Review

Cutaneous polyarteritis nodosa: a comprehensive review

Aaron Joseph Morgan[1], MD, and Robert A Schwartz[2], MD, MPH

[1]Dermatology and Pathology, New Jersey Medical School, Newark, NJ, USA, and [2]Dermatology, New Jersey Medical School, Newark, NJ, USA

Correspondence
Robert A Schwartz, MD, MPH
Dermatology, New Jersey Medical School
185 South Orange Avenue, Newark
NJ 07103, USA
E-mail: roschwar@cal.berkeley.edu

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Abstract

Cutaneous polyarteritis nodosa is a rare form of vasculitis relating to small-to-medium-sized arteries. Its etiology is unknown. Clinical manifestations include tender subcutaneous nodules, livedo reticularis, cutaneous ulcers and necrosis. Although it is distinct from systemic polyarteritris nodosa in that it lacks significant internal organ involvement, extra-cutaneous manifestations may be evident. Commonly encountered symptoms include fever, malaise, myalgias, arthralgias, and paresthesias. Exclusion of systemic polyarteritis nodosa is essential in diagnosis. The clinical course is chronic with remissions, relapses, and a favorable prognosis. Mild cases may resolve with nonsteroidal anti-inflammatory drugs. If more severe, treatment with systemic corticosteroids generally achieves adequate response; however, adjunctive therapy is often necessary to allow reduction in steroid dosage.

Introduction

Classic polyarteritis nodosa was the first systemic vasculitis to have been described. In 1866, Kussmaul and Maier[1] characterized this fatal condition which was originally called ''periarteritis nodosa.'' In 1903, Ferrari[2] described the transmural nature of arterial inflammation involved and proposed the term ''polyarteritis nodosa (PAN)''. It was not until 1931 that Lindberg[3] first recognized PAN limited to skin. Although cutaneous polyarteritis nodosa (CPAN) predominantly affects the skin, extra-cutaneous findings include fever, malaise, myalgias, arthralgias, and neuropathy. While systemic PAN frequently is first evident with the cutaneous findings of CPAN, multi-organ involvement in systemic PAN is pervasive, particularly in the kidneys, heart, and liver.[3] This distinction is essential.

Epidemiology

Systemic polyarteritis nodosa is rare; cutaneous PAN is even more so, the true incidence of which is unknown.[4] This cutaneous vasculitis affects all ages, ranging from 3 d to 81 years.[5–9] While most small studies do not demonstrate any gender predominance among patients with CPAN, a large one found a male : female ratio of 1 : 1.7.[9–11] The average age at the time of diagnosis was 43.5 years (range, 6–72) for patients without skin ulceration, and 47 years (range 16–81) for those with ulcers.[9] Another analysis of 22 patients with CPAN disclosed an age of onset ranging from 17 to 77 years with female patients comprising 86%.[12]

Etiology

The etiology of CPAN is unknown. Cutaneous polyarteritis nodosa is probably best viewed as an immune complex-mediated disease.[10,13] Direct immunofluorescence (DIF) often shows IgM and C3 deposits within affected arterial walls.[13,14] The 77.8% prevalence of IgM anti-phosphatidylserine–prothrombin complex among patients with CPAN has shaped the hypothesis that prothrombin bound to apoptotic endothelial cells induces an immune response, thus leading to the development of anti-phosphatidylserine–prothrombin complex antibodies.[13] These immunoglobulins presumably activate the classical complement pathway to cause CPAN.[13]

Cutaneous polyarteritis nodosa may reflect underlying disease, infection, or medication use. The most common inciting agent identified is Group A β hemolytic Streptococcus. A preceding upper respiratory infection with Streptococcus has been detected in many adults and children, employing anti-streptolysin O antibody titers or throat swab cultures.[8,9,15–17] Antecedent streptococcal upper respiratory infections were noted in all four children with CPAN in one analysis.[18] Cutaneous polyarteritis nodosa has also been reported 6 weeks following

necrotizing fasciitis caused by group A β hemolytic Streptococcus.[19]

A relationship between CPAN and hepatitis B infection (four out of nine patients) has been demonstrated.[20] Although hepatitis B routinely causes systemic PAN, the correlation between CPAN and the virus is not consistently seen.[9,21–23] Others have found a relationship to inflammatory bowel disease.[9,24–28] In one report, five cases of inflammatory bowel disease were identified among 79 patients with CPAN (four with Crohn's disease and one with ulcerative colitis).[9] In this study, 10% of the patients with CPAN-induced skin ulcers were afflicted with inflammatory bowel disease.[9] Case reports are available that associate CPAN with infection by hepatitis C, parvovirus B-19, and mycobacterium tuberculosis.[8,29–31] Minocycline-induced CPAN is a well documented phenomen.[32–36] It occurs after extended treatment of acne with minocycline and resolves following discontinuation of the drug.

Clinical manifestations

Cutaneous polyarteritis nodosa usually appears first as livedo reticularis (Fig. 1a), tender subcutaneous nodules, or cutaneous ulcerations.[9] Other findings include petechiae, purpura, cutaneous necrosis, autoamputations, and local extracutaneous manifestations. This most commonly occurs on the legs.[9,11,12,22,37] In fact, the legs are affected 97% of the time, followed by the arms in 33%, and the trunk in 8%.[9] Additional involvement of the head and neck has been noted in nine of 23 patients (39%) with CPAN.[11]

Small tender nodules that are more easily palpated than visualized are among the most common findings.[9,11,22,23,31,38] These nodules, with- or without livedo reticularis, are usually the first manifestation of the disease[16], and are the predecessor to ulceration in 50% of the cases.[9,13] Figure 1b illustrates several of these tender subcutaneous nodules on the finger of a 57-year-old woman. A typical "burst" pattern of irregularly shaped livedo reticularis around an ulcer is highly suggestive of CPAN.[11,39]

The most extensive retrospective study to date, analyzing 79 cases of CPAN, found that painful nodules on the lower extremities with edema and swelling were the most common clinical findings, seen in 80% of the cases.[9] Livedo reticularis was present in 56%, skin ulcers in 49%, and tender indurated plaques in 10%.[9] Another report of 16 patients described the presence of livedo reticularis in 14 (87.5%), and subcutaneous nodules in all patients analyzed.[13] Others have found painful subcutaneous nodules in only 30–50% of the patients.[11] Fifty per cent of patients also have skin ulcers and 31.3% have hemorrhagic lesions, ranging from petechiae to extensive purpura.[13]

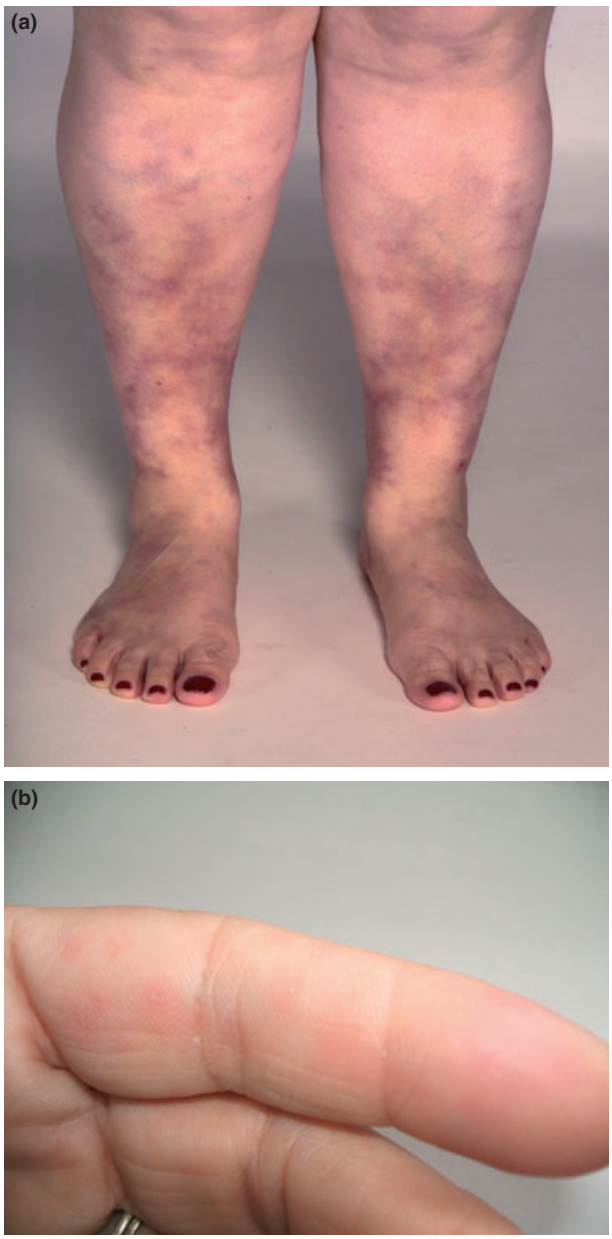

Figure 1 (a) Extensive livedoid pattern of the legs in a case of cutaneous polyarteritis nodosa (Courtesy of Lawrence E Gibson MD), (b) Subtle painful subcutaneous nodules on the finger of a 57-year-old woman

Extra-cutaneous manifestations of CPAN include constitutional symptoms, myalgias, arthralgias, and neuropathy (mononeuropathy and mononeuropathy multiplex).[9] The pathologic basis of these findings have not been established. Constitutional symptoms such as fever have been reported in 25–30% of the patients.[9,11] Neuropathy

has been demonstrated by electromyography in 22% of 79 patients with CPAN.[9] As many as 31.2% of patients with CPAN experience myalgias. The myositis and neuritis usually resolve within months.[4] Arthralgias occur in up to 69%.[11,13,23] Arthralgias are generally mild, transient, and are occasionally associated with radiographically established nondeforming arthritis. However, few patients had CPAN and a severe and progressive arthritis.[38,40,41]

Cutaneous polyarteritis nodosa runs a chronic, relapsing and remitting benign course. Although recurrences are typical, remission may occur spontaneously or following steroid therapy.[42] The clinical course may last months to several years, with acute symptoms or flares persisting for 2–8 weeks. The subcutaneous nodules may also take years to clear.[4] No relationship between the age of onset and the disease severity in CPAN has been demonstrated.[10] However, autoamputations of fingers and toes occur more frequently in patients under 10 years of age.[5–7,43] Otherwise, the prognosis of CPAN is favorable in both children and adults.[9]

Perhaps the most concerning aspect of CPAN is the possibility of progression to systemic PAN. Fortunately, the progression to systemic PAN has been only been documented in one study where two out of 20 patients with CPAN developed systemic PAN after 18 and 19 years of follow-up.[22] Other analyses have failed to demonstrate progression to systemic PAN. For example, over an average of 6.9 years of follow-up, none of the 79 patients with CPAN developed any signs of systemic vasculitis, and renal function remained within the normal range for age among all patients.[9] Other studies have followed patients for up to 30 years without any evidence of systemic involvement.[8,9,16,17]

Diagnosis

Cutaneous polyarteritis nodosa is a small- to medium-sized arterial vasculitis. There is no specific serologic test for CPAN; the diagnosis requires clinicopathologic correlation. The characteristic tender subcutaneous nodules on the lower extremities, in the background of livedo reticularis and/or cutaneous ulceration, should prompt suspicion for CPAN. Extra-cutaneous manifestations such as constitutional symptoms, myalgias, arthralgias, and paresthesias may also be evident. A biopsy specimen should be obtained to aid in the diagnosis.

When sampling tissue from a patient with suspected CPAN, it is essential to obtain an adequate sample. If ulceration is present, tissue sampling should be done with a deep incisional biopsy of the ulcer border, rather than a punch biopsy.[10] Adequate amounts of subcutaneous tissue, tissue central to the ulcer, and normal tissue should be obtained in order to optimize diagnostic yield. The most common reason for repeated biopsy in patients with CPAN is a lack of adequate tissue central to the ulcer border. This may be compounded by an inadequate amount of subcutaneous tissue in biopsy specimens.[44]

After histologic confirmation of the presence of vasculitis involving small- and/or medium-sized arteries, the diagnosis of CPAN can only be made following the exclusion of systemic PAN. Thus, systemic manifestations of PAN must be ruled out. Baseline measurements of arterial blood pressure, complete blood count, erythrocyte sedimentation rate (ESR), liver and renal function tests, cryoglobulins, anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor, and complement levels are indicated to exclude other causes of vasculitis, and to distinguish CPAN from systemic PAN. Further evaluation should be based upon specific symptoms; a search for a possible etiology should be undertaken.[16] Evaluation of symptomatology in CPAN includes electromyogram and muscle enzymes in patients with myalgias and muscle weakness, nerve conduction studies for those with paresthesias, stool guaiac with consideration of mesenteric angiography and colonoscopy for patients with abdominal pain, and renal angiogram for patients with renal dysfunction and/or hypertension.[16]

A causal factor in the onset of the vasculitis should also be sought employing ASO titers or throat swab culture, viral hepatitis serology, tuberculin skin testing, and an evaluation for possible concomitant medical conditions such as inflammatory bowel disease, infection, and a medication history.[16] Follow-up should take place twice yearly to yearly during asymptomatic periods, with increased frequency during exacerbations. At each routine check-up patients should be evaluated for possible systemic PAN. This encompasses a complete history and physical examination including vital signs, serologic testing of ESR, complete blood count, complement levels, and liver and renal function studies.[16]

Laboratory abnormalities

Laboratory abnormalities that are frequently encountered include mild anemia, moderate leukocytosis, and an elevated ESR.[11] Erythrocyte sedimentation rate is elevated in up to 60% of CPAN patients.[9] Anti-streptolysin O titers and/or throat swab cultures may be of value in detecting streptococcal infection, especially in children.[8,10,18] In general, serologic testing for syphilis, ANA, rheumatoid factor, and ANCA are negative. However, perinuclear-ANCA positivity has been found in an isolated case of CPAN[45] and is frequently evident with minocycline induced CPAN.[32–36]

A recent study correlating the presence of antibodies associated with anti-phospholipid syndrome in CPAN has found that 13 of 16 CPAN patients (81.3%) were positive for IgM anti-phosphatidylserine–prothrombin complex (anti-PS/PT) antibodies, while none of the controls were positive.[13] The remaining three patients were positive for either lupus anticoagulant (LAC) or IgG anti-PS/PT. In comparison to patients with systemic lupus erythematosus, patients with CPAN had significantly higher levels of IgM anti-PS/PT (mean ± standard deviation: 19.9 ± 12.4 units/ml for CPAN, vs. 5.7 ± 5.9 units/ml for systemic lupus erythematosus; $P < 0.01$). A total of seven patients (43.8%) with CPAN were positive for LAC. In LAC-positive patients with CPAN, a significant positive correlation was found between IgM anti-PS/PT and C-reactive protein ($r = 0.83$, $P = 0.021$).[13]

Histopathology

Deep incisional skin biopsy specimen, including the subcutaneous tissue, reveals the presence of leukocytoclastic vasculitis in the small- and medium-sized arteries of the deep dermis or hypodermis (Fig. 2). Four stages of histologic findings in CPAN have been described: degenerative, acute inflammatory, granulation tissue, and healed end-stages.[16] The degenerative stage is characterized by degradation of the arterial wall with deposition of fibrinoid material and partial or complete destruction of the internal and external elastic laminae.[4] The acute inflammatory stage involves a mainly neutrophilic infiltrate with eosinophils, around and within the arterial wall.[11] In the granulation stage, this infiltrate is composed of increased lymphocytes and macrophages, with intimal proliferation and thrombosis of the artery leading to ulceration. The healed end-stage shows a fibroblastic proliferation extending perivascularly.[22,46]

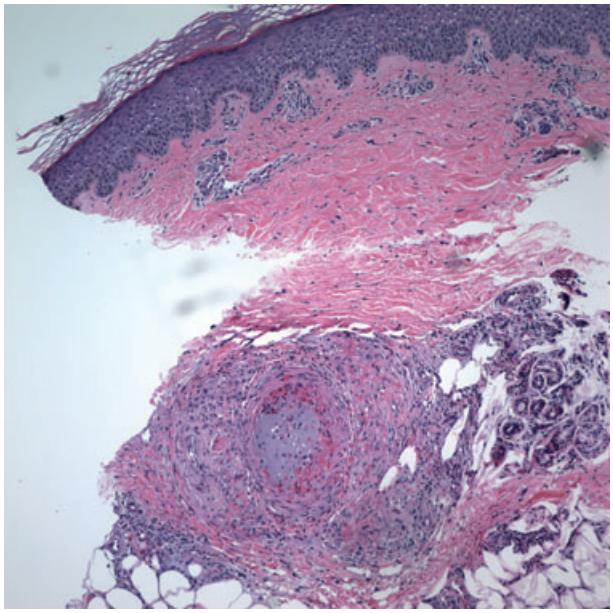

Figure 2 Histologic view of the lesion in Fig. 1 illustrating vasculitis of a medium-sized artery (Hematoxylin-eosin stain, original magnification ×10)

Direct immunofluorescence results are variable and of little value in distinguishing CPAN from systemic PAN. Direct immunofluorescence performed on nine CPAN skin biopsy specimens showed C3 deposits within necrotizing vasculitis in seven cases (77.8%), IgM deposits within the affected vessels of three samples, and the absence of deposits at the dermoepidermal junction in all.[13] An additional analysis employing DIF of 10 CPAN biopsy specimens demonstrated IgM deposition within the vessel wall in 60%, C3 deposition in 40%, and both C3 and IgM deposits in 20%.[14] Conversely, DIF of four patients in one sample population showed an absence of IgM and C3 in all cases, and the presence of perivascular fibrinogen in only one case.[16]

Differential diagnosis

Painful subcutaneous nodules on the lower extremities of patients with CPAN may suggest a diagnosis of erythema nodosum. However, nodules of erythema nodosum tend to be symmetric with a histologic picture of a septal panniculitis.[47] Cutaneous polyarteritis nodosa must be distinguished from systemic polyarteritis nodosa. Systemic PAN is characterized by identical cutaneous findings, and by the presence of systemic organ involvement including, but not limited to, liver, kidneys, and heart. It has also been suggested that the extra-cutaneous manifestations of peripheral neuropathy and myalgia in CPAN occur only adjacent to the cutaneous lesions, while they may be disparate in systemic PAN.[12]

Furthermore, other vasculitides require distinction, including microscopic polyangiitis (MPA), Wegener's granulomatosis, Churg–Strauss syndrome, erythema induratum, and urticarial vasculitis (Table 1).[48–50] Microscopic polyangiitis typically affects small vessels including capillaries, venules, or arterioles, especially in the kidneys and lungs. Wegener's granulomatosis and Churg–Strauss syndrome also affect small- to medium-sized vessels; however, pulmonary involvement, granulamatous inflammation, and serum ANCA positivity are common to both.[51] Urticarial vasculitis is a small-vessel vasculitis that occasionally requires differentiation from CPAN. It is seen with urticaria lasting greater than 24 h that may be accompanied by pain, burning, fever, and arthralgias.[52] However, the main finding in urticarial vasculitis remains urticaria, which does not occur in CPAN.

Table 1 Differential diagnosis of cutaneous polyarteritis nodosa

Differential diagnosis of cutaneous polyarteritis nodosa	Clinical manifestations	Histopathology	Laboratory findings
Systemic polyarteritis nodosa	Punched out ulcers, hypertension, renal failure, abdominal pain	Medium-sized arterial vasculitis	Leukocytosis, elevated ESR, thrombocytosis, hematuria, microaneurysms on MRI
Erythema nodosum	Erythematous, tender pre-tibial subcutaneous nodules	Septal panniculitis	
Microscopic polyangiitis	Palpable purpura, constitutional symptoms, glomerulonephritis, alveolar hemorrhage	Small- and medium- sized vessel vasculitis, involving the kidneys and lungs	p-ANCA > c-ANCA
Churg–Strauss syndrome	Asthma, allergic rhinitis palpable purpura, subcutaneous nodules	Granulomatous vasculitis	p-ANCA peripheral eosinophilia
Wegener's granulomatosis	Palpable purpura, cutaneous and oral ulcerations, upper and lower respiratory tract involvement, glomerulonephritis	Necrotizing granulomatous small vessel vasculitis	c-ANCA
Livedoid vasculopathy	Atrophie blanche with peripheral telangiectasia and punched out ulcers on ankles	Superficial dermal vasculopathy	
Erythema induratum	Erythematous nodules and plaques that may ulcerate on dorsal legs	Lobular or mixed panniculitis small- or medium- sized vessel vasculitis	
Urticarial vasculitis	Urticaria lasting >24 h	Leukocytoclastic vasculitis	Low complement levels may indicate more severe disease

ANCA, anti-neutrophil cytoplasmic antibody; ESR, erythrocyte sedimentation rate.

Treatment

Although treatment of acute systemic PAN and MPA involves high-dose corticosteroids and cyclophosphamide[53], less aggressive treatment for CPAN should be instituted first.[10,16,54] Mild cases, consisting of mainly nodules and livedo, may require only nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine.[15] In addition to their anti-inflammatory properties, NSAIDs are preferred for their analgesic affects.[10] Topical corticosteroids, such as 0.1% mometasonfuroate, have proven effective in some mild cases with only erythema, achieving complete regression in as little as 4 weeks.[37]

Patients refractory to more conservative treatment and those involving severe pain, ulcerations, necrosis, or extracutaneous symptoms such as myalgias, paresthesias, and arthralgias may require a more aggressive approach.[9,15,37,38,55] In these instances, corticosteroids are indicated, and have been proven to control acute exacerbations of CPAN. Prednisolone 30 mg daily or less is often effective[4,10,40], but a dosage of 1 mg/kg/d may be required.[9,15–17] Unfortunately, exacerbations occur with the tapering of the corticosteroids and adverse effects limit their long-term usage.[9,40] Additional medications may be necessary to maintain control of the disease and allow reduction in steroid dosage. Agents that have been used for this purpose include NSAIDs, colchicine, hydroxychloroquine, dapsone, azathioprine, cyclophosphamide, methotrexate, sulphapyridine, pentoxyphylline, and intravenous immunoglobulin.[8,9,17,40,55–58] These drugs are utilized in conjunction with corticosteroids and may be continued following the steroid taper. Their effectiveness has not been evaluated in a prospective trial; insufficient evidence exists to recommend any specific drug combination. Immunosuppressive agents are frequently effective in CPAN resistant to high-dose corticosteroids, and should be reserved for these severe relentless forms.[9,16,56,59]

Penicillin or a suitable alternative is indicated in patients with antecedent streptococcal infection; prophylaxis may be necessary in patients whose relapses correspond to recurrent infections.[9,11,60] Thus, assessment of anti-streptolysin O titer is recommended in all patients with CPAN, especially children.[9,61] Relapses sometimes occur despite penicillin prophylaxis.[8]

The prognosis of CPAN is favorable with no known mortality from the disease itself. The course is chronic with relapses and remissions that may occur spontaneously or following treatment.[42] Cutaneous polyarteritis nodosa has the tendency to "slowly fade away".[4] Treatment may hasten recovery and result in the rapid improvement of constitutional symptoms, myalgias, arthralgias, paresthesias, nodules, and ulcers.[17,37,56,58]

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