Cutaneous panarteritis as a late manifestation of the erythema nodosum leprosum

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Summary

The authors studied 11 cases of multibacillary Hansen's disease (9 lepromatous and 2 borderline-lepromatous) with late erythema nodosum leprosum manifestations. The systemic symptoms were mild and there was low number of cutaneous lesions in lower limbs. Histologically, those lesions presented necrotizing and exsudative segmental arteritis in the deep dermis, with discrete inflammatory reaction in the neighboring dermis and sub-cutis. There were discrete or absent evidences of previous involvement by Hansen's disease, however, in seven patients, acid fast bacilli were found on the wall of involved vessels. Probably there are pathogenic similarities between these arteritis and the necrotizing vasculitis that occurs in severe and generalized episodes of erythema nodosum leprosum throughout specific treatment due to persistence of mycobacterial antigen on the vessel wall, even after their elimination from other cutaneous sites. The eventual exposure of mycobacterial antigens would stimulate immune complex formation and acute inflammatory and necrotizing reaction. In addition, the histolopathological and even clinical aspects of these arteritis are very similar to cutaneous polyarteritis nodosa. These clinical and structural similarities may correspond to similar pathogenic mechanisms between the two cutaneous vasculitis.

Uniterms: Hansen's disease, erythema nodosum leprosum, cutaneous panarteritis, vasculitis.

INTRODUCTION

The erythema nodosum leprosum (ENL) is an acute manifestation that occurs in Hansen's disease patients with minimal resistance (polar and sub-polar lepromatous and borderline-lepromatous), more frequently during treatment, but sometimes before its beginning. Clinically it is characterized by sudden appearance of disseminated painful erythematous subcutaneous nodules or erythematous plaques, followed by systemic manifestations, fever, disseminated linphadenopathy, iritis, iridociclitis, neuritis and arthritis, and visceral acute manifestations. It occurs in about 60% of cases in episodes lasting around 15 to 20 days, and subsides in variable intervals[11,13]. Under the histological point of view, an acute or sub-acute inflammatory reaction is observed in any site with regressive lepromatous infiltrate, with variable amounts of granular bacilli or even absence of bacilli. There is congestion and vasodilation, endothelial swelling, edema and fibrin interstitial deposition, neutrophilic migration, sometimes abscesses and thrombus in the vessels of terminal circulation [5,6,7,9,10,15,18]

The presence of vasculitis involving terminal circulation is controversial. For some authors this is found in half of the cases 6,9 For others, the vascular changes, mainly in the venulo-capillary territory correspond to the participation of these vessels in the intense acute inflammatory reaction[10,19] However, in severe episodes of ENL, arteritis and phlebitis in deep dermis and sub-cutis are followed by necrosis and cutaneous ulceration [4,5,10,20]

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The polyarteritis nodosa in its exclusive cutaneous form is characterized by painful subcutaneous nodules, more frequently in lower extremities, associated to livedo reticular. Ulceration of these nodules may occur without systemic manifestations. Histologically, acute inflammatory involvement is observed, surrounding all arterial layers (panarteritis). Therefore, the involved segments can be alternated with preserved arterial segments, or cicatricial changes[1,2,12,17].

For about 20 years we observed the crops of scarce inflammatory lesions in lower limbs of 11 Hansen's disease patients with minimal resistance (polar lepromatous and borderline-lepromatous), in advanced regressive or inactive phase, and in most of the cases, without systemic manifestation. The histological structure of this lesion showed an isolated segmental acute arteritis in the deep dermis and sub-cutis, very similar to the cutaneous polyarteritis nodosa.

There are no references to this type of late manifestation of Hansen's disease in the literature, and the authors believe to be interesting the description of clinical and histological aspects of the 11 referred patients.

PATIENTS AND METHODS

Data was collected from clinical records of 11 patients with Hansen's disease and erythema nodosum, and by direct contact with clinicians in charge of out-patient cases, whose biopsies were sent to the pathology laboratory of the ILSL* between 1979 and 1999. Biopsies were taken from nodular erythematous lesion or from plaques with acute onset observed in the lower limbs of patients, mostly without clinical active Hansen's disease. New histological sections of paraffin blocks were stained by hematoxylineosin, Fite-Faraco, and Verhoeff for elastic fibers.

RESULTS

The main data about evolution of Hansen's disease, treatment, previous episodes of ENL and other diseases, are exposed on tables 1, 2 and 3. In the analysis of the data, it was verified that most of the patients presented lepromatous leprosy and only 2 had previous diagnosis of borderline lepromatous leprosy confirmed by histopathology.

As this evaluation was done for the period of 20 years, the therapeutic regimens varied. All patients who finished the treatment presented the late episode of ENL between 2 to 22 years after discharge. Only one patient was still under treatment for Hansen's disease.

The majority of the patients of this group presented ENL as the first manifestation of Hansen's disease, before the beginning of treatment when there was only a diffuse and mild specific infiltrate without lepromas (solid lesions). The late episode is characterized by a few painful erythematous nodules on legs and thighs, except for one patient who developed erythematous plaques and ecchymosis. In 2 patients, nodules appeared also in upper limbs. One patient presented neuritis. In 5 patients, cutaneous lesions were followed by discrete systemic symptoms: fever, arthralgias, myalgias, and the other 6 patients had only complaints related to the erythematous nodules. One of the patients had clinical aspect very similar to cutaneous polyarteritis nodosa with livedo reticular and isolated erythematous nodules. A nodule in the thigh was ulcerated. (Figure 1)

The histopathologic sections showed inflammatory reaction restricted to vessels in the deep dermis and the subcutis (Figures 2 and 3). In some cases, there were arterial segments with acute inflammation and necrosis (Figures 3 and 4), alternated with preserved segments and segments with cicatricial changes (Figure 5). The inflammatory reaction was absent or mild, and was restricted to the surrounding tissue (Figures 2 and 3). A few signs of previous involvement of Hansen's disease, such as foci of residual lepromatous infiltrate, nervous branches with Virchow cells and/or nervous branches with endoneural hyalinization, were detected.

The staining by Verhoeff for elastic fibers confirmed the arterial nature of the involved vessels, and the staining by Fite-Faraco showed granular bacilli on the involved arterial wall of 7 cases. (Figure 6)

DISCUSSION

There are 3 aspects that allow us to link these episodes of arteritis to ENL, they are: a) All patients had confirmed diagnosis of lepromatous or borderline-lepromatous Hansen's disease; b) In 7 of the 11 cases, acid fast bacilli were detected on the wall of involved vessels; c) Arteritis, that can lead to necrosis and ulceration, occur in well-characterized ENL.

During well-established episodes of ENL vasculitis develop as acute inflammatory reactions on regressive lepromatous lesions and may involve multiple vessels (arteries and veins). Vasculitis are a lot more intense and destructive.

The pathogenesis of the ENL is still controversial[3]; nonetheless, it is accepted that there is a phase of immune-complex deposition in tissues containing [10,21]lepromatous infiltrates, bacilli or mycobacterial antigens[3,10,21]. For Ridley & Ridley[16], immune-complexes are formed in extravascular sites, instead of the deposition of circulating immune-complexes on the wall of small vessels of the terminal circulation.

In lepromatous leprosy, the wall of major skin vessels

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and sub-cutis are filled with bacilli and involved by lepromatous infiltrate. In the pathogenesis of ENL, the adventitia, muscle and sub-endothelial layers of these vessels would play the same role as the interstitial tissue in relation to the venulo-capillary segment of the circulation. Thus, in ENL, there would be immune complex formation in the interstitial tissue between vessels of terminal circulation and in the same way on the walls of major vessels of the dermis and sub-cutis. This would stimulate the afflux of exsudate to the interstitial tissue and to the wall of vessels originated from the adjacent venulo-capillary territory. Therefore, this vasculitis would be defined *as* secondary, in contrast to the necrotic vasculitis of small vessels that result from the deposition of circulating immune-complexes on vessels of the terminal circulation[17]

The isolated arteritis, which are detected in the Iate period after inactivation of lepromatous and borderline-lepromatous patients, can be interpreted in the same way. The exposure of bacillary antigens, that remain sequestered in the muscle wall of vessels for many years, would stimulate an antigen-antibody reaction and the development of vasculitis with the described characteristics. Being the remaining vascular system preserved, this segmental vasculitis would be exteriorized only through a few inflammatory nodules without infarction or cutaneous ulceration, which occur in the most severe and disseminated forms of the ENL involving these vessels[4,10,20]

The histological and partially clinical similarities of these arteritis with the cutaneous polyarteritis nodosa induce us to question if the pathogenesis of these would not be similar, that is, eventual exposure of sequestered antigens (bacterial, viral, parasitic) in the vascular wall, immune complex formation and inflammatory cells migration from the adjacent terminal circulation.

TABLE 1: Clinical and therapeutic data of lepromatous and borderline-lepromatous patients with Iate episodes of cutaneous panarteritis.

Identification	Age	Clinical Form	Treatment	Evolution of Treatment
1 - C.L.O	29 y	LL	DDS, DDS e RFP, MDT-MB	Inactivation 18 y after
2 - J.S.R.	37 y	LL	DDSI	Inactivation 6 y after
3 - J.C.O.	49 y	BL	DDS,DDS e RFP	Inactivation 7 y after
4 - L.C.R.P.	49 y	BL	DDS	Inactivation 18 y after
5 - T.L.F.	42 y	LL	DDS	Inactivation 7 y after
6 - P.T.M.V.	62 y	LL	DDS	Inactivation 8 y after
7 - M.A.Q.	36 y	LL	MDT-MB	Inactivation 2 y after
8 - R.J.G.	53 y	LL	DDS	Inactivation 13 y after
9 - G.S.	37 y	LL	MDT-MB	Inactivation 4 y after
10 - M.P.V.	32 y	LL	MDT-MB	Inactivation 2 y after
11 - O.D.M.R.	40 y	LL	DDS,MDT-MR	Still active

MDT-MB - multidrugtherapy multibacilar
RFP - rifampicin
BL - borderline-lepromatous
DDS — dapsone
LL - lepromatous
y- years

TABLE 2: Complementary clinical data about duration of Hansen's disease, characteristics of previous ENL, and time between inactivation and late episode of cutaneous panarteritis in lepromatous and borderline-lepromatous patients.

Identification	Duration of Disease	Time Between Inactivation and Vasculitis	Number of Previous ENL Episodes	Severity of Previous ENL Episodes
1 - C.L.O.	20 y	2 y, 2 mo	several	6 severe episodes
2 - J.S.R.	13 y	6 y, 5 mo	few	Moderate
3 - J.C.O.	16 y	3 y	few	Mild
4 - L.C.P.	28 y	22 y	few	Mild
5 - T.L.F.	12 y	5 y	few	Mild
6 - PT.M.V.	18 y	10 y	few	Mild
7- M.AQ.	4 y	4 y	few	Mild
8 - R.J.G.	21 y	21 y	few	Mild
9 - G.S.	7y	7y	few	Mild
10-M.P..V.	9y	9y	few	Mild
11 - O.D.M.R.	4 y	still active	few	Mild

y — years mo - months

TABLE 3: Clinical characteristics of late episodes of cutaneous panarteritis in lepromatous and borderline-lepromatous patients.

Identification	Clinical Manifestation	Location	Other symptoms
1 - C.L.O.	Erithematous Nodules	LLL	No
2 - J.S.R.	Erithematous Nodules	LL, UL	Arthralgias, edema of limbs
3 - J.C.O.	Erithematous Plaques, ecchymosis	LL	No
4 - L.C.P.R.	Erithematous Nodules	LLL	No
5 - T.L.F.	Erithematous Nodules	RLL	Arthralgias
6 - P.T.M.V.	Erithematous Nodules	LL	No
7 - M.A.Q.	Erithematous Nodules	LL, UL	Edema, pain in knee and ankle
8 - R.J.G.	Erithematous Nodules	LL	Neuritis
9 - G.S.	Erithematous Nodules	LL	Pain, edema in LL
10 - M.P.V.	Erithematous Nodules	RLL	No
11 - O.D.M.R.	Erithematous Nodules and Ulceration	LL	Fever, myalgia e malaise

LL — lower limbs
UL — upper limbs
LLL — left lower limbs
RLL - right lower limbs

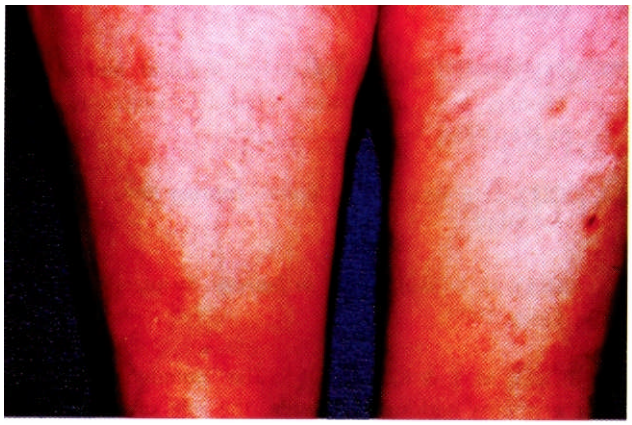

Figure 1. Case 11 — Erithematous nodules and livedo reticulares in tighs.

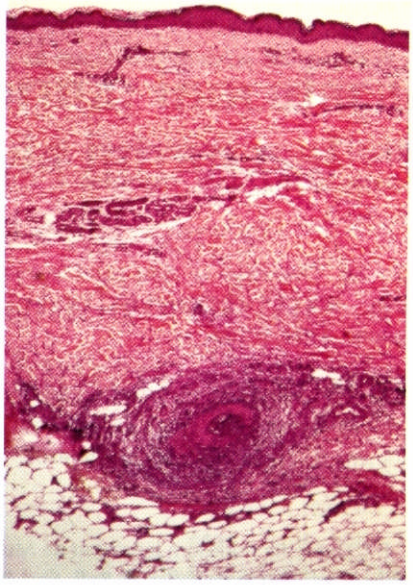

Figure 2. Case 4 - Arteritis in deep dermis inflammatory reaction limited to perivascular area. H.E. 40x.0x.

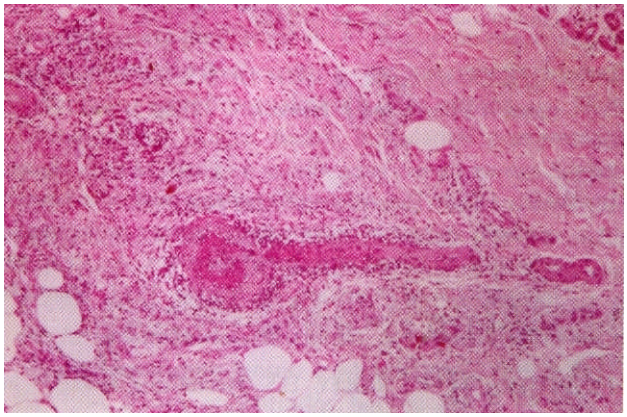

Figure 3. Case 6 — Segmental acute arterites in deep dermis. H.E. 40x

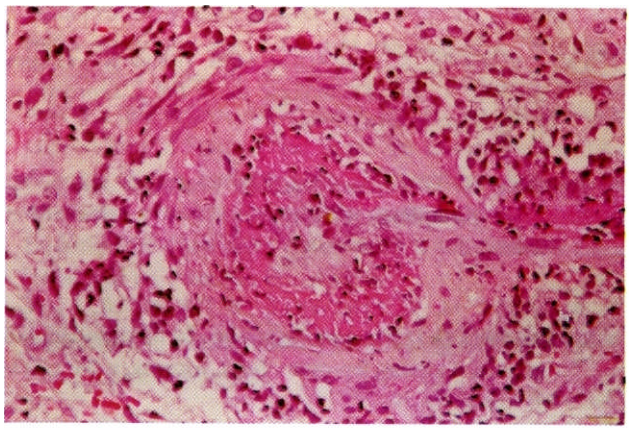

Figure 4. Case 6 – Segmental acute arterites, necrosis, neutrophilic infiltrate and fibrin vessel wall. H.E. 160x.

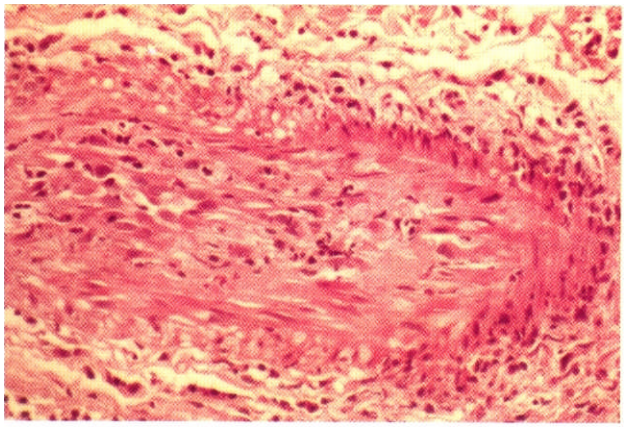

Figure 5. Case 10 — Arteritis. Exsuclative reaction and subendothelial fibrous thickening. H.E. 160x.

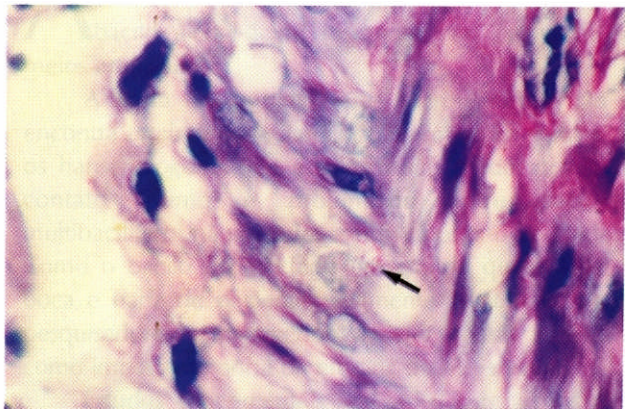

Figure 6. Case 10 — Arteritis granular bacilli in vessel wall Faraco Fite 400x.

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