ERYTHEMA NODOSUM LEPROSUM

A CLINICO-PATHOLOGIC STUDY

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Erythema nodosum is a well known complication in leprosy. It was described as early as 1912 ([11]). An excellent description of the condition was given by Barrera and Chavarria in 1924 ([1]). Since then several authors have described the clinical and histopathologic picture as seen in different countries ([2, 4, 6, 10, 12, 14, 15]). In this paper it is aimed to present the manifestations of this common condition in leprosy as seen in South India.

MATERIALS AND METHODS

Thirty-six patients with lepromatous leprosy at the Schieffelin Leprosy Research Sanatorium, Karigiri, who were willing to undergo biopsy studies, were chosen. Soon after a patient with erythema nodosum leprosum (ENL) was admitted into the wards a detailed history of the disease was taken and a thorough clinical examination was made. Biopsy examinations of one of the nodules and of a lepromatous lesion of the skin were made on the same day. The tissues were fixed in Zenker solution and after processing were embedded in paraffin and cut into sections 5-7 micra in thickness. A hematoxylin and eosin stain and an acid-fast stain ([5]) were made in each case. Skin smears were taken by the Wade technic ([16]) and the bacteriologic index was estimated.

RESULTS

In most cases the eruption was preceded by general malaise and vague pain all over the body. Sometimes there was a rise in temperature. Within 24 to 48 hours of onset of these prodromal symptoms the skin lesions developed. They were round or oval, and were present on the face, trunk and extremities, with a special predilection for the extensor aspect of the upper extremities. The nodules were more numerous on the face and the extremities than on the trunk (Table 1f). Their diameters varied from 0.5 cm. to 4 cm. The nodules were found both in the skin and the subcutaneous tissue. In an occasional case they showed a tendency to coalesce to form large, red, warm plaque-like lesions. This tendency was noticed more often in the lesions present in the extremities. These nodules were often painful and tender.

The mucous membranes of the body were rarely affected. The authors have seen only one case of ENL in the mucous membrane of the nose and pharnyx. In two cases the lesions were seen in the conjunctiva also.

When the lesions began to resolve the color changed from red to dark-red and then to dark-brown. The brown stain might persist for several days. In some cases the superficial part of the epithelium peeled off, with scaling.

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TABLE 1.—*Data as respects sex, age, and other features in 36 cases of ENL.*

Analysis of features	Number of cases
a. *Sex*	
Males	32
Females	4
Total	36
b. *Age*	
11 to 20 years	12
21 " 30 "	12
31 " 40 "	8
41 " 50 "	3
51 " 60 "	1
Total	36
c. *Duration of disease*	
Under 3 years	1
3 - 5 "	12
5 - 10 "	17
Over 10 "	6
Total	36
d. *Bacteriologic index*	
Under 1	3
Between 1 and 2	11
" 2 " 3	18
Over 3	4
Total	36
e. *Signs and symptoms*	
Fever	32
Polyarthralgia	17
Polyneuritis	6
Edema of extremities	5
Swelling and tenderness of breasts	3
Orchitis	2
Iritis	2
f. *Distribution of nodules*	
Extremities	36
Face	32
Trunk	27
All 3 sites	25
Extremities only	2
Face only	0
Trunk only	0
g. *Temperature range*	
Above 102°F	13
Between 100 and 102	10
Below 100	6
No fever	3
Not recorded	4
Total	36
h. *Histopathology*	
Prickle cell proliferation	36
Macrophages	36
Neutrophil leucocytes	36
Lymphocytes	6
Panniculitis	30
Vasculitis	16
Abscess formation (dermis, 12; subcutaneous, 4)	16
Acid-fast bacilli	21

In severe cases a central yellowish spot developed in the nodules, which later broke down and ulcerated. The pus obtained from these lesions, in 3 of our cases, was subjected to routine culture and found sterile on culture. However, it showed a large number of broken and granulated acid-fast bacilli singly and in clumps. The ulcerated lesions often healed within 3 weeks, but in some cases they took nearly 2 months to heal. The ulcers were superficial and healed without fibrosis or scarring, unless they were secondarily infected.

The eruptions of ENL were often accompanied by fever (32 cases), polyarthritis (17 cases) and polyneuritis (6 cases). Iritis and orchitis were present in 2 cases each (Table 1e).

Uually an attack of ENL resolved within 3 weeks. In some cases the nodules appeared in crops and the patient was sick for several weeks, even up to 12 weeks. In some others, one attack followed closely

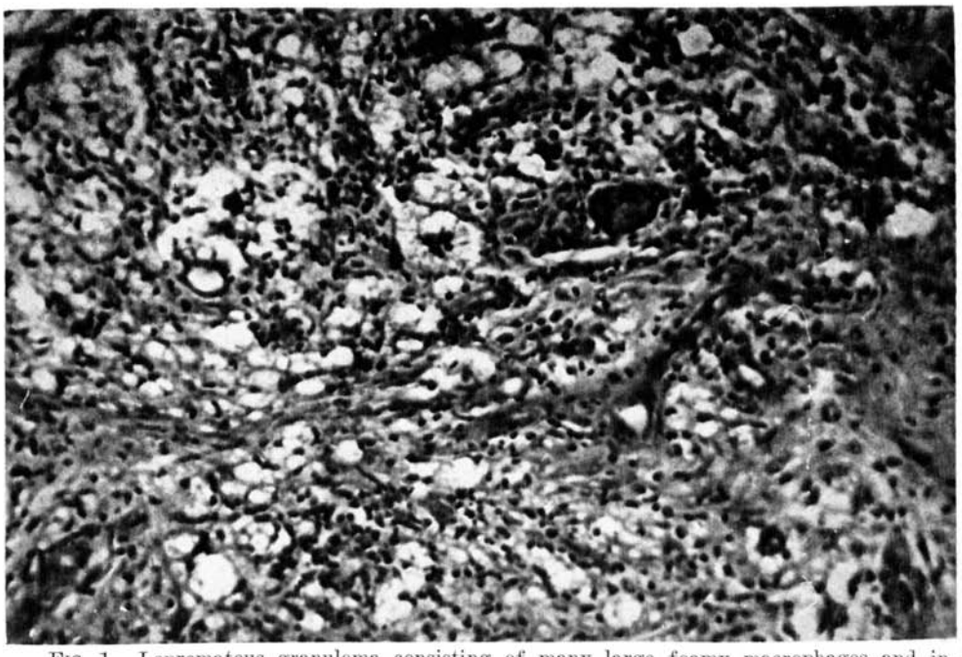

FIG. 1. Lepromatous granuloma consisting of many large foamy macrophages and infiltrating polymorphonuclear leucocytes (H & E, high power).

upon the previous one, so that they had to be hospitalized for more than 3 years.

PROGRESS

Of these 36 patients, 22 were followed for periods ranging from 8 months to 2 years and 10 months. In 12 of the 22, the ENL resolved within 3 weeks and they were able to tolerate full doses of antileprosy treatment. In 2, the ENL lasted for a longer duration. They received antileprosy treatment intermittently and had to wait for 3 to 4 months before effective doses of antileprosy treatment could be administered. Eight of them were continuously developing nodular eruptions and so could not be treated at all for leprosy. The bacteriologic index improved in 17 cases, which included 6 in which crops of ENL were still developing. No improvement was noticed in 3 cases and one became worse. These 4 cases also were having continuous nodular eruptions.

HISTOPATHOLOGY OF ENL

The epidermis in all cases showed flattening of the rete pegs and minimal but obvious proliferation of the prickle cell layer. There was some increase in pigment in the cells of the basal layer. The main changes were noticed in the dermis and the subcutaneous tissue. The upper part of the dermis showed pronounced increase in vascularity, with many dilated capillaries. There was minimal hemorrhage into the interstitial tissue. Large collections of neutrophil leucocytes were seen to infiltrate the lepromatous granulomata in the dermis (Fig. 1). In

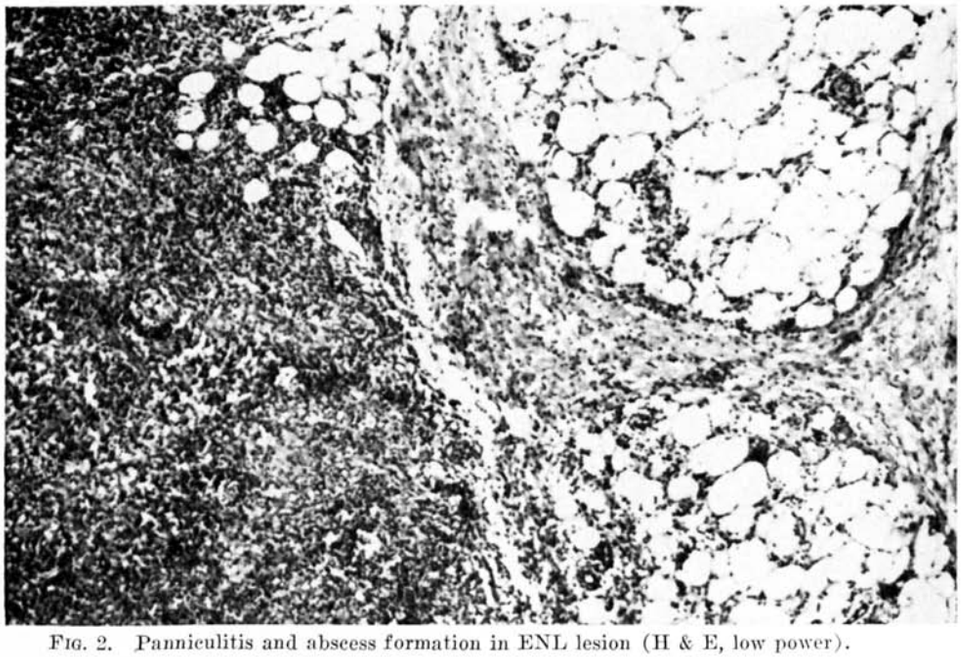

FIG. 2. Panniculitis and abscess formation in ENL lesion (H & E, low power).

30 cases the inflammation extended down toward the subcutaneous tissue. The fat septa were infiltrated with neutrophils (Fig. 2) and a few fat cells had a ground glass appearance. In 16 cases necrosis and abscess formation were noticed both in the dermis and in the sub-

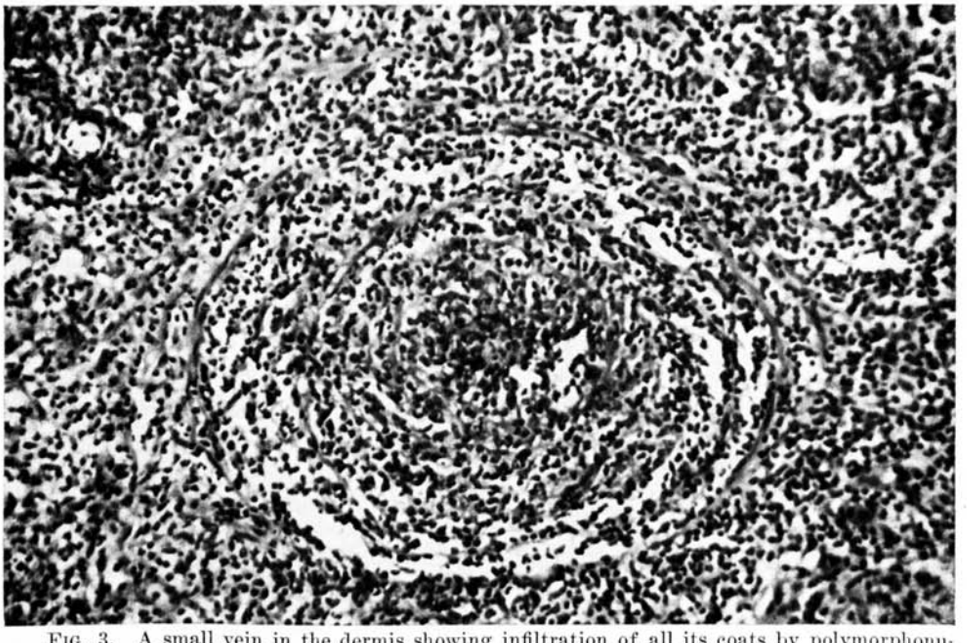

FIG. 3. A small vein in the dermis showing infiltration of all its coats by polymorphonuclear leucocytes and obliteration of its lumen (H & E, high power).

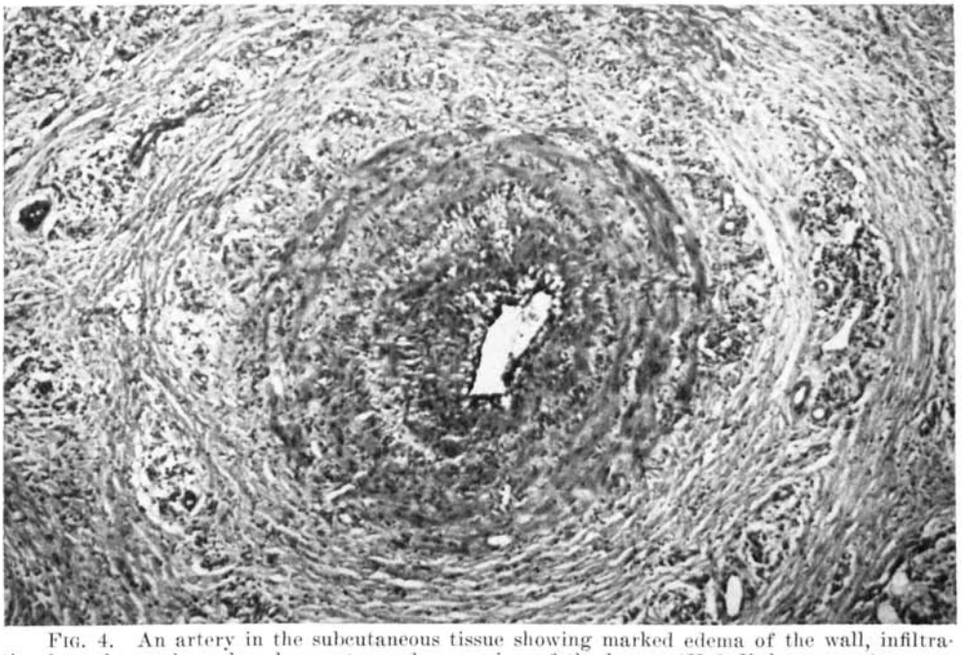

FIG. 4. An artery in the subcutaneous tissue showing marked edema of the wall, infiltration by polymorphonuclear leucocytes and narrowing of the lumen (H & E, low power).

cutaneous tissue. The abscess cavities were filled with neutrophils. There was also interstitial edema of varying degree, both in the dermis and in the subcutaneous tissue.

In 16 cases the veins and the arteries in the lesion showed pronounced inflammatory reaction involving the entire wall, and in some lesions necrotizing arteritis with much destruction of the vessel wall and total obliteration of the luman was seen (Figs. 3 and 4).

There was scattered and scanty lymphocytic infiltration in the majority of cases, and a few showed significant collections of lymphocytes around blood vessels. In an occasional section eosinophils and plasma cells were seen. Epithelioid cells and giant cells were invariably absent, even in older lesions. Acid-fast stains showed bacilli in 21 cases. Most of the bacilli were broken and granular.

In the follow-up studies of 12 cases that showed speedy recovery from ENL, only one was found to have vascular lesions as described above, but 4 showed necrosis and abscess formation. Among the 8 cases continuously having ENL symptoms, 5 had vasculitis and 4 had abscesses in the lesions.

DISCUSSION

All the 36 patients were cases of lepromatous leprosy. It is well known that ENL occurs only in lepromatous leprosy ([3]).

In the group of 36 cases studied there was a predominance of males (Table 1a), but this might only reflect the high proportion of male patients attending our hospital (10:1). Browne ([2]) has reported

a slightly greater incidence among males, whereas Guinto *et al.* ([6]) found more females.

The incidence was highest at ages between 11 years and 40 years (Table 1b), which corresponded to the highest age incidence of leprosy in South India ([8]).

Thirty-five of the 36 cases studied were of lepromatous leprosy established for more than 3 years (Table 1c). Thirty-three patients had a high bacterial population (bacterial index more than 1) (Table 1d). Most of the bacilli were broken and granulated. Ridley ([13]) found that the bacilli were granular even before the onset of ENL. It is reasonable to suggest that ENL often occurs in long-standing lepromatous patients with moderately large numbers of broken and granulated bacilli.

The hyperpigmentation of the skin in resolving lesions was due mainly to the increase in vascularity in the region with extravasation of red blood cells in the interstitial tissue. A reactive increase of melanin in the basal cells would also contribute to the discoloration. In all cases there was proliferation of prickle cells in the epidermis. This could be a reaction to the underlying inflammatory reaction.

The tissue reaction in ENL was somewhat different from that in erythema nodosum as seen in tuberculosis or sarcoidosis in that there were no epithelioid cells or giant cells. Vasculitis was a prominent feature in 16 cases. It is well recognized in erythema nodosum occurring in the course of other diseases ([9]). In this study vasculitis was seen usually in severe cases and when present was a poor prognostic sign. Pepler *et al.* ([12]) preferred to term the ENL lesions as "acute panniculitis nodosa leprosa." Acute panniculitis was seen in 30 cases, and in 6 the lesion was limited to the dermis, with no involvement of subcutaneous fat (Table 1h).

The view that ENL is a hypersensitivity reaction and that the inflammation is of an allergic nature is generally accepted. The histopathologic changes resemble very much an Arthus reaction. It is possible that the large amount of circulating antibodies in lepromatous cases ([7]) may react with the locally released antigens from the dead bacteria, to produce the ENL.

ENL is a well-defined entity in lepromatous leprosy with specific clinical and histopathologic appearances. As seen in this study, it has 3 phases. The first is an acute phase characterized by a generalized, red, tender, nodular eruption, often accompanied by fever, polyarthralgia or polyneuritis, which is followed by resolution within 2 or 3 weeks. In the subacute phase crops of nodules follow one after another at frequent intervals and it might take 2 to 3 months to resolve. In the chronic phase the nodules may continue to erupt in crops and the attacks last for several years.

The histopathologic changes vary from a mild lesion with tissue edema and scattered infiltration of the dermis and subcutaneous tissue

with neutrophil leucocytes to a very severe and acute lesion showing vasculitis, necrosis and abscess formation. In some cases it may be so severe as to resemble the tissue reaction seen in the Lucio phenomenon. This makes us wonder if the Lucio phenomenon may be a severe form of ENL.

SUMMARY

The manifestations of ENL as seen in leprosy patients in South India are similar to those described in other parts of the world. It presents itself as a well-defined complication in established lepromatous leprosy patients. It may be encountered in acute, subacute and chronic phases, depending on the duration of the lesions. The histopathologic changes in all these phases are essentially the same, consisting of neutrophilic infiltration of the skin and subcutaneous tissue containing leprotic granulomata.

RESUMEN

Las manifestaciones de ENL vistas en los pacientes leprosos en el Sur de la India, son similares a aquellas descriptas en otras partes del mundo. Se presenta como una bien definida complicación en pacientes establecidos como lepra lepromatosa. Puede ser encontrado en las fases agudas, subagudas y cronicas, dependiendo de la duración de las lesiones. Los cambios histológicos en todas estas fases son esencialmente las mismas, consistiendo en infiltración neutrofila de la piel y tejidos subcutaneos que contienen granulomas leproticos.

RESUMÉ

Les manifestations de l'erythème noueux lépreux telles qu'elles apparaissent chez les malades du Sud de l'Inde sont semblables à celles qui ont été décrites dans d'autres parties du monde. L'ENL se présente comme une complication bien définie chez les malades atteints de lèpre lépromateuse établie. Il peut être observé sous une forme aigue, subaigue, ou chronique, ceci dépendant de l'âge des lésions. Les modifications histologiques observées dans ces differentes phases sont essentiellement les mêmes, et consistent en une infiltration neutrophile de la peau et du tissu sous-cutané contenant les granulomes lépreux.

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