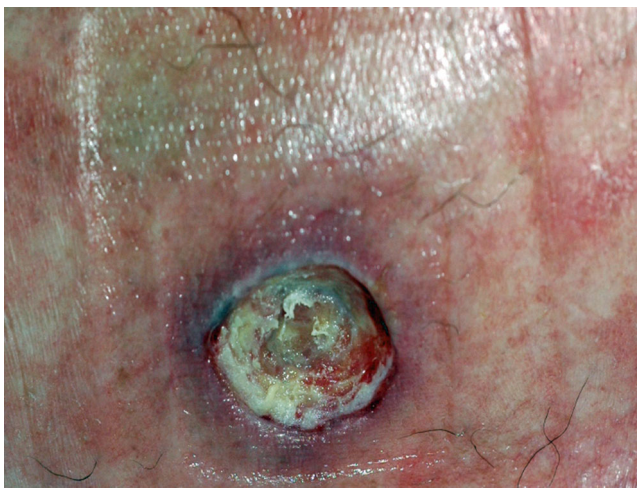


Fig. 13 Painful ulceration (size 2 × 1.6 cm) of the leg in a woman with cutaneous polyarteritis nodosa

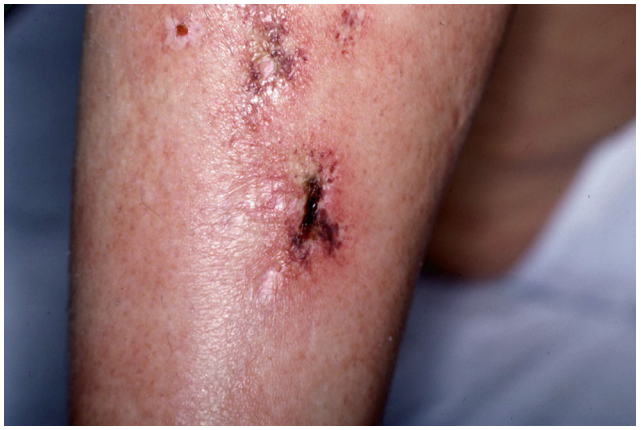


Fig. 14 A rare manifestation of cutaneous polyarteritis nodosa: livedoid vasculitis-like lesions

Extracutaneous manifestations include mild fever, myalgias (29–31%), arthralgias (69%), and mainly sensitive neuropathy (9–22%) in the areas of cutaneous involvement [60, 92]. There are no specific laboratory findings; mild anemia, moderate leukocytosis, and increased erythrocyte sedimentation rate are frequently encountered in cutaneous PAN. The detection of ANCA is usually negative except perinuclear ANCA in minocycline-induced cutaneous PAN or perinuclear ANCA not directed against myeloperoxidase [90]. In one study from Japan, a high percentage of patients with cutaneous PAN (13/16; 81.3%) were positive for IgM anti-phosphatidylserine-prothrombin complex antibodies while

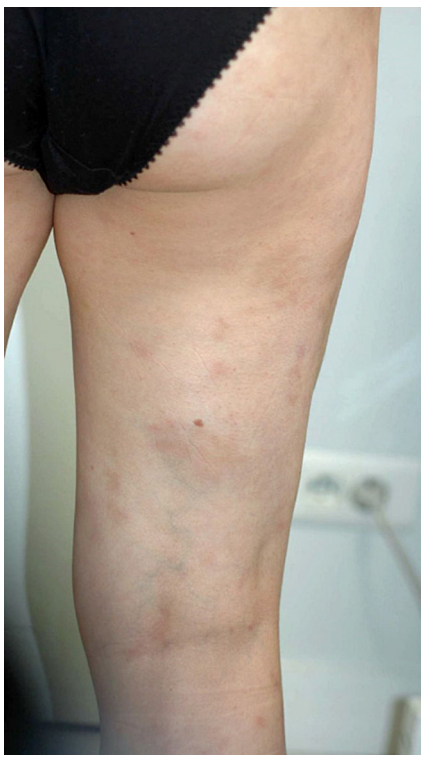


Fig. 15 Macular lymphocytic arteritis of the leg

none of the controls were positive [93]. Further studies are needed to confirm this association and to assess its significance.

The course of cutaneous PAN is most often benign, prolonged over years, with frequent relapses, sometimes triggered by infectious episodes, especially streptococcal infections in a child [94]. No relationship between the age of onset and the severity of cutaneous PAN has been demonstrated. Treatment is highly variable, depending on the severity of the disease [65]. No clinical trials have been performed in cutaneous PAN; therefore, there is no strong evidence-based recommendations and treatment choices are guided by case series and case reports. Of note, cutaneous PAN is a chronic benign disorder. Treatment should not be more toxic than the disease itself. Depending on the severity of the cutaneous PAN and the frequency of flare-ups, treatment may be intermittent during flare-ups or permanent during several years in case of frequent relapses. Some patients may have no treatment or only wear support stockings. Penicillin is indicated in patients with streptococcal infection, especially in children.

First-line therapy with salicylates, other non-steroidal anti-inflammatory drugs, colchicine or rather dapsone is usually recommended [65]. Before therapy with dapsone, initial laboratory investigations should include a complete blood cell count to determine basal white blood cell count and hemoglobin; glucose-6-phosphate dehydrogenase (G6PD) deficiency should be ruled out, as well as significant hepatic or renal dysfunction. The initial prescribed dose of dapsone varies from 50 to 150 mg/day, usually associated with folate supplementation. The main adverse effects are hemolysis and methemoglobulinemia. Others include a mononucleosis-like hypersensitivity syndrome termed the *sulfone syndrome*, occurring usually during the first month of treatment, neuropathy, and agranulocytosis. Checking methemoglobin levels is unnecessary in the absence of symptoms. Patients who are refractory to these first-line therapies and those with severe pain, ulcerations, necrosis, or extracutaneous symptoms such as myalgias, paresthesias, or arthralgias may require a more aggressive approach. In these patients, corticosteroids are usually prescribed (0.5–1 mg/kg/day) with good efficacy. Unfortunately, exacerbations occur frequently with the tapering of corticosteroids and adverse events limit their long-term use. Additional medications including hydroxychloroquine, azathioprine, methotrexate, mycophenolate mofetil, rituximab, cyclophosphamide, or intravenous immunoglobulins may be necessary to maintain the control of disease and are used as steroid-sparing agents [60, 65, 95, 96]. In children without streptococcal infection, treatment is generally more aggressive with corticosteroids [86]. Most of the literature series show no evolution of cutaneous to systemic PAN. In a retrospective case series of 35 patients with idiopathic cutaneous PAN and a median follow up of 11 years, complete remission occurred in 54% of cases and transient remission in 11%. All the patients were treated with various usual first-line therapies. Half of them required the addition of a second-line treatment [62].

Deficiency of Adenosine Deaminase Type 2

Cutaneous lesions similar to cutaneous PAN have been recently described in patients with autosomal recessive mutations in the cat eye syndrome chromosome region candidate 1 gene (CECR1), associated with low adenosine deaminase type 2 (ADA2) level in plasma [97, 98]. Various mutations in the CERC1 gene on chromosome 22q11 have been described; these mutations may be homozygous or compound heterozygous. They have been found firstly in patients with Georgian-Jewish ancestry (10% mutation carriers for a mutation encoding a Gly47-Arg substitution in Georgian-Jewish population [99]) and further described in many cases of various countries [58, 98]. The prevalence of these mutations remains unknown across the world. The disease is probably still underdiagnosed because of its recent description. The clinical

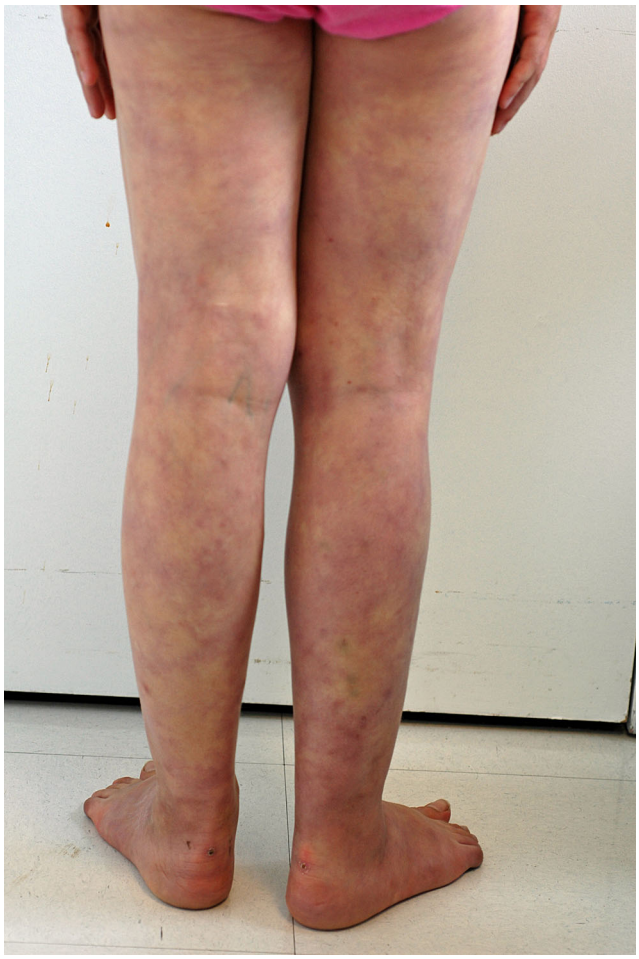


Fig. 16 Livedo racemosa and nodules on the legs of a 12-year-old child with chronic cutaneous polyarteritis nodosa for 6 years. The past history of ischemic stroke led to suggest the diagnosis of deficiency of adenosine deaminase 2

features of ADA2 deficiency are characterized by variable severity and organ involvement. Age of onset is mainly in the childhood but ranged from 2 months to 59 years. Infiltrated livedo racemosa (Fig. 16), nodules, ulcerations, and ischemic lesions are the main clinical cutaneous manifestations [97]. Non-granulomatous necrotizing vasculitis of a medium-sized vessel is usually observed in biopsies of nodules and infiltrated livedo; however, some patients can present small-vessel leukocytoclastic vasculitis or perivascular T lymphocytes, without the characterized vasculitis [58, 99]. A history of recurrent bacterial and viral infections is usual, leading to the hypothesis that ADA2 could act as a modulator of vascular inflammation triggered by intercurrent infections. Systemic forms include fever, arthralgia, myalgia, ischemic or hemorrhagic strokes, peripheral neuropathy, and hepatosplenomegaly with portal hypertension [58]. Other clinical phenotypes have been described such as common variable immunodeficiency or atypical systemic lupus erythematosus [93]. Common laboratory abnormalities include cytopenias and hypogammaglobulinemia. Treatment depends on the severity of the disease. Anti-TNF treatment have shown promising results for severe cutaneous lesions such as skin ulcerations or necrosis [91, 93]. Hematopoietic cell transplantation has been effective in some severe cases with prominent hematological abnormalities [98].

Conclusion

In conclusion, the dermatological manifestations of LVV are unusual, sometimes of prognostic significance or associated with a disease activity. A specific treatment is not necessary in most cases. Dermatologic manifestations of KD are essential for the diagnosis of the disease but do not predict the existence of coronary vasculitis. Skin manifestations of systemic PAN frequently affect small dermal vessels. Neurological involvement in cutaneous PAN does not indicate evolution toward systemic PAN. Future studies are needed to clarify the characteristics, the frequency, and the role of genetic abnormalities in medium-sized vasculitis or vasculopathy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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