Cutaneous polyarteritis nodosa

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SUMMARY

Classic polyarteritis nodosa (PAN) is a segmentary leucocytoclastic vasculitis that affects small- and medium-sized arteries. In 1931, Lindberg described the existence of a cutaneous variant of PAN, without visceral involvement and with a more favourable prognosis. We present four patients diagnosed with cutaneous PAN in our hospital between 1987 and 1998. The study group was composed of three women and one child, whose ages ranged from 11 to 70 years old. The follow-up period was between 2 and 13 years. Each patient was submitted for an initial clinical, histological and laboratory evaluation and subsequent follow-up. The presence of nodules was the most frequent cutaneous lesion, preferentially located in the lower limbs. The erythrocyte sedimentation rate was the only parameter that was altered in all patients. Cutaneous biopsies from all patients showed a segmentary leucocytoclastic vasculitis in the arteries of the deep dermis and⁄or hypodermis. Direct immunofluorescence was positive in just one patient. No visceral involvement was found in any patient. There is confusion about the correct definition of cutaneous PAN. Some clinical findings, such as nodules or livedo reticularis, typical of cutaneous PAN suggest a good prognosis; however, we consider that it is necessary to evaluate these patients for systemic involvement for the possibility of arteritis in other organs as the term polyarteritis suggests.

KEY WORDS

Classic polyarteritis nodosa, cutaneous polyarteritis nodosa, livedo reticularis, nodules

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Classic polyarteritis nodosa (PAN) is a segmentary leucocytoclastic vasculitis that affects small- and medium-sized arteries.[1] Although any organ may be involved, those principally affected are the kidney, liver, heart or the gastrointestinal tract. If left untreated, the disease is fatal.[2] In 1931, Lindberg described the existence of a cutaneous variant of PAN that was not associated with visceral symptoms and that presented a more favourable prognosis.[3] Subsequently, many cases of cutaneous PAN have appeared in the literature confirming its benign character.

In this paper we present four new cases of cutaneous PAN. As the result of a medium- and long-term study based on laboratory and clinical findings, we consider that the localized and benign nature of this disease was confirmed in each case.

PATIENTS AND METHODS

We have retrospectively reviewed the clinical and laboratory data obtained during the period between 1987 and 1998 from four patients diagnosed with cutaneous PAN. The patients included in this study all fulfilled the following criteria: cutaneous lesions typical of PAN (nodules, livedo, purpura) and cutaneous biopsies characterized by the presence of leucocytoclastic vasculitis of small- and medium-sized vessels. Moreover, no visceral complications were detected at the time of diagnosis nor during the evolution of the disease. The study group comprised three women and one child whose ages ranged from 11 to 70 years of age. The follow-up period was between 2 and 13 years. Each patient was submitted for an initial clinical, histological and laboratory evaluation, and subsequent follow-up.

RESULTS

The most frequent cutaneous lesion in all patients was the presence of nodules with or without livedo reticularis (Fig. 1) and this was the first manifestation of the disease in all cases (Table 1). In patient 4 skin ulceration was also observed. In all cases, the cutaneous lesions were localized in the lower limbs, although patient 1 also had lesions in the arms. The paediatric patient developed several extracutaneous symptoms (Table 1). In the adult group, patients 2 and 3 presented arthralgias, whereas patient 2 also presented occasional headache. Other related diseases such as chronic sinusitis (patient 4) and recurrent tonsillitis (patient 1) were observed. In addition, patient 2 developed discoid lupus erythematous lesions several years after the diagnosis of PAN, although she did not fulfil the diagnostic criteria for systemic erythematous lupus established by the American Rheumatism Association. Other relevant findings are reflected in Table 1.

The erythrocyte sedimentation rate (ESR) was the only parameter that was altered in nearly all patients (Table 2). In one patient a light haematuria was detected in an isolated analysis that was not confirmed in later analyses. Another patient registered an elevated antistreptolysin O antibody (ASO) titre that was probably related to a chronic

tonsillitis. Serological tests for hepatitis B and C, brucella, syphilis and salmonella, and the tuberculin test were all negative when carried out (Table 2).

Chest X-ray, electrocardiogram and abdominal ultrasonography, were normal in all patients. In patient 3, a renal angiogram was performed that did not show any alterations. Patient 2 presented irregularities in electromyograms showing a diminished response in the anterior tibial and quadriceps muscles. No alterations in either motor or sensorial conduction speeds were observed in the cases studied (Table 2).

Deep incisional biopsies were obtained from all the patients, showing the presence of a segmentary leuco-cytoclastic vasculitis in the arteries of the deep dermis and⁄or hypodermis, with vascular occlusion in each case (Figs 2 and 3). Segmented fibrinous deposits that stained with fuchsin appeared at the wall of the damaged vessels. The inflammatory infiltrate was lymphocytic or of a lymphomacrophagic type with a smaller neutrophilic component. Direct immunofluorescence showed the presence of perivascular deposits of fibrinogen in only one case (patient 2). Granulomas were not observed. In patient 3, a dense interstitial inflammatory eosinophilic infiltrate was observed that was not associated with vascular damage. In all cases, the small vessels of the middle and upper dermis did not show any alterations. In addition, the presence of necrosis, both in the subcutaneous fat lobules and the epidermis were observed, probably as a result of ischaemia. No histological differences were found between biopsies from the adults and the child.

Treatment was initially carried out with oral prednisone in nearly all patients at doses that varied between 20 and 60 mg daily. One of the adult patients was partially controlled with a dose of 20 mg daily and a decrease in the number of nodules was seen a few months after beginning the treatment (patient 2, Table 3). Another patient from this group required high doses of corticosteroids along with sulphone, finally achieving a disappearance of the lesions (patient 3, Table 3). Patient 4 presented persistent cutaneous lesions in spite of the treatment with prednisone and non-steroidal anti-inflammatory drugs (NSAIDs). At the end of the study patient 3 is currently free of lesions without any treatment and patient 2 remains without lesions but continues under treatment with low doses of prednisone. The remaining patient is still treated with low doses of oral prednisone but in the continued presence of isolated cutaneous lesions. So far, no visceral involvement has been observed in any patient. The paediatric patient initially required the association of prednisone and cyclophosphamide to achieve response as well as various cycles of antibiotics for chronic tonsillitis. To date, he remains asymptomatic without treatment.

DISCUSSION

Cutaneous PAN is considered a localized form of PAN. Diagnosis requires the presence of cutaneous lesions typical of PAN (nodules, livedo, ulceration, purpura), the demonstration of a leucocytoclastic vasculitis in the arteries of the deep dermis or

hypodermis, with or without associated fibrinoid necrosis; and the absence of visceral involvement at the time of diagnosis.[1] The clinical manifestations are characterized by the presence of cutaneous nodules and livedo reticularis, mainly localized at the lower extremities.[2] Other symptoms may be associated with cutaneous PAN, including constitutional symptoms, musculoskeletal and neurological symptoms, limited to the affected areas.[1,4] The ESR is usually the only laboratory parameter altered in most of the patients with cutaneous PAN, as occurred in all our patients.[2] In contrast, the typical cutaneous lesions in the systemic form are usually palpable purpura,[2,5] and the presence of nodules, livedo, ulcers, necrosis or gangrene being rare. Systemic PAN is also often associated with vasculitis in other organs such as the kidney, liver, heart and the gastrointestinal tract.[2] Characteristic findings in systemic PAN that differentiate it from the cutaneous form, are the presence of leucocytosis and eosinophilia, persistent proteinuria, high blood pressure, and diffuse neuromuscular involvement all giving rise to a poor short-term prognosis.[6,7] Two of our patients diagnosed with cutaneous PAN had high blood pressure for 1–2 years before the appearance of the cutaneous lesions, which was being controlled by antihypertensive treatment. However, the diagnosis of arterial hypertension that is readily controlled and that does not have any repercussions in the retina, prior to the appearance of cutaneous lesions, is not indicative of systemic PAN.[8]

PAN is a rare disease in childhood.[9] Although the systemic form is less favourable in children than in adults,[10] the prognosis of cutaneous PAN is the same in childhood as it is in adults.[2] The only child in our study presented many constitutional symptoms but showed a more favourable prognosis than the adults, as the cutaneous lesions disappeared after 2–3 years of treatment and he remained without them until the end of the time of study.

Histopathological studies are necessary for the accurate diagnosis of this disease. A deep incisional biopsy, including subcutaneous tissue, is needed. The microscopic findings of cutaneous PAN can be divided into four stages: (i) degenerative stage with degeneration of arterial wall and deposition of fibrinoid material and partial or complete destruction of internal and external elastic laminae;[11] (ii) acute inflammatory stage with an infiltrate mostly composed of neutrophils with some eosinophils around and within the arterial wall;[6] (iii) granulation tissue stage with an infiltrate also containing lymphocytes and macrophages and intimal proliferation and thrombosis with occlusion of the lumen leading to ulceration; and (iv) healed end-stage with fibroblastic proliferation extending in the perivascular area.[4,12] The small vessels of the middle and upper dermis may show only a non-specific lymphocytic perivascular infiltrate and focal panniculitis surrounding the involved artery may be present in contrast to the more diffuse form usually found in other nodular diseases. All of our patients were confirmed to have histological lesions of acute inflammatory and granulation tissue stages in their skin biopsies. With regard to direct immunofluorescence findings, the presence of IgM or C3 deposition in the vessel walls has been found in some patients, not only in the deep involved artery but also in the superficial and uninvolved small vessels.[13,14] In this

study, direct immunofluorescence was carried out in three patients and only one case showed the presence of perivascular fibrinogen.

The aetiology of cutaneous PAN is unknown. Some authors think that immunological mechanisms might only participate in systemic vasculitides but not in cutaneous PAN.[2] Hepatitis viruses B and C have been implicated mainly in the pathogenesis of systemic PAN, and they have been associated with cutaneous PAN only in isolated cases.[15,16] Indeed, in our patients, serological tests for hepatitis B and C all proved negative when they were performed. Nevertheless, other infectious agents such as streptococcus could be implicated in some cases of cutaneous PAN and some authors recommend the systematic determination of the ASO titre in all patients with cutaneous PAN.[2,10] In one of our patients we confirmed the presence of a raised ASO titre associated with a chronic tonsillitis that might support this hypothesis, although it is difficult to discard a casual relationship. Mycobacterium tuberculosis is another agent that has occasionally been implicated in cutaneous PAN.[14] On the other hand, the presence of perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) has been documented in some patients with systemic PAN,[17] but also in isolated patients with cutaneous PAN.[18,19] In our patients the analysis of ANCA was negative when it was done. Thus, although the relationship of ANCA with classical PAN is not clear, it appears that patients with both large and small vessel arteritis are sometimes P-ANCA or cytoplasmic-ANCA positive, whereas those with exclusively large vessel arteritis are generally ANCA negative.[20]

Cutaneous PAN does not require the intense treatment to bring about remission that is necessary for systemic PAN. Because of the benign course of the cutaneous form, a conservative therapeutic plan should be followed. Although there are no doubleblind prospective placebo-controlled trials for therapy, treatment could be initiated with low doses of sulphapyridine, NSAIDs or salicylate, that may induce remission or relieve the symptoms or signs of the disease.[21] Antibiotic treatment may be needed in patients with documented streptococcal or other bacterial infections.[2] If there is no response, low or moderate doses of corticosteroids or weekly methotrexate have been used with good responses.[22]

In the light of these findings, we consider that most of the patients with cutaneous PAN are associated with a good prognosis. We should keep in mind that the presence of some extracutaneous symptoms such as constitutional symptoms, local neurological and musculoskeletal manifestations, may also be associated with cutaneous PAN without indicating its evolution to systemic PAN. However, as cutaneous involvement may also occur in 20–30% of cases of systemic PAN[2] and there are cutaneous forms that have aneurysms in renal angiogram,[23] perhaps we can consider that the spectrum of PAN is depicted as a disease continuum ranging from skin disease alone to life-threatening systemic disease, the same as cutaneous and systemic lupus erythematosus.[21] We think that is very important to check these patients carefully to exclude systemic involvement, not only in the first visit but also in a continuous follow-up (Table 4).

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Table 1. Clinical symptoms and related diseases

	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis (years)	11	39	44	70
Sex	M	F	F	F
Time of follow-up (years)	13	3	5	2
Nodules	+	+	+	+
Livedo reticularis	+	–	+	+
Purpura	–	–	–	–
Ulcers	–	–	–	+
Legs involvement	+	+	+	+
Arms involvement	+	–	–	–
Another location	–	–	–	–
Fever	+	–	–	–
Asthenia	+	–	–	–
Abdominal pain	+	–	–	–
Arthralgia	+	+	+	–
Headache	+	+	–	–
Paraesthesias	Feet	–	–	–
	Hand	–	–	–
Myalgia	–	–	–	–
Related diseases	CT	DLE	CG	CS
Arterial hypertension	–	+	–	+

+, symptom present; –, symptom absent; CT, chronic tonsillitis; DLE, discoid lupus erythematous; CG, chronic gastritis; CS, chronic sinusitis; M, male; F, female.

Table 2. Laboratory results and complementary explorations

	Patient 1	Patient 2	Patient 3	Patient 4
Full blood count	N	N	N	N
ESR	52/90	102/118	9/22	ND
Urinalysis	Haematuria	N	ND	N
Creatinine	N	N	N	N
Liver function tests	N	N	N	N
ASO (UI)	↑↑↑	N	ND	ND
Complement	N	ND	N	N
ANA	–	–	–	–
ANCA	ND	ND	–	–
RF	–	–	–	–
Cryoglobulins	ND	–	–	ND
Tuberculin	–	–	–	ND
HB antibodies	ND	ND	antiHbs	ND
HC antibodies	–	ND	–	–
EMG	N	Response ↓	N	ND
Conduction speeds	N	N	N	ND
Renal angiogram	ND	ND	N	ND

N, normal; ND, not done; –, negative; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasm antibodies; antiHbs, anti-hepatitis B surface antigen; ASO, antistreptolysin O; EMG, electromyogram; ESR, erythrocyte sedimentation rate; HB, hepatitis B; HC, hepatitis C; RF, rheumatoid factor.

Table 3. Treatment and prognosis

	Patient 1	Patient 2	Patient 3	Patient 4
Treatment	P + C + A	P	P + S	P + NSAID
Present clinical situation	NL	NL	NL	WL
Visceral involvement	–	–	–	–
Present treatment	No	P	No	P

P, prednisone; C, cyclophosphamide; A, antibiotics; S, sulphone; NSAID, non-steroid anti-inflammatory drugs; NL, no lesions; WL, with cutaneous lesions; –, without visceral involvement

Table 4. Initial evaluation and follow-up	
First visit	
Evaluation for systemic involvement	Anamnesis and complete physical examination (collaboration with internal medicine physician or paediatrician). Arterial pressure.
	Full blood count, ESR, liver and renal function tests, cryoglobulins, ANA, ANCA, RF and complement.
	If paraesthesias: neural conduction speeds.
	If high pressure or renal dysfunction: renal angiogram.
	If abdominal pain: blood in stool, colonoscopy or mesenteric arteriography.
	If myalgias or muscle weakness: electromyogram and muscle enzymes.
Evaluation for aetiology	Anamnesis (drugs, infections, other diseases) and complete physical examination.
	ASLO, tuberculin and virus hepatitis B and C serology.
Follow-up (every 6–12 months)	
	If patient is asymptomatic: anamnesis and complete physical examination. Arterial pressure.
	Full blood count, ESR, complement, liver and renal function tests.
	If symptoms (as shown above).
ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasm antibodies; RF, rheumatoid factor; ASLO, antistreptolysin O.	

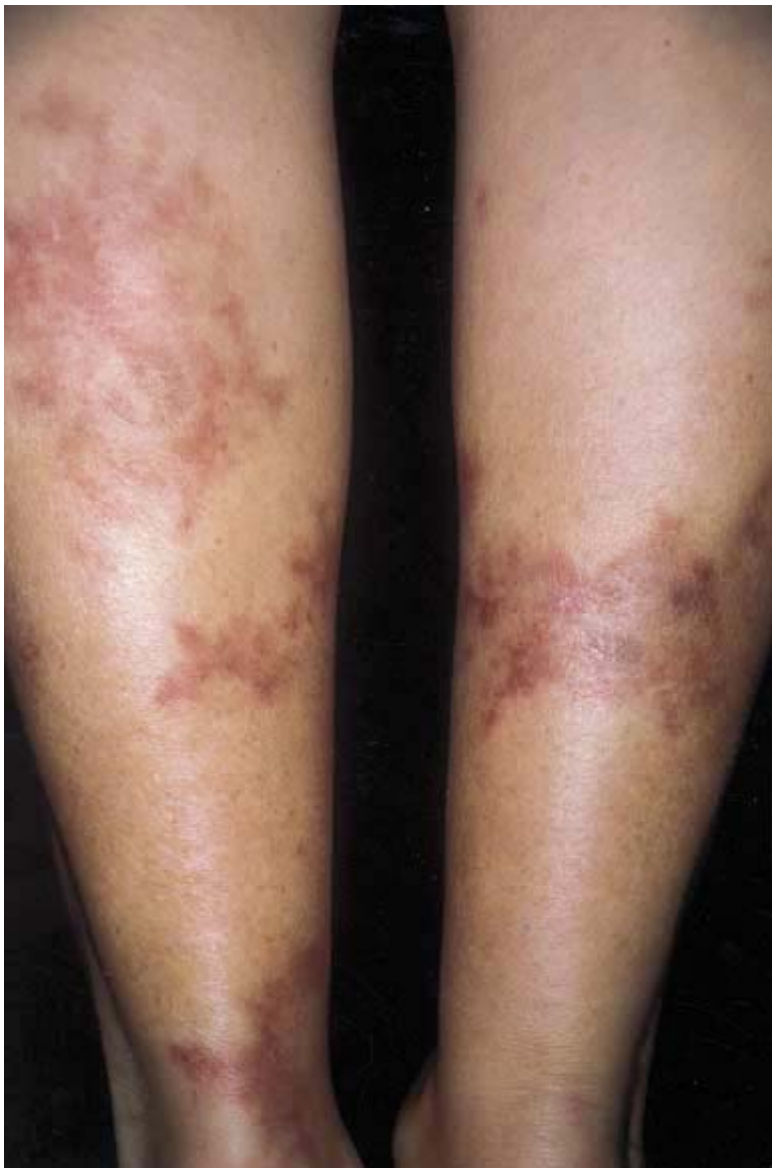

Figure 1. Cutaneous nodules and livedo reticularis in patient 4.

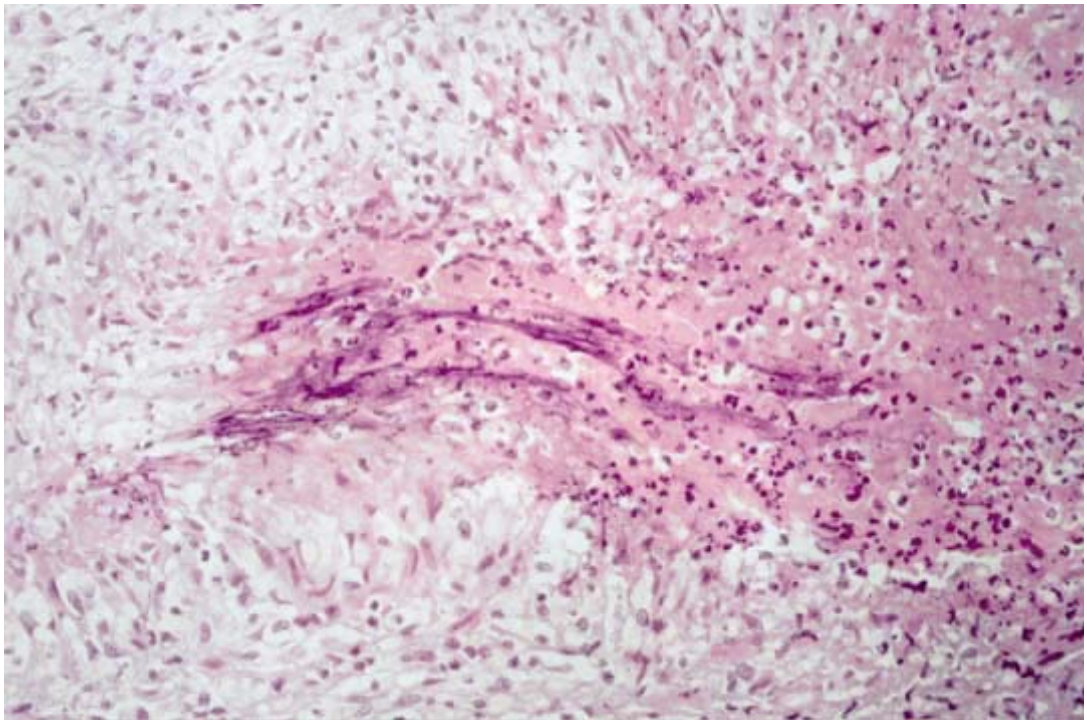

Figure 2. Segmentary effects in a medium-sized artery. Note the presence of fibrinogen deposits that stain with fuchsin (Masson's trichromate, original magnification x 100).

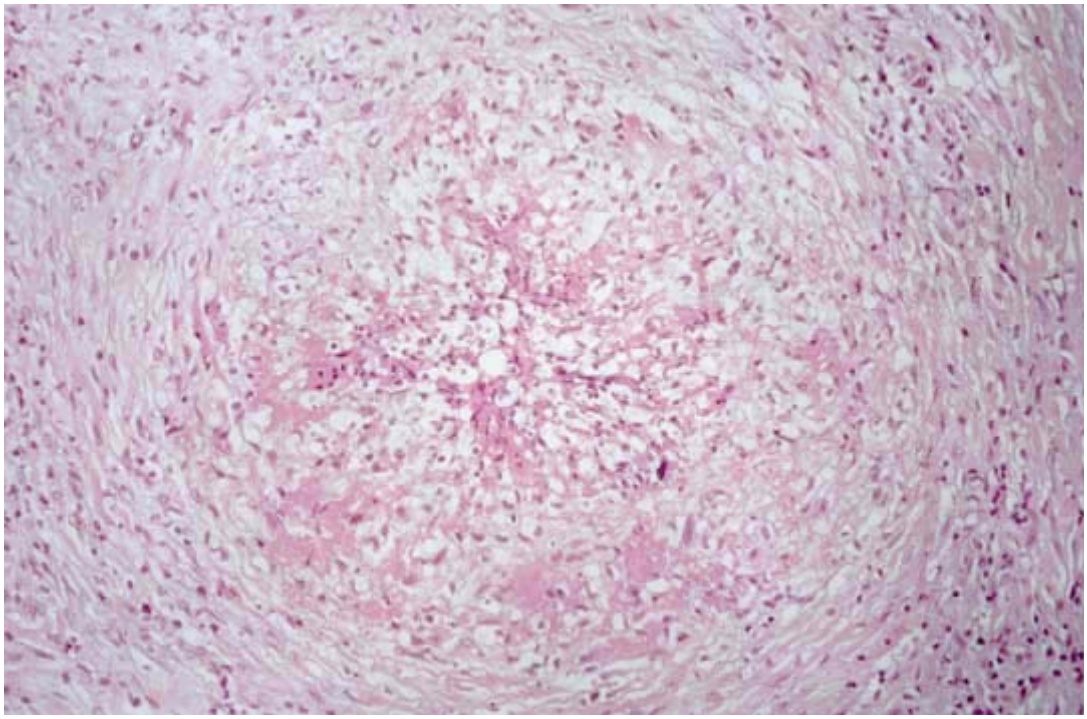

Figure 3. Transverse section of a cutaneous medium-sized artery that shows an intense lymphomacrophage infiltration of the vessel's wall causing vascular distortion and occlusion of the light (haematoxylin and eosin, original magnification x 200).