Localized nodular vasculitis: A new variant of localized cutaneous polyarteritis nodosa?

G. Quintana[1], E.L. Matteson[2], A. Fernández[1], J.F. Restrepo[1], A. Iglesias[1]

[1]Rheumatology Unit, School of Medicine, National University of Colombia, Bogotá, Colombia; [2]Mayo Clinic College of Medicine, Rochester, Minnesota, USA.

Gerardo Quintana, MD; Eric L. Matteson, MD; Andrés Fernández, MD; José Félix Restrepo, MD; Antonio Iglesias, MD.

Please address correspondence to: Eric L. Matteson, MD, MPH, Division of Rheumatology, Mayo Clinic, 200 1st St. SW, Rochester, MN 55905, USA. E-mail: matteson.eric@mayo.edu

Received on May 24, 2004; accepted in revised form on September 2, 2004.

Clin Exp Rheumatol 2004; 22 (Suppl. 36): S31-S34.

© *Copyright* CLINICALAND EXPERIMENTAL RHEUMATOLOGY *2004.*

Key words: Polyarteritis nodosa, cutaneous polyarteritis nodosa, nodular vasculitis.

ABSTRACT

Cutaneous polyarteritis nodosa (PAN) was first described by Lindberg in 1931. This initial description was followed by many case reports and series, including those of Díaz-Pérez and Winkelmann, who used a strict definition based on cutaneous involvement, and Chen and Daoud who classified the condition into three well differentiated groups. The cutaneous form of PAN is distinct from the systemic form due to its chronic, recurrent, benign nature, the absence of internal organ involvement, and the presence of inflammation in medium and small vessels of the deep dermis and panniculus. In the present article we report our findings for 12 patients with a variant of cutaneous PAN consisting of painful erythematous nodular lesions not preceded or followed by livedo reticularis, that were located exclusively on the lower third of the legs and responded slowly to treatment with corticosteroids and immunosuppressants.

Introduction

In 1866, Kussmaul and Maier described a 27-year-old patient whose condition was characterized by fever, cough, proteinuria, abdominal pain, mononeuritis multiplex, muscular weakness, and subcutaneous nodules (1). Thereafter, polyarterititis nodosa (PAN) was always described as a vasculitis with systemic involvement until Lindberg's description in 1931 of two patients with skin lesions and necrotizing arteritis without end organ disease (2). A separation of classic PAN from microscopic polyarteritis was defined by the Chapel Hill consensus conference in 1994, whereby both these forms of systemic vasculitis may have skin involvement (3). Cases of PAN limited to cutaneous involvement included cases of cutaneous PAN with livedo reticularis (4-12). Most of these descriptions cited only the cutaneous aspects of the nodular lesions of cutaneous PAN.

In 1974, two dermatologists – Richard R. Winkelmann of the Mayo Clinic and José L. Díaz-Pérez, at the University of Bilbao in Spain – established the first criteria for cutaneous PAN based on their analysis of 23 patients, and followed this article with others establishing the nature of this disease, including a report of 33 patients in 1980 (13, 14). They defined this condition as a strictly cutaneous variant characterized by chronic, recurrent, benign nodular lesions. Some patients with the disease exhibit recurrent nodular lesions over a period of up to 20 years which particularly affect the lower limbs. These nodular lesions are painful and may or may not be associated with livedo reticularis and ulceration. Some patients present with systemic manifestations such as arthralgia, fever, malaise, and neuromuscular findings, especially neuropathy. An immunofluorescence study of 10 of their patients with cutaneous PAN demonstrated IgM and/or C3 deposits in vessel walls (15).

The etiology of PAN remains obscure. Hepatitis B has been detected in a variable percentage of cases of classical PAN, while it has only been described in isolated cases of cutaneous PAN (16, 17). Nosologically, cutaneous PAN has been distinguished by numerous authors from classic, systemic PAN, and conversion of cutaneous PAN into systemic PAN has only been reported once (18-21).

Chen and Daoud *et al*. classified cutaneous PAN into three groups (18, 19): (i) a mild cutaneous form consisting of nodular lesions and reticular livedo; (ii) a severe cutaneous form consisting of livedo, ulceration, and pain; and (iii) necrotizing livedo and gangrene. To date, no internationally accepted diagnostic criteria for cutaneous PAN have been established.

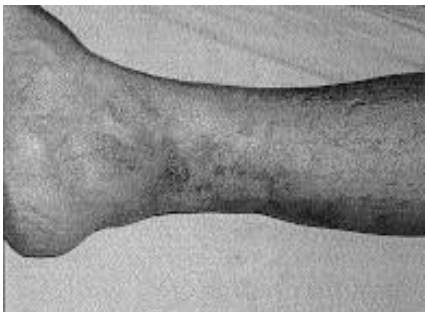

Fig. 1. A female patient in the acute phase with very painful nodular erythematous lesions in the lower third of the right leg (socking distribution). There was no evidence of livedo reticularis.

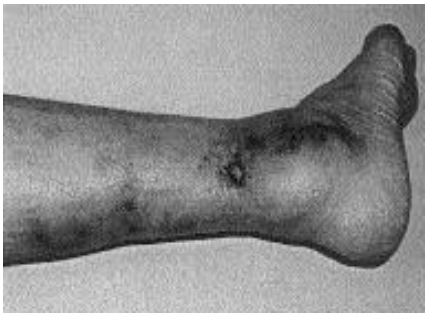

Fig. 2. Resolving ulcerated lesions with nodules.

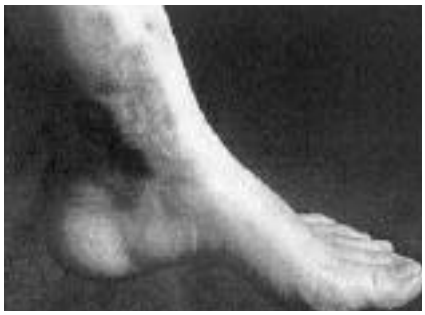

Fig. 3. Healed lesions with chronic scaring and trophic changes in a second female patient, one year after resolution of active disease.

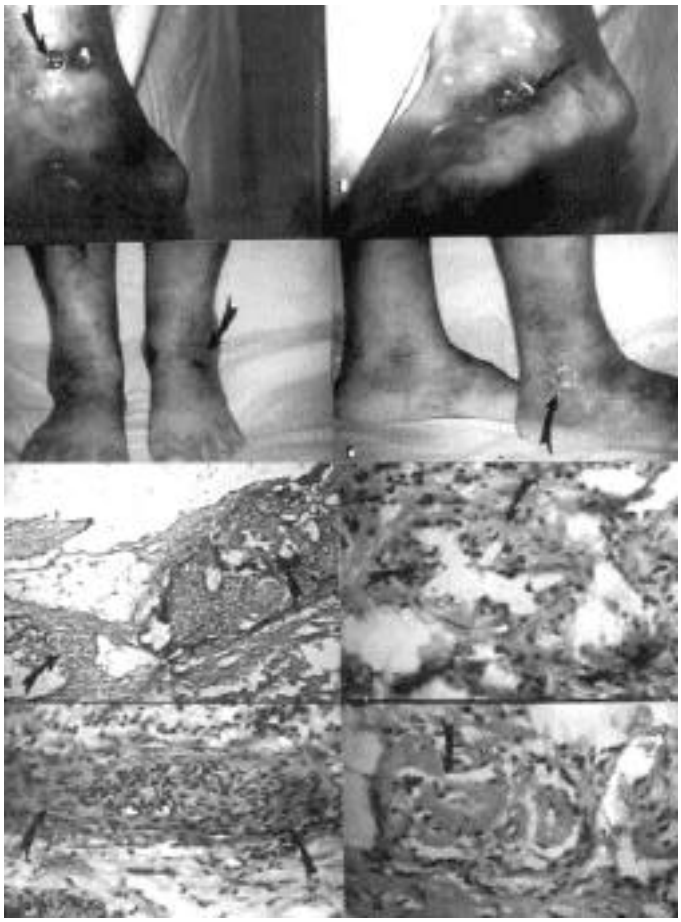

Fig. 4. Active (**above**) and healing (below) lesions in a female patient. Histopathologic examination demonstrated arteritis of the small arteries, especially of the dermal reticular and subcutaneous tissue.

Materials and methods

Since 1985, we have followed a cohort of 12 patients with cutaneous PAN (11 females, 1 male) at the Rheumatology Unit of the National University of Columbia School of Medicine in Bogotá. These patients had painful nodular erythematous lesions, always accompanied by recurrent ulcers without livedo. The lesions occurred symmetrically on the lower third of the legs, the back, and on the lateral part of the feet. No association of the disease with medications or other coexistent diseases was found in any patient. Routine laboratory evaluation including ESR, C-reactive proteins, chest radiograph, renal ultrasound, rheumatoid factor, ANCA, antinuclear antibodies (ANA), serology for hepatitis B and C was performed. Biopsies of involved skin were performed on all patients. All patients were treated with prednisone at an initial dose of 30 to 45 mg/day in divided doses. Five patients also received azathioprine, 5 patients methotrexate (7.5 mg – 15 mg weekly), and 5 patients oral colchicine. Patients were generally followed every three months for an average of 6.5 years.

Results

Most of the patients were women (n = 11; 1 male). The patients ranged in age from 16 to 56 years (average 29.6 years). All the patients had the same clinical characteristics, including erythematous nodular lesions of the lower limbs in a stocking distribution which became ulcerated and left scars (Figs. 1, 2, and 3). Relapse of the lesions was frequent, especially if the condition was not adequately treated with prednisone in doses of 30 to 45 mg/day and, usually, immunosuppressants. Lesions were always accompanied by fever, but were neither preceded nor followed by livedo reticularis. Three patients had polyarticular arthralgia without arthritis of the upper and lower limbs, associated with lower limb paresthesia including numbness in a stocking distribution. None of the patients had skin involvement outside the stocking distribution, and none had visceral involvement. All patients had a good prognosis with proper medication.

A definitive diagnosis was often delayed. In 6 patients the diagnosis was made after 8 years and in 4 patients after 4 years. Eight patients responded after 6 months of treatment, but 2 patients showed no improvement for the entire first year of therapy. No systemic

Table I. Comparison of the clinical characteristics of cutaneous PAN*.

	Diaz-Perez and Winkelmann (n = 23)		Daoud *et al.* NU (n = 40)		Daoud *et al.* Ulc (n = 39)		Current series (n = 12)	
	N	%	n	%	n	%	n	%
Pain	22	95%	39	97.5%	39	100%	12	100%
Nodules	19	8%	40	100%	23	59%	12	100%
Arthritis	3	13%	0		0		0	
Arthralgia	12	52%	10	25%	8	20.5%	3	3%
Livedo reticulares	18	78%	20	50%	24	61.5%	0	
Ulceration	9	39%	0		39	100%	12	100%
Myalgia	11	48%	10	25%	8	20%	0	
Fever	7	30%	10	25%	8	20%	9	75%
Neuropathy	4	17%	5/16	31.2%	12/18	66.6%	3	25%
Visceral involvement	0		0		0		0	
Other areas	22	95%	23	57.5%	9	23%	0	
Prognosis	Good, recurrent		Good, recurrent		Good, recurrent		Good, recurrent	

NU: non-ulcerating; Ulc: ulcerating. The number of patients in each series is shown in parentheses.
*Diaz-Perez and Winkelmann (ref. 13); Daoud *et al*. (ref. 19, subdivided into ulcerating and nonulcerating lesions).

Table II. Laboratory findings in cutaneous PAN*.

	Diaz-Perez, Winkelmann (n = 23)		Daoud *et al*. NU (n = 40)		Daoud *et al*. Ulc (n = 39)		Current series (n = 12)	
	N	%	N	%	N	%	N	%
Leukocytosis	9/23	39%	ND		ND		9/12	75%
Neutrophilia	6/23 **	26%	ND		ND		9/12	75%
Anemia	9/23	39%	13/40	33%	12/39	31%	3/12	25%
Proteinuria	4/23 **	17%	ND		ND		0/12	
Leukocyturia	4/23 **	17%	ND		ND		0/12	
Hematuria	2/23 **	8.7%	9/40	23%	3/39	8%	0/12	
Elevated ESR	22/23	95%	24/40	60%	23/39	59%	12/12	100%
Elevated blood pressure	3/23		0/40		0/39		0/12	
Elevated creatinine	0/23		0/40		0/39		0/12	
HBV	ND		0/8		0/29		0/12	
HCV	ND		0/7		1/13	8%	0/12	
ANA	1/8	12.5%	4/31	13%	9/32	28%	0/12	
RF	0/9		1/28	4%	1/28	4%	0/12	
Complement	0/6		0/22		0/29		0/12	
ANCAs	ND		0/22		0/14		0/12	

ND: no data; ESR: erythrocyte sedimentation rate; AP: blood pressure; HBVand HCV: hepatitis B and C viruses; ANAs: antinuclear antibodies; RF: rheumatoid factor; ANCAs: antineutrophil cytoplasmic antibodies; NU: non-ulcerating; Ulc: ulcerating.
*Diaz-Perez and Winkelmann (ref. 13); Daoud *et al.* (ref. 19, subdivided into ulcerating and nonulcerating lesions).
** These findings were related to causes other than the underlying disease (2).

involvement was observed during an average of 6 years of follow-up. Hepatitis B, C, and ANCAwere not detected in any patients. Renal ultrasound was normal in all patients. Skin biopsies revealed arteritis of the small and medium caliber arteries particularly in the reticular dermis and subcutaneous tissue (Fig. 4). Most patients with active lesions had a mild-to-moderate leukocytosis and an elevated erythrocyte sedimentation rate, while 3 patients had a normocytic normochromic anemia.

Our 12 cases provide further confirmation that this disease may be considered a distinct entity as defined by Díaz-Perez and Winkelmann (13). The clinical features of cutaneous PAN are as characterized by Díaz and Winkelmann, Chen, and Daoud *et al.*, but these authors described it as being associated with livedo, involvement of medium-sized arteries, and frequently neuropathy.

Typical in our patients was the involvement of the small arteries and arterioles with neutrophilic infiltration and fibrinoid necrosis, but without disruption of the inner elastic layer. Lesions were symmetrical and confined to the lower limbs, so the picture differs from that reported by these other authors. Table I compares the clinical features of the three series.

All patients had mild anemia, mild-to-moderate leukocytosis, and an elevated ESR. There were important differences in the three groups. Daoud *et al.* reported mild hematuria in 23% of the patients without ulcerations and in 8% of the patients with ulcerating lesions; positive ANA in a significant number of patients (20.6% of the patients in whom this was measured); and hepatitis C antibody in one patient. In our series, only a small percentage of patients had mild-to-moderate leukocytosis and an elevated ESR associated with active lesions, and a small percentage had mild anemia. Table II presents the laboratory findings in the three cohorts of patients.

Discussion

This is the first report to document a variant of recurrent symmetrical nodular vasculitis in a stocking distribution in the absence of livedo reticularis, without any association with hepatitis B or C, ANCA, ANA, or rheumatoid factor. This variant differs from the form described by Diaz-Perez and Winkelmann, Chen, and Daoud *et al*.

The clinical manifestations of cutaneous vasculitis clearly differentiate it from the systemic form. The association of livedo reticularis has been described, particularly with a “burst” pattern or an irregularly shaped livedo reticularis around the ulcer. This pattern is highly suggestive of cutaneous PAN. Lesions that might be observed in cutaneous PAN are listed in Table III. Atypical presentations include a solitary breast mass or migratory soft tissue edema (22).

Lindberg reported two patients with PAN confined to the skin and postulated that it could be a benign form of the disease (2). This proposal has not been widely accepted for several reasons: (i)

Table III. Characteristics of cutaneous polyarteritis nodosa in descending order of frequency.

Pain
Increased erythrocyte sedimentation rate
Subcutaneous nodules
Arthritis and arthralgia
Livedo reticularis
Ulceration
Myalgia
Fever
Peripheral neuropathy

Several diseases appearing in the lower limbs should be considered in the differential diagnosis of cutaneous PAN (Table IV). There has been only case report of a patient who initially exhibited cutaneous lesions with normal blood pressure, urinalysis, ESR, and blood tests and subsequently developed fulminant systemic PAN (21).

Table IV. Differential diagnosis of cutaneous polyarteritis nodosa.

Chronic cutaneous leukocytoclastic vasculitis
Cellulitis
Necrotizing vasculitis
Nodular vasculitis
Erythema nodosum
Erythema induratum
Weber-Christian disease
Recurrent thrombophlebitis
Systemic polyarteritis nodosa with skin involvement

some authors consider any case of PAN with cutaneous involvement as cutaneous PAN, including cases with visceral involvement and a poor prognosis; (ii) uniform histological criteria are not utilized, and other cutaneous vasculitides are often grouped together with true cutaneous PAN; (iii) the long-term course of patients with skin involvement is not always described in case reports; and (iv) conflicting hypotheses regarding etiology and classification have been inferred by authors reporting on patients with a prolonged benign evolution.

We believe that cutaneous PAN has two types of phenotypical expression in the skin, depending on the degree of involvement and the size of the arteries involved. When medium-caliber arteries are involved, livedo with ulcerating nodules may form part of the natural history of the disease. If small arteries are involved, only the reticular dermis and upper layer of the subcutaneous tissue are affected and nodules appear that subsequently become ulcerated. Skin biopsies reveal only fibrinoid necrosis and fibrinoid deposits with increased polymorphonuclear infiltration of the subdermis.

References

1. KUSSMAUL A, MAIER R: Ueber eine bisher nicht beschriebene eigenthumliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht. *Dtsch Arch Klin Med* 1866; 1: 484-518.
2. LINDBERG K: Ein Beitrag zur Kenntnis der Periarteritis Nodosa. *Acta Med Scand* 1931; 76: 183-225.
3. JENNETTE JC, FALK RJ, ANDRASSY K *et al*.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
4. CAROL W, PRAKKEN J: Die kutane Form der Periarteritis nodosa. *Acta Derm Vener* 1937; 18: 102-18.
5. MIESCHER G: Uber kutane formen del Periarteritis nodosa. *Dermatologica* 1946; 92: 225-45.
6. LINDGREN I, LUNDMARK C: Periarteritis nodosa as a skin disease. *Acta Dermatol Venereol* 1956; 36: 343-54.
7. RUITER M: The so-called cutaneous type of periarteritis nodosa. *Br J Dermatolol* 1958; 70: 102-6.
8. BELISARIO JC: Cutaneous manifestations in polyarteritis nodosa: Report of a case with livedo reticularis. *Arch Dermatol* 1960; 82: 526-32.
9. WINKELMANN R, MONTGOMERY H: Uber die cutane Periarteritis nodosa. *Hautarzt* 1960; 11: 82-6.
10. FISHER I, ORKIN M: Cutaneous form of periarteritis nodosa: an entity ? *Arch Dermatol* 1964; 89: 180-9.
11. BORRIE P: Cutaneous polyarteritis nodosa. *Br J Dermatol* 1972; 87: 87-95.
12. VERBOV J, STANSFELD AG: Cutaneous polyarteritis nodosa and Crohn's disease. *Trans St Johns Hosp Dermatol Soc* 1972; 58: 261-8.
13. DIAZ-PEREZ JL, WINKELMANN RK: Cutaneous periarteritis nodosa. *Arch Dermatol* 1974; 110: 407-14.
14. DIAZ-PEREZ JL, WINKELMANN RK: Cutaneous periarteritis nodosa: a study of 33 cases. *Major Probl Dermatol* 1980; 10: 273-84.
15. DIAZ-PEREZ JL, SCHROETER AL, WINKELMANN RK: Cutaneous periarteritis nodosa: immunofluorescence studies. *Arch Dermatol* 1980; 116: 56-8.
16. GOCKE DJ, HSU K, MORGAN C *et al*.: Vasculitis in association with Australia antigen. *J Exp Med* 1971: 134: 330s-336s.
17. WHITTAKER SJ, DOVER JS, GREAVES MW: Cutaneous polyarteritis nodosa associated with hepatitis B surface antigen. *J Am Acad Dermatol* 1986; 15: 1142-5.
18. CHEN KR: Cutaneous polyarteritis nodosa: a clinical and histopathological study of 20 cases. *J Dermatol* 1989; 16: 429-42.
19. DAOUD M, HUTTON KP, GIBSON L: Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. *Br J Dermatolol* 1997; 136: 706-13.
20. KHOO BP, NG SK: Cutaneous polyarteritis nodosa: a case report and literature review. *Ann Acad Med* 1998; 27: 868-72.
21. DYK T: Cutaneous polyarteritis. *Br Med J* 1973; 1: 551.
22. BRAVERMAN IM: The angiitides. In: *Skin Signs of Systemic Disease*. Philadelphia, W.B. Saunders 1981: 384.