Cutaneous Polyarteritis Nodosa

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Abstract

Cutaneous involvement of medium vessel vasculitis most commonly presents with features of inflammatory subcutaneous nodules, purpura, livedo reticularis, and ulceration. The clinical and histopathologic features of isolated cutaneous polyarteritis nodosa (c-PAN) are indistinguishable from the cutaneous involvement of systemic polyarteritis nodosa; however, these conditions differ in their prognosis and treatment. An approach to distinguish between these clinical entities is herein described. In addition, conditions commonly mimicking cutaneous polyarteritis nodosa are reviewed.

Keywords

Cutaneous · Polyarteritis nodosa · Livedo reticularis

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13.1 Introduction

Cutaneous polyarteritis nodosa (c-PAN) is a form of vasculitis that predominantly affects the medium-sized arteries of the dermis and the subcutaneous tissue without evidence of systemic involvement. Historically, it has been considered a subset of classical (systemic) polyarteritis nodosa (PAN). More recent nomenclature has suggested revised terminology classifying c-PAN as a single organ vasculitis (SOV) and recommended use of the term "cutaneous arteritis" [1]. However, given this entity has distinct clinical and histopathologic characteristics that differ from cutaneous small-vessel vasculitis, another subgroup of SOV, but analogous pathologic arterial findings indistinguishable from patients with systemic PAN that have cutaneous involvement, the term c-PAN remains in frequent use and will be utilized herein.

13.2 Epidemiology, Genetics, Pathogenesis

While the first descriptions of systemic PAN were reported in 1866 by Kussmaul and Maier (originally termed periarteritis nodosa) [2], it was not until 1931 that Lindberg described a separate cutaneous-limited form [3]. The true incidence and prevalence of c-PAN is unknown due to the combination of its rarity and lack of population-based studies. It is considered rarer than systemic PAN and accounts for less than 5% of described PAN variants [4]. The average age of presentation of c-PAN is in the fourth decade of life but can range from newborn (3–5 days old) to 81 years [5–8]. A female predominance has been reported with a male-to-female ratio ranging from 1:1.7 to 1:3.4 [5, 6]. Ethnic and geographic distribution has been less well-studied. Of reported cases, Caucasians appear to have a higher frequency of diagnosis, but c-PAN has also been observed in patients of African-American, Asian, and Middle-Eastern descent [5, 6, 9–11].

The etiology and pathogenesis of c-PAN remain unknown. Deposition of complement C3 and immunoglobulin M in the arterial walls has been observed through direct immunofluorescence and suggests the possibility of an immune-complex-mediated disease [12, 13]. Elevated levels of circulating antibodies, including anti-phosphatidylserine-prothrombin complex, have been noted with increased frequency in some series of c-PAN but have not been validated in all cases [14]. Although only three descriptions have been reported, c-PAN present in newborns of mothers with historical or active c-PAN at the time of delivery further supports a possible mechanism of transferred circulating antibodies resulting in arterial inflammation [7, 8, 15]. Mutations in the *CERC1* gene which encodes for adenosine deaminase 2, a plasma protein involved in the differentiation of leukocytes and endothelial cells have been observed in a small subset of patients with childhood-onset, refractory c-PAN suggesting genetic predisposition may also play a role [16, 17].

The majority of cases of c-PAN are considered idiopathic, but an associated medical condition or potential inciting event may be described in 30–40%. Inflammatory bowel disease has been observed in up to 6% of patients with c-PAN

in one series [5]. Antecedent or active infections have also been demonstrated among patients developing c-PAN. The most common, particularly in childhood-onset c-PAN, is Group A β hemolytic *Streptococcus* [18, 19]. Hepatitis B and C, parvovirus B19, as well as *Mycobacterium tuberculosis* have also been reported, but with notably lower frequency [6, 20–22]. Drug-induced c-PAN is notably uncommon; however, prolonged use of minocycline for treatment of moderate–severe acne vulgaris is a well-established culprit [23–26].

13.3 Clinical Manifestations and Laboratory Markers

13.3.1 Clinical Manifestations

The definitions of the commonly occurring skin findings observed in c-PAN are listed in Table 13.1. The most frequent early manifestation of c-PAN is small (0.5–3.0 cm), tender, palpable subcutaneous nodules which are present in 80–100% of patients [5, 6, 9]. The lower extremities are preferentially affected (95–100%), but nodules can also be located on the upper extremities (16–45%) and trunk (13%) [5, 9]. Head and neck involvement has been reported in 39% of c-PAN in one series [27] but has not been demonstrated with regularity in larger cohorts [5, 28]. Subcutaneous nodules are typically present concomitantly with ulceration or may precede sites of ulcer formation by several weeks to months; however, painful ulceration may be the only finding on initial examination in up to 10% of patients (Fig. 13.1) [5]. Ulcers may be superficial or deep and often have a punched-out appearance with a necrotic center (Fig. 13.2). Distribution is similar to subcutaneous nodules with lower extremity predilection (100%) and less commonly concomitant ulceration on the upper extremities (20%) and trunk (3–5%) [5, 6, 9].

Table 13.1 Definitions of skin findings in cutaneous polyarteritis nodosa

Term	Definition/description
Subcutaneous nodules	Abnormal skin tissue growth resulting from inflammation of the vessels with muscular walls present in the deep dermis and subcutis, commonly tender and erythematous
Retiform purpura	Non-blanchable hemorrhagic skin lesions resulting from the leakage of red blood cells into the skin due to vascular damage or occlusion following an angulated or branched distribution
Livedo reticularis/ racemosa	Mottled reticulated vascular pattern appearing as a net-like or lace-like purplish discoloration of the skin
Atrophie blanche	Ivory-colored stellate or angular scar, predominantly on the lower extremity, occurring after skin injury for which the presence of impaired blood supply resulted in poor or delayed healing
Ulceration	Disruption of the skin accompanied by disintegration of tissue which can result in complete loss of the epidermis and portions of the dermis and subcutaneous fat, resulting from reduced vascular perfusion. When present in the phalanges, this can lead to digital necrosis and gangrene

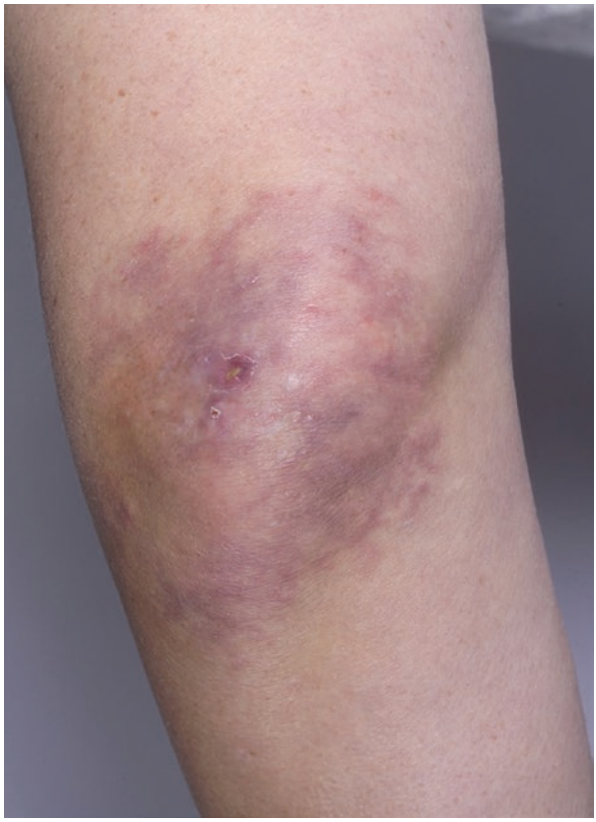

Fig. 13.1 Inflammatory retiform purpura with small subcutaneous nodules overlying cutaneous erosion involving the posterior elbow in patient with cutaneous polyarteritis nodosa

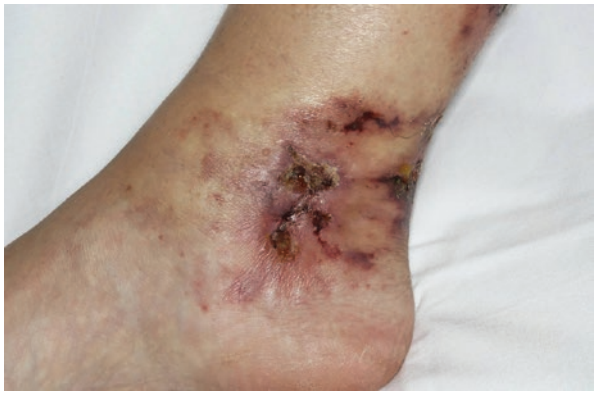

Fig. 13.2 Inflammatory retiform purpura and healing "punch out" ulcers of medial right ankle

Livedo reticularis and livedo racemosa are observed in 55–78% of patients and is noted in areas of dependency or points of pressure such as the legs, feet, buttock, and scapulae (Fig. 13.3) [5, 6, 9, 27]. Atrophie blanche is isolated to the lower extremities [6] and if present in a patient without evidence of venous insufficiency or thrombophilic state is strongly suggestive of an underlying necrotizing

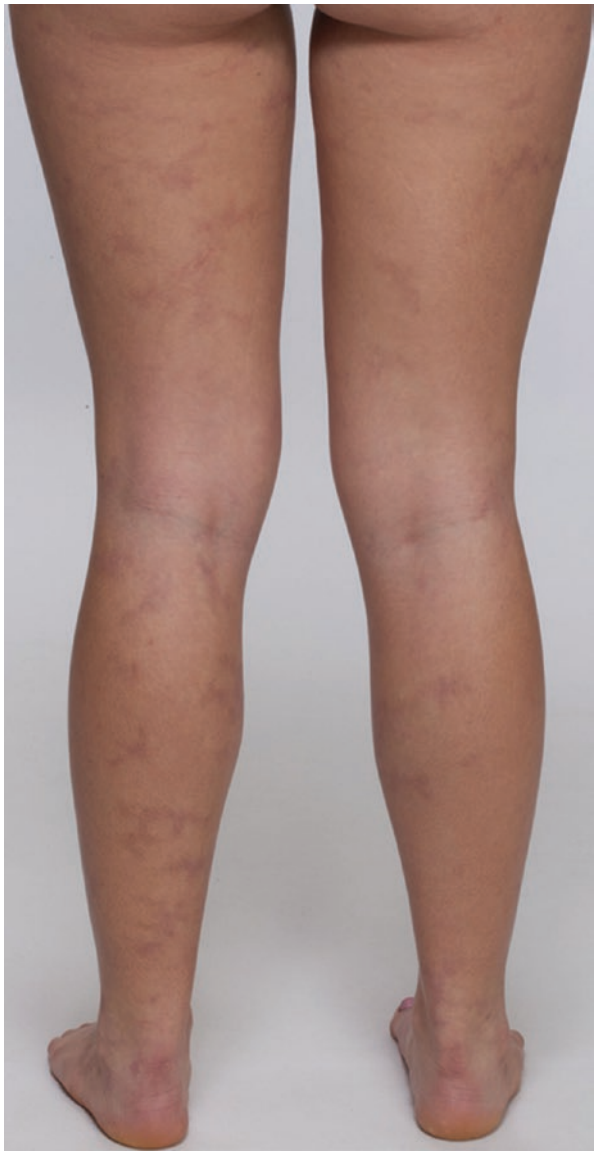

Fig. 13.3 Livedo racemosa involving the lower extremities in a young patient with cutaneous polyarteritis nodosa

medium-sized vessel vasculitis within the reticular dermis and subcutis [29]. Digital arterial involvement due to fibrinoid necrosis and thrombotic occlusion is exceptional but can lead to gangrene [30].

Localized symptoms resulting from sequelae of cutaneous inflammation are frequently seen and include edema, pain, and paresthesias. Myalgia and arthralgia may also occur but are typically mild–moderate and transient. Constitutional symptoms of fever, weight loss, and fatigue are observed in approximately one-third of patients.

13.3.2 Laboratory Markers

There are no specific or diagnostic laboratory parameters for c-PAN. Erythrocyte sedimentation rate and C-reactive protein elevation are observed in 60% of patients and mild anemia in 33% [5, 9]. Antinuclear antigen (ANA) has been observed in up to 28% of patients but is commonly low-titer [5, 6]. Rheumatoid factor, cryoglobulins, and antineutrophilic cytoplasmic antibodies should be negative although the latter may be present in low levels among patients with minocycline-induced disease. Urinalysis should be void of features suggestive of glomerular irritation, such as proteinuria or hematuria. Evaluation of potential infectious triggers is suggested. Hepatitis B and C serologies should be obtained but are less strongly associated with c-PAN in comparison to the systemic form. Due to associations with streptococcal infections, throat culture or antistreptolysin-O titers may be considered in patients with current or recent symptomatology. The association of *Mycobacterium tuberculosis* exposure with c-PAN appears to have geographic variance; therefore, the threshold for screening with tuberculin skin testing or interferon gamma release assay is dependent on the patient and population risk profile.

13.4 Histopathology

A skin biopsy is requisite to confirm the presence of c-PAN. Cutaneous medium-sized vessels are located at the dermal-subcutaneous junction, deep dermis, or subcutis. Therefore, an incisional or deep punch biopsy of adequate depth should be performed to obtain a specimen that includes the deep dermis and subcutis to provide appropriate assessment for c-PAN. Biopsies lacking sufficient subcutis sampling increase the likelihood of a non-diagnostic biopsy [31]. Preferred locations for biopsy are lesions that have recently developed within 24–48 h. If an ulcer site is chosen, sampling should ideally include parts of the central and peripheral ulcer as well as adjacent normal skin if feasible [31]. Care should be given to avoid areas of marked necrotic tissue as viable vessel architecture may not be present in such samples to sufficiently evaluate for the presence of arterial inflammation. Direct immunofluorescence is variable and non-diagnostic for the diagnosis of c-PAN but may provide assistance in ruling out the presence of the ulcerative or bullous variants of immunoglobulin A vasculitis (i.e., Henoch Schönlein purpura). Repeat biopsy may be required to accurately secure the diagnosis, particularly if initial samples are negative despite a high clinical suspicion.

The histopathologic features of c-PAN are dependent on the stage at which the sample is obtained. Early lesions show evidence of fibrinoid necrosis with vessel wall thickening due to infiltration of neutrophils, lymphocytes, and to a lesser extent eosinophils (Figs. 13.4 and 13.5). Later stage vessels demonstrate intimal proliferation resulting in luminal narrowing or occlusion. Chronic changes include vessel wall fibrosis with associated neovascularization around the occluded arteriole lesions [5].

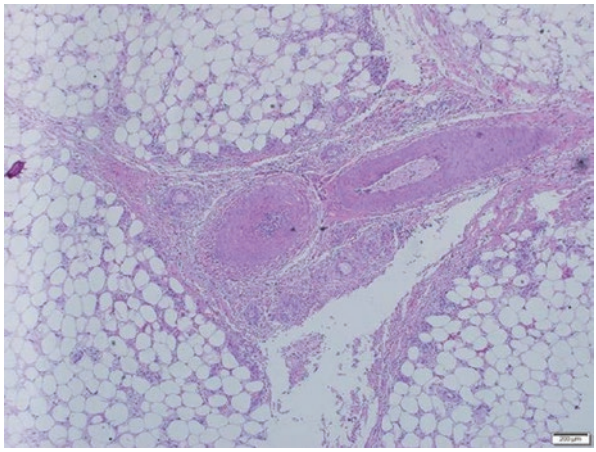

Fig. 13.4 Necrotizing vasculitis of medium-size vessel in the subcutaneous fat

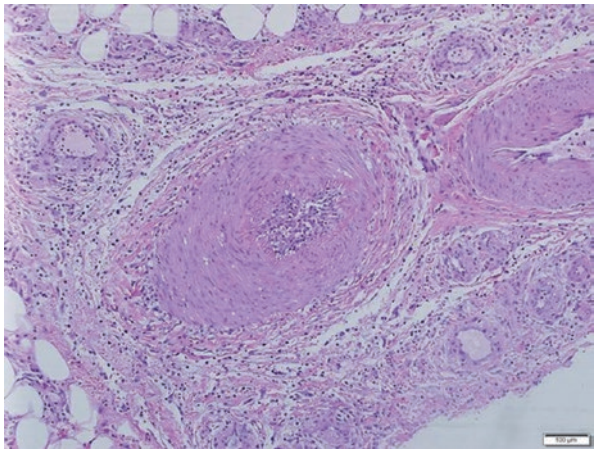

Fig. 13.5 Full-thickness inflammation and fibrinoid change of a medium-sized vessel with associated perivascular mixed inflammatory infiltrate

13.5 Diagnosis and Differential Diagnosis

The histopathological findings of c-PAN are indistinguishable from cutaneous involvement in patients with systemic PAN. While there are classification criteria for systemic PAN, currently there are no accepted classification or diagnostic criteria for c-PAN. Diagnostic criteria for c-PAN have been proposed by Nakamura and colleagues [9] but have not been formerly tested or prospectively validated (Table 13.2). Therefore, diagnosis of c-PAN is based on the presence of characteristic histopathological findings on skin biopsy in the appropriate clinical context in combination with exclusion of systemic involvement.

Although patients with c-PAN may have regional paresthesia and neuropathy due to localized cutaneous swelling, features of motor deficit (i.e., foot drop) should

Table 13.2 Nakamura drafted diagnostic criteria for cutaneous polyarteritis nodosa

1. Cutaneous manifestations—Subcutaneous nodules or Livedo or Purpura or Ulcers
2. Histopathological findings—Fibrinoid necrotizing vasculitis of small- and medium-sized arteries
3. Exclusion manifestations
   (a) Fever ≥38 °C for ≥2 weeks)
   (b) Weight loss (≥6 kg in 6 months)
   (c) Hypertension
   (d) Rapidly progressive renal failure, renal infarction
   (e) Cerebral hemorrhage or infarction
   (f) Myocardial infarction, ischemic heart disease, pericarditis, heart failure
   (g) Pleuritis
   (h) Intestinal hemorrhage or infarction
   (i) Peripheral neuropathy outside of the affected skin lesion area(s)
   (j) Arthralgia (arthritis) or myalgia (myositis) outside of the affected skin lesion area(s)
   (k) Abnormal arteriography (multiple microaneurysms, stenosis, occlusion)
4. Decision—A patient can be diagnosed with cutaneous polyarteritis nodosa if they fulfill both the cutaneous manifestations (1) and the histopathological findings (2) without the presence of any exclusion manifestations (3)

Adapted from Nakamura T. et al. Arch Dermatol Res 2009;301:117–121

raise the suspicion of systemic involvement with vasculitic neuropathy. In these circumstances, electromyogram and neurology consultation should be obtained to assist in determining if nerve biopsy is warranted. Abdominal pain is uncommon in patients with c-PAN and if present should prompt further investigation with advanced imaging such as an abdomino-pelvic computed tomography (CT) with angiography may assist in ruling out systemic PAN. Blood pressures should be obtained in all patients with c-PAN and if elevated evaluation of renal artery stenosis via ultrasonography or CT angiography should take place, given renal artery stenosis is a feature commonly observed in patients with systemic PAN. Due to an observed association of minocycline-induced disease, all patients presenting with c-PAN should be screened for current or recent long-term (>1 month) use of this medication.

In addition to systemic PAN, the differential diagnosis for c-PAN includes other disease entities that can involve inflammation of the subcutaneous fat as well as other vasculitides affecting the small- to medium-sized blood vessels. A summary of conditions that must be considered as well as their clinical features, laboratory parameters, and biopsy findings are listed in Table 13.3.

13.6 Treatment

To date there have been no controlled clinical trials evaluating treatment in patients with c-PAN. As such, therapeutic suggestions are based on limited retrospective studies, case series, and expert consensus. Agents chosen for therapeutic intervention in c-PAN depend on the severity of the cutaneous manifestations. Localized disease with limited, superficial inflammation may respond favorably to high

Table 13.3 Conditions considered in differential diagnosis of cutaneous polyarteritis nodosa

Condition	Common clinical features	Laboratory markers	Histopathology
Vasculitides			
Systemic polyarteritis nodosa	*Skin:* tender nodules, ulcers, livedo reticularis *Systemic:* hypertension, constitutional symptoms, visceral infarcts/aneurysm, testicular pain, mononeuritis multiplex	Elevated ESR, CRP	Identical to cutaneous polyarteritis nodosa
Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)	*Skin:* palpable purpura *Systemic:* sinonasal inflammation, pulmonary nodules, hemoptysis, glomerulonephritis	c-ANCA > p-ANCA PR3 > MPO Detectable in 80–90% Hematuria	Leukocytoclastic vasculitis
Eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome)	*Skin:* tender nodules on extensor surfaces, palpable purpura *Systemic:* sinusitis, asthma, pericarditis, myocarditis, eosinophilic gastroenteritis, mononeuritis multiplex	p-ANCA > c-ANCA MPO > PR3 Detectable in 30–60% Peripheral eosinophilia	Purpuric lesions with leukocytoclastic vasculitis Nodules with eosinophilic-rich granulomas
Microscopic polyangiitis	*Skin:* palpable purpura *Systemic:* glomerulonephritis, alveolar hemorrhage	p-ANCA > c-ANCA MPO > PR3 Detectable in 60–80% Hematuria	Leukocytoclastic vasculitis
IgA vasculitis (formerly known as Henoch–Schönlein purpura)	*Skin:* leukocytoclastic vasculitis more common; ulceration, bullous lesions less common *Systemic:* arthralgia, abdominal pain, hematochezia	Hematuria Serum IgA not reliable	Leukocytoclastic vasculitis with IgA (predominant) deposition on direct immunofluorescence
Behcet's syndrome	*Skin:* oral/genital ulceration, nodules, pseudofolliculitis erythema nodosum *Systemic:* intestinal ulceration, uveitis		Septal panniculitis with medium vessel vasculitis (in 50%)

(continued)

Table 13.3 (continued)

Condition	Common clinical features	Laboratory markers	Histopathology
Vaso-occlusive disease			
Livedoid vasculopathy	*Skin:* deep livedoid changes with reticular or angular pattern. Atrophie blanche and stellate ulceration may be present		Blood vessel thickening and focal thrombosis with endothelial proliferation and hyaline degeneration of the subintimal layer. Elastic laminae and vascular wall should be preserved. Vasculitis is absent
Antiphospholipid antibody syndrome	*Skin:* Livedo reticularis, livedo racemosa *Systemic:* recurrent venous > arterial clots, multiple miscarriages	Lupus anticoagulant Anti-cardiolipin Anti-β2 glycoprotein Anti-phosphatidylserine prothrombin complex	Fibrin thrombi in dermal vessels ± necrosis of overlying epidermis, dermal hemorrhage. No evidence of vasculitis
Inflammatory skin disease			
Pyoderma gangrenosum	*Skin:* Papule or pustule that expand into erosion/ulcer *Systemic:* fever variable		Perifollicular inflammation and intradermal abscess formation. Lymphocytic and/or leukocytoclastic vasculitis may be present. Palisading granulomas in vegetative variant
Erythema nodosum	*Skin:* tender, erythematous, non-ulcerated nodules, typically on the anterior lower leg (shin)		Septal panniculitis without vasculitis
Erythema induratum (nodular vasculitis, Bazin's disease)	*Skin:* tender, erythematous nodules, typically on the posterior lower leg (calf)		Lobular panniculitis with mixed infiltrate (lymphocytes, plasma cells, histiocytes, neutrophils, eosinophils); extravascular fibrinoid necrosis; vasculitis may involve the arteries, arterioles, veins, and venules in the subcutaneous septa or lobules

ANCA anti-neutrophil cytoplasmic antibody, *c-ANCA* cytoplasmic-ANCA, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IgA* immunoglobulin A, *MPO* myeloperoxidase, *p-ANCA* perinuclear-ANCA PR3, proteinase-3

potency topical glucocorticoids [32]. Non-steroidal anti-inflammatory medications appear to have marginal benefit and are typically insufficient for control of cutaneous disease but may be of use as an adjunct for mild to moderate pain control from swelling. Colchicine (0.6 mg twice daily) and dapsone (50–150 mg daily) have been suggested by some experts, but supportive data is limited and mostly extrapolated from use of these therapies in other cutaneous forms of vasculitis [33]. For patients with nodules, livedo, and particularly those with ulceration or features of ischemia, glucocorticoids are requisite with doses of 0.5–1.0 mg/kg/day initially, followed by slow taper over 2–6 months. Patients with refractory or recurring symptoms on steroid therapy or during tapering require additional steroid-sparing immunosuppressive agents. Among these, the most commonly used are low- to moderate-dose methotrexate (7.5–20 mg/week) and azathioprine (1.5–2.0 mg/kg/day) [5, 34–37]. Limited case reports have shown potential benefit among patients using anti-tumor necrosis factor alpha agents such as etanercept [38–40] and infliximab [41]. Cyclophosphamide is reserved for patients with severe ischemia, gangrene, or failure to respond to lower level immunosuppression [5, 37, 42, 43]. Use of prophylactic penicillin and tonsillectomy remain controversial [44, 45]. For patients with confirmed streptococcal infections at the time of c-PAN diagnosis or with recurrent infections corresponding with cutaneous relapses, an antibiotic trial can be considered but insufficient data is available to recommend routinely [42, 46, 47]. Intravenous immunoglobulin (1 g/kg/day for 2 days, monthly) has been used in rare recalcitrant cases but results are variable [48–50].

13.7 Prognosis and Disease Activity

While some patients may have a monophasic course, relapses and recurrences are common and disease duration may range from several months to greater than 20 years [5]. Patients with ulcers present at initial diagnosis tend to have a more chronic course [5, 37]. The greatest concern for patients and providers is whether c-PAN will subsequently convert into systemic PAN, the latter heralding a poorer prognosis. For patients with isolated c-PAN without features or findings of systemic PAN at the time of diagnosis, this transition is notably rare. Indeed, among combined cohorts of c-PAN with long-term follow-up, the frequency of isolated cutaneous to systemic PAN transition was only observed in 3 of 92 (3%) cases [6, 9, 28, 51].

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