Cutaneous polyarteritis nodosa in three patients: disease course and our experience leading to faster remission

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Abstract

We present three new cases of cutaneous polyarteritis nodosa with a follow-up ranging from 38 to 49 months, describing their clinical and histological findings, as well as treatment options leading to sustained remission. All patients met the criteria for diagnosis. The presence of extracutaneous symptoms and laboratory analysis differed among our patients, as did various elements of the workup in comparison to published studies. We concluded that dapsone alone, or in combination with systemic steroids, proved superior and highly effective despite being less frequently used. More aggressive therapy for shorter intervals could lead to quicker remission of cutaneous lesions and symptoms without chronic relapses, which are commonly noted.

Keywords: dapsone, livedo reticularis, polyarteritis nodosa, vasculitis

Introduction

Polyarteritis nodosa (PAN) is a segmental necrotizing vasculitis predominately affecting small and medium-sized arteries. It is a potentially life-threatening systemic disease that can involve any organ, most commonly the liver, heart, kidney, and/or gastrointestinal tract, while often sparing the lungs. Alternatively, cutaneous PAN (cPAN) is skin limited, and shows a benign, chronic course with remissions and relapses but favorable prognosis. cPAN predominately affects women, with a mean age of 39 (1), but there have been rare cases reported in children (2, 3). Whether cPAN is a skin-restricted variant of PAN or a separate clinical entity is debated. Despite lacking internal organ involvement, cPAN is associated with common extracutaneous signs and symptoms such as fever and malaise, with myalgia and peripheral neuropathy limited to the same area as skin lesions (4).

This report presents three new cases of cPAN with a follow-up ranging from 38 to 49 months, describing their clinical findings and treatment options leading to sustained remission. All patients met the criteria for diagnosis with typical cutaneous lesions (nodules, livedo reticularis, and ulcers) and histopathological findings. Upon thorough systemic evaluation for PAN, no internal organ involvement was detected during the diagnosis and subsequent follow-up.

Case reports

Patient 1

A 45-year-old Caucasian female was admitted to the hospital with a 10-year history of erythematous papules and nodules on the lower extremities (Fig. 1a). Concomitant diseases included arterial hypertension. The patient reported mild arthritis, peripheral neuropathy, and myalgia, which were all localized to the affected extremities. Laboratory tests and clinical features are listed in Table 1 (for all patients). A deep incisional biopsy was performed, confirming cPAN (Figs. 2a, b). A combination of prednisone 40 mg daily (0.57 mg/kg/day) and methotrexate 15 mg/weekly was initi-

ated but subsequently stopped after 3 months due to ineffectiveness and gastrointestinal side effects. Dapsone 100 mg daily and prednisone 25 mg every other day (EOD), with tapering to prednisone 5 mg EOD over the course of 6 months, led to remission of cutaneous lesions. Maintenance therapy of low-dose prednisone (5 mg EOD) was continued for 12 months (lesion-free during this period) and then discontinued. For the following period, there were no recurrences (Fig. 1d).

Patient 2

A 68-year-old Caucasian female developed erythematous nodules and multiple ulcers on her lower extremities over the course of 2 months (Fig. 1b). She denied extracutaneous symptoms, including fever, headache, peripheral neuropathy, myalgia, and arthralgia. Her medical history was positive for arterial hypertension and diabetes mellitus type 2. Deep incisional biopsy confirmed cPAN (Figs. 2c, d). Therapy with oral prednisone 50 mg daily (0.59 mg/kg/day), subsequently tapered, led to remission in 6 months. Relapse occurred 5 months after prednisone was discontinued, and dapsone 100 mg daily was initiated, leading to clearance of lesions within 1 month. The same dosage was continued for 5 months, and then a maintenance dose of dapsone 50 mg daily was administered for 12 months in total. The patient was lesion-free during this entire period and during the follow-up period (Fig. 1e).

Patient 3

A 33-year-old Caucasian female was admitted with a 4-month history of multiple erythematous, infiltrating nodules along with livedo reticularis (Fig. 1c). She presented with intense, localized arthralgia, myalgia, and peripheral neuropathy. Furthermore, she presented a diagnostic challenge, with a 10-year history of recurrent fevers of unknown etiology, anemia, hepatosplenomegaly, gastric pain, and headaches prior to cutaneous symptoms. An extensive workup was performed: esophagogastroduodenoscopy revealed chronic gastritis; colonoscopy, fecal occult blood test, and biopsy revealed no bleeding or pathological changes with intact

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vasculature; and the symptoms were diagnosed as irritable bowel syndrome. The headaches were diagnosed as migraines. Positron emission tomography scan revealed increased glucose uptake in the spleen leading to splenectomy. Histopathological analysis of the spleen revealed sarcoidosis. Recurrent fevers ceased after splenectomy. In conclusion, systemic PAN was excluded in the patient. cPAN was confirmed by cutaneous punch biopsy (Figs. 2e, f). Due to elevated antistreptolysin O (ASO), the patient received amoxicillin without clinical effect. Further treatment included prednisone 30 mg daily (0.5 mg/kg/day) with slow tapering and nonsteroidal anti-inflammatory drugs (NSAIDs) over 3 months, leading to remission. After splenectomy in May 2018, despite cPAN resolution, prednisone was given for sarcoidosis for the following 12 months. Since then, with no maintenance therapy, remission lasted during the entire follow-up period (Fig. 1f).

Discussion

Specific and universal criteria for diagnosis and treatment of cPAN are lacking. The etiology and exact cause are also unknown and the immunological mechanisms applicable to systemic vasculitides are not applicable for cPAN (5). According to previous diagnostic criteria of the American College of Rheumatology, cutaneous lesions and at least one extracutaneous manifestation, even if limited, with the correct histopathological finding could be classified as PAN (6). Problems can arise due to differences in therapy and prognosis between cPAN and PAN. Accepted opinion now states that cPAN diagnosis can be made when associated symptoms, peripheral neuropathy, and/or muscular symptoms are localized to the area of cutaneous lesions. Nakamura et al. proposed new diagnostic criteria, including both cutaneous

Table 1 | Clinical features, symptoms, laboratory findings and workup.

	Patient 1	Patient 2	Patient 3
Age at diagnosis: years, sex	45, female	68, female	33, female
Duration of symptoms at diagnosis	10 years	2 months	4 months
Follow-up time	38 months	48 months	49 months
Associated diseases before presentation of symptoms	Hypertension	Hypertension, diabetes mellitus type 2	Sarcoidosis, anemia, hepatosplenomegaly
Location of skin lesions	Legs	Legs	Legs
Cutaneous manifestations at diagnosis			
Nodules	+	+	+
Livedo reticularis	–	–	+
Purpura	–	–	–
Ulcers	–	+	–
Necrosis	–	–	–
Extracutaneous symptoms at diagnosis	Yes	No	Yes
Arthralgia	+	–	+
Myalgia	+	–	+
Peripheral neuropathy	+	–	+
Fever	–	–	+
Headache	–	–	+
Abdominal pain	–	–	+
Laboratory results and complementary workup			
CBC with differential	WNL	WNL	WNL
CRP (mg/l)	WNL	N/A	N/A
ESR (mm/h)	$\uparrow$ 22, 28	$\uparrow$ 88, 52	$\uparrow$ 100, 38
Hemostasis	$\downarrow$ aPTT PT, INR, fibrinogen: WNL	$\uparrow$ Fibrinogen	Fibrinogen WNL, $\uparrow$ D-dimer
Urinalysis	WNL	WNL	WNL
Hepatogram	WNL	WNL	WNL
Creatinine, BUN	WNL	WNL	WNL
Remaining biochemical analysis	WNL	WNL	β2−microglobulin: WNL $\downarrow$ Fe, TIBC, transferrin $\uparrow$ D-dimer
Hepatitis serology (HbsAg, anti-HCV)	N/A	–	–
ASO (IU/ml)	N/A	WNL	$\uparrow$ 720, 664
Throat and nose swab	WNL	N/A	N/A
Quantiferon TB Gold Test	N/A	–	–
Imaging	N/A	CXR lungs: WNL	N/A
Stool culture	–	N/A	–
Complement (C3, C4)	N/A	WNL	WNL
ANA	–	–	+ (1:80)
ANCA	–	–	–
RF	N/A	N/A	WNL
Other immunological analysis	ENA screen: negative	TPHA, cryoglobulin, cryofibrinogen: negative	$\uparrow$ IgA; VDRL, CIC, ACL, IgG, IgM: negative
Additional diagnostic testing	Doppler U/S legs: WNL	N/A	SPEP: WNL

+ = symptoms present / analysis positive, − = symptoms not present / analysis negative, $\uparrow$ = elevated, $\downarrow$ = decreased, WNL = within normal limits, N/A = not applicable / not done, CBC = complete blood count, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, aPTT = activated partial thromboplastin time, PT = prothrombin time, INR = international normalized ratio, BUN = blood urea nitrogen, Fe = iron, TIBC = total iron binding capacity, HBsAg = hepatitis B surface antigen, anti-HCV = antibodies against hepatitis C virus, ASO = antistreptolysin O titer, CXR = chest X-ray, ANA = antinuclear antibody, ANCA = antineutrophil cytoplasmic antibodies, RF = rheumatoid factor, ENA = extractable nuclear antigen, TPHA = *Treponema pallidum* particle agglutination assay, VDRL = venereal disease research laboratory test, IgA = immunoglobulin A, IgG = immunoglobulin G, IgM = immunoglobulin M, CIC = circulating immune complexes, ACL = anti-cardiolipin antibody, U/S = ultrasound, SPEP = serum protein electrophoresis, TB = tuberculosis.
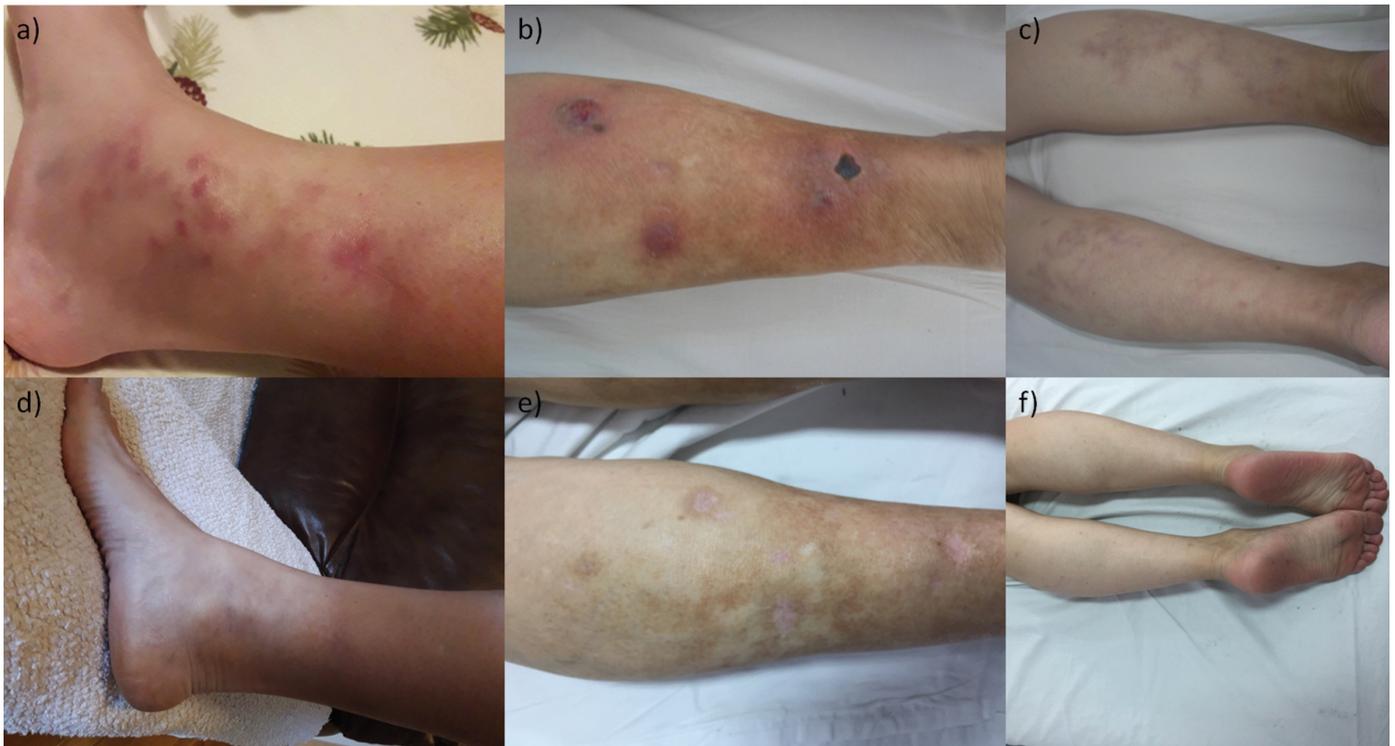
Figure 1 | (a–c) Skin lesions upon admission in Patients 1–3, respectively; (d–f) skin lesions after a follow-up at 27 months (Patient 1), 37 months (Patient 2), and 38 months (Patient 3), respectively.
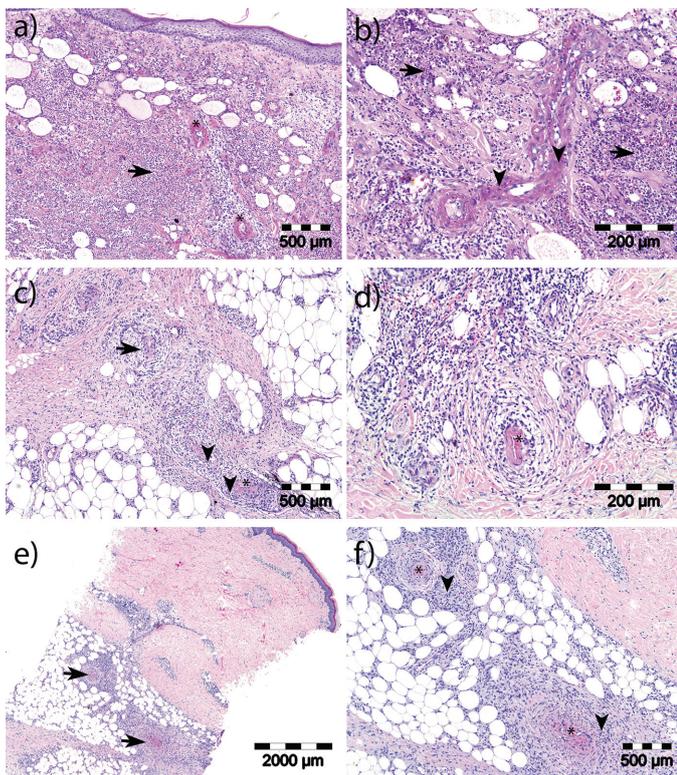

Figure 2 | (a, b) Deep incisional biopsy in Patient 1 showed intimal fibrinoid necrosis and neutrophils in superficial (asterisk) and deeper blood vessels (arrowhead) and diffuse interstitial infiltration with neutrophils (arrow; H&E stain, magnification 100× and 200×, respectively); (c, d) deep incisional biopsy in Patient 2 showed fibrinoid necrosis of medium-sized arteries (asterisk), intra- and perivascular infiltration with neutrophils (arrowheads), and fibroblastic proliferation in the vessel wall with narrowing of the lumen (arrow; H&E stain, magnification 100× and 200×, respectively); (e, f) punch biopsy in Patient 3 showed changes in deep-seated medium-sized arteries (arrows) consisting of intimal fibrinoid necrosis (asterisk) and perivascular and intravascular neutrophils (arrowheads; H&E stain, magnification 40× and 100×, respectively).

manifestations (nodules, livedo, purpura, and ulcers) and histopathology (fibrinoid necrotizing vasculitis of small and medium-sized arteries), without any exclusion of manifestations (4). In our experience, our patients fit Nakamura's criteria (Patient 3 had to undergo detailed examination to exclude PAN).

Peripheral neuropathy and myalgia/myositis have been reported in 22 to 66% of patients (4, 5, 7–10). Clinically, depending on the study, nodules are the predominant lesion (82–100% patients), followed by livedo (45–80%) and ulcers (20–49%) (4, 5, 7–10). This aligned with our findings. All our patients had nodules, with Patient 2 also having ulcers and Patient 3 having livedo. The accepted consensus is that cPAN has a chronic, benign course without systemic involvement. Daoud et al. reported no progression to PAN in 79 cases of cPAN (5). Nonetheless, long-term monitoring is recommended because rare cases of cPAN have been reported to progress to PAN after many years (8).

Laboratory analyses tend to be non-specific in cPAN. A study of 16 cases of cPAN by Ishiguro et al. reported accelerated erythrocyte sedimentation rate (ESR) in five cases and complement elevation in 10 cases, and nine patients were antinuclear antibody (ANA) positive (11). Despite our smaller number of cases, this is a stark contrast to our patient group, in which all three had accelerated ESR and only one was ANA positive. None had elevated components of complement. Our findings are similar to a case series by Bauza et al. of four patients with ESR elevated in all patients (3). Furthermore, although hepatitis B and C have been associated with the pathogenesis of PAN, only isolated cases have been reported for cPAN (12), which is in line with our results because both Patients 2 and 3 were negative when tested. Recessive loss of function of mutation of adenosine deaminase 2 has been shown to cause PAN with a heterogenous clinical expression (13) and has been suggested as a genetic cause of cPAN in some patients (14).

There are no specific guidelines for treating cPAN. Generally, for

treating underlying inflammation, NSAIDs, topical or intralesional corticosteroids, and, in more severe cases, oral corticosteroids are considered first-line therapy. Second-line therapy includes methotrexate (7.5–15 mg/week), dapsone, hydroxychloroquine, and intravenous immunoglobulin in more severe cases (15). Chen et al. reported 10 out of 16 cases treated with NSAIDs and six with low-dose prednisone (< 20 mg/daily) (8). Ishiguro et al. reported 11/16 patients treated with NSAIDs, 1/16 with dapsone and NSAID, and 5/16 with prednisone 10–35 mg daily initially; good control was maintained with prednisone 2–5 mg daily (11). In our experience all patients received oral prednisone with initial doses of 30–50 mg (range 0.50–0.59 mg/kg/day), which are higher than in other studies, but tailored toward the patients' body weight and clinical manifestations. For example, Patient 2 was initiated on a slightly higher dose (0.59 mg/kg/day) because she was the only patient presenting with ulcers with inflamed and active borders. Patient 3 received prednisone (for sarcoidosis, as well as cPAN) only after extensive evaluation was finished, and this led to remission in skin lesions without any additional medication needed. In general, patients were treated with prednisone on consecutive days until clinical improvement and then switched to alternate day regimens with gradual tapering of doses. Patient 1 received methotrexate 15 mg weekly combined with low-dose prednisone, which was ineffective compared to dapsone and prednisone. In this case, methotrexate along with prednisone failed to induce remission during the first 3 months while also causing gastrointestinal side effects. This warranted switching to dapsone 100 mg daily, while keeping a lower dose of prednisone 25 mg EOD, which quickly led to remission of cutaneous lesions, thus showing dapsone to be more effective; moreover, no side effects were noted. Furthermore, Patient 1 had the longest duration (10 years) of symptoms before diagnosis and was the most resistant to treatment. We can speculate about a possible association between longer duration of active disease and cPAN chronicity with increased risk of therapeutic resistance.

Relapse occurred only in Patient 2, 5 months after discontinuing low-dose prednisone; quicker remission was achieved with dapsone 100 mg daily and proved to be more effective for treatment and maintenance therapy. Dapsone 50 mg daily maintenance therapy was used for a longer period, 12 months, to avoid another relapse. After discontinuation, no relapse occurred and dapsone presented no side effects. Despite the small sample size, dapsone alone, or in combination with systemic steroids, proved to be superior and highly effective with no side effects despite being less frequently used due to being considered second-line treatment (11, 15). Some authors suggested ASO titer determination in all cPAN patients (16). In our experience, antibiotic therapy alone in our ASO-positive patient had no discernible clinical effect. Overall, all our patients were treated for shorter intervals with shorter time to remission of cutaneous lesions and symptoms, and without chronic relapses, which are commonly noted in other studies.

Conclusions

cPAN can be a tricky diagnosis. It has a favorable benign course with nonspecific laboratory markers, and so diagnosis relies on clinical symptoms and histopathology. Furthermore, despite our limited number of patients and short follow-up, our experience showed that more aggressive therapy, such as higher doses of corticosteroids or second-line agents such as dapsone, alone or in combination with corticosteroids, could be more beneficial for faster achievement of remission, a shorter therapy period, and decreased incidence of relapse.

Acknowledgments

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