

THE HISTOPATHOLOGY OF ACUTE PANNICULITIS NODOSA LEPROSA (ERYTHEMA NODOSUM LEPROSUM)

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The term "erythema nodosum leprosum" has frequently appeared in the literature on leprosy since the 1930's, apparently popularized by the Japanese (9). The occurrence of "erythema nodosum" in leprosy had previously been noted at the end of the nineteenth century by Brocq (6) and by Hansen and Looft (8), but the term seems to have fallen into disuse.

As will become clear from our clinical and histological descriptions of the phenomenon commonly known as erythema nodosum leprosum, we believe the title to be a misnomer. We suggest that it would be more accurate to call it panniculitis nodosa leprosa (P.N.L.).

This condition is commonly confused with acute lepra reaction, both processes being referred to as "acute reactions"; but a sharp line of distinction must be drawn between them. P.N.L. occurs only in patients with lepromatous leprosy as an acute, subacute or chronic skin eruption, with or without fever. It is characterized by showers of dusky red nodules, 0.5 to 2 cm. in diameter, on the extensor surfaces of the limbs, on the face, and, less often, on the trunk. The number of lesions appearing in an attack varies from a few to several hundreds, and they sometimes coalesce to form plaques.

The nodules may be painful, and they are usually tender to touch. They last in acute cases from a few days to several weeks. An attack often begins quite suddenly, and the body may be covered with lesions within a few hours. The temperature may rise to 103°-104°F. The general condition usually remains little affected. Recurrent attacks are the rule. In other patients the course is less acute, and they may continue to show a few scattered, evanescent nodules over long periods of time with a minimum of fever and discomfort. Suppuration is not uncommon. Healing is usually not accompanied by any scarring, but there is frequently residual hyperpigmentation. Although P.N.L. occurs in untreated patients it is much more common after treatment, and its incidence has greatly increased since the advent of sulfone therapy. Further details of the condition and its differentiation from acute lepra reaction will be found in an article by Wolcott (18).

Although the individual lesions of P.N.L. may sometimes closely resemble those of classical erythema nodosum, there are major differences in the clinical pictures. P.N.L. affects areas— e.g., the face— seldom or never affected in erythema nodosum; the numbers of lesions and the areas covered are usually greater; and the frequent recurrences and suppuration of lesions in P.N.L. are not a feature of erythema nodosum. Even the clinical resemblance of P.N.L. to erythema nodosum is not always very striking; in subacute and chronic cases P.N.L. lesions have a greater resemblance to those of erythema induratum, the sarcoid of Darier and Roussy, or the cutaneous form of polyarteritis nodosa.

The descriptions of the histopathological picture in the literature we have studied are confusing.

According to Stein (16) the "new" lesions (erythema nodosum leprosum) developed on pre-existing but inapparent infiltrations. Reiss (15) found the greatest pathological changes in the vessels and the perivascular region of the cutis. Ermakova (7) states that there appear numerous lymphoid, plasma and polymorphonuclear cells in the picture of the specific leprous tissue of erythema nodosum leprosum. In Wolcott's (18) opinion the basic feature in erythema nodosum leprosum is vascular changes in the small subcutaneous vessels and their branches in the corium. The most striking change he found was edema of the corium.

In a communication on erythema nodosum leprosum at the recent International Congress at Madrid, Wade (17) stated that the impression was gained that the eruption occurs only where there are accumulations of old, bacillus-poor lepra cells; that it is situated primarily in the cutis and not predominantly in the subcutis as in ordinary erythema nodosum; that it is not at all distinctive histologically; and that its resemblance to ordinary erythema nodosum is more distinct clinically than otherwise. He remarked, however, that his material was limited, especially as regards early acute lesions, and that few of his specimens contained much subcutis.

PRESENT STUDY

The present study is based on 20 specimens from 19 cases of P.N.L. in Bantu patients, aged from 8 to 53 years, at the Westfort Institution near Pretoria, as shown in Table 1. Our findings do not correspond to those quoted above. The major lesions in our cases were centered in the subcutis, and they consisted of panniculitis (*syn.* nonspecific inflammation of subcutaneous fat; *stéatonecroses microcystiques disséminées*; lipogranuloma, etc.).

HISTOPATHOLOGY

The main histopathological findings in the individual cases are summarized in the table referred to. Attention should, however, be drawn to the following facts:

Subcutaneous tissue.—The main lesion appears to be centered in the subcutaneous tissue, and more specifically in the fat lobule. In order to be able to study the pathological features of this condition, therefore, it

TABLE 1.—Data on the 19 cases with panniculitis nodosa leprosa involved, and the histopathological findings in the 20 specimens examined.

Case number	Sex	Duration	Dermis ^a		Subcutis ^b		
			Lepromatous	Inflammatory	Fat lobules	Septa	Blood vessels
7155	M	12 hr	+	1 + Ac.	V. sl. ac. inflam.	Normal	Normal
18381	M	12 hr	+	1 + Sub.	Serous atrophy; fat necroses, focal	Sl. ac. inflam.	Normal
10900	F	12 hr	+	1 + Sub.	Sub. pannic.	Sub. inflam.	Normal
8429	F	24 hr	+	1 + Sub.	Ac. pannic.; abscesses entire fat lobules	Sub. inflam.	Sl. edema, arteries
10944	M	24 hr	+	1 + Sub.	Ac. pannic.; abscess	Ac. inflam.	Edema 2+; sl. sub. infiltration arteries
11956	M	24 hr?	+	2 + Sub.	Ac. pannic., entire lobules; abscess	Chr. inflam.	Edema arteries, endothelial swelling, ac. infiltration
10999	F	36 hr	+	1 + Sub.	Ac. pannic., very diffuse	Ac. inflam.	Sl. ac. panarteritis
10693	M	48 hr	+	1 + Ac.	Normal	Normal	Normal
11632	F	48 hr	+	1 + Sub.	Ac. pannic. & abscess; serous atrophy	Ac. inflam.	Ac. capillaritis, arteriolitis & phlebitis
10984	M	Few da	+	1 + Chr.	Sl. diffuse chr. pannic.	Sl. chr. inflam.	Lymphocyte infiltration arteries
10694	F	Few da	+	1 + Sub.	Sub. pannic.; sl. ac. focus with abscess	Sl. sub. inflam.	Sub panarteritis; edema & swelling
11681	F	Few da	+	Nil	Sl. lepromatous infiltrate only		Normal
11634	M	3 da	+	Nil	Chr. pannic.; sl. serous atrophy	Chr. inflam.	Normal
11102	F	± 4 da	+	3 + Ac.	Ac. pannic., diffuse; abscess formation	Ac. inflam.	Edema
11390	M	5 da	+	1 + Chr.	Ac. pannic.; small abscesses in fat	Sub. inflam.	Normal
8973	M	± 1 wk	+	Fib. ^c	Diffuse fibrosis; sl. lymphocytic infiltration	Fibrosis	Endarteritis
11198	F	1-2 wk	+	2 + Sub.	Sub. pannic.; serous atrophy	Sub. inflam.	Edema; endothelial proliferation; sl. lymphocytic infiltration.
10981 No. 1 & 2	M	Few wk	+	Nil	Chr. pannic. (both specimens)	—	Endarteritis (both specimens)
11232	M	Chr.	—	1 + Chr. Fib. 2 +	Sl. chr. pannic.; 1 + fibrosis	Sl. chr. inflam.	Endarteritis

^a The headings here refer to the presence of cell infiltrates. Ac = acute; Sub = subacute; Chr = chronic; Fib = fibrosis. The epidermis was normal in all instances.

^b Pannic. = panniculitis; inflam. = inflammatory reaction; Ac. inflam. = infiltrate consisting predominantly of polymorphonuclear leucocytes; Sub. inflam. = infiltrate consisting of approximately equal numbers of polymorphonuclear leucocytes and lymphocytes and plasma cells; Chr. inflam. = infiltrate composed mainly of lymphocytes, plasma cells and histiocytes.

^c Diffuse fibrosis, no inflammatory reaction.

is necessary to take biopsy specimens that include the entire thickness of the subcutis. In early cases the histological picture varies from that of small foci of acute inflammatory-cell infiltration or serous atrophy of fat and small foci of necrosis, to an extensive acute panniculitis with numerous areas of abscess formation (Fig. 1). In more chronic cases the infiltrate consists predominantly of lymphocytes and plasma cells, and in cases of a few weeks duration there appears evidence of fibrous replacement of the fat lobules. It should be noted that foci of lepra-cell reaction could frequently be demonstrated in the region of the main lesion in the subcutis. However, only very occasional bacilli could be demonstrated in these foci.

Septa.—The septa, although usually also involved in the reaction, show a much less extensive infiltrate.

Blood vessels.—The pathological changes in the blood vessels varied from case to case. In a few of the acute cases the blood vessels were normal, or showed only slight edema of the walls. In yet other acute cases there could be demonstrated clear evidence of acute capillaritis, phlebitis and panarteritis (Fig. 2). In cases with vascular involvement, edema of the wall and swelling of endothelial cells were frequently very prominent features. This occasionally resulted in marked narrowing of the lumen. In order to assess the extent and type of vascular involvement, serial sections of the specimens were cut in four of the cases with acute panniculitis. In none of these specimens could vascular occlusion or any evidence of fibrinoid necrosis be demonstrated. Although vascular lesions were frequently observed, we did not gain the impression that they represented the primary site of reaction in these acute cases. Endarteritic changes were frequently present in some of the older lesions.

Dermis.—In addition to the lepromatous infiltrate, a diffuse acute, subacute or chronic inflammatory-cell infiltration was nearly always present.

Epidermis.—The epidermis showed no significant pathological changes in any of the cases examined.

DIFFERENTIAL DIAGNOSIS

Before discussing some of the nodose lesions which have to be differentiated from P.N.L., it seems appropriate to give a short classification of the nonspecific inflammatory lesions involving the subcutaneous fat (panniculitis). The available data suggest that panniculitis has a complex etiology, and that it should be considered as a syndrome. It is not possible to use the histological pictures as a basis for classification of the varieties of panniculitis.

1. Panniculitis as a secondary reaction in the neighborhood of other processes.

2. Primary panniculitis, of which the external cause is known or suspected:

- (a) Mechanical trauma;
- (b) Physical trauma (cold, heat);
- (c) Chemical causes (bromides, iodides, sulfonamides, etc.);
- (d) Infections (specific or nonspecific) such as syphilis, tuberculosis, sportrichosis, typhus fever, etc., including leprosy (lepromatous type only).

3. "Spontaneous" panniculitis, with the following clinical variants:

- (a) Relapsing febrile, nodular, nonsuppurative panniculitis (Weber-Christian syndrome).¹
- (b) "Nodular vasculitis," or erythema induratum nontuberculosum (Whitefield).
- (c) Indefinite type.

For more detailed studies of panniculitis we may refer to the works of Baumgartner and Riva (1), Bendel (2), Kooij (10), and Blanc (5).

P.N.L. could be classified under heading 2d as a primary panniculitis.

From the point of view of histopathology, it is necessary to consider the following four conditions: classical erythema nodosum, erythema induratum, the sarcoid of Darier and Roussy and the cutaneous form of polyarteritis nodosa.

Classical erythema nodosum.—This condition is characterized mainly by changes in the septa between the fat lobules (Fig. 3). These septa are enlarged by a fibrinous and often hemorrhagic exudate containing nests of polymorphonuclear leucocytes, eosinophils, and some giant cells. Vascular changes are usually extensive and severe, especially in the larger arteries and veins (11). A few polymorphonuclear leucocytes are frequently present between the fat cells, but abscess formation does not occur. (Abscess formation is one of the striking features of the early cases of P.N.L.). A nearly constant finding in erythema nodosum, confirmed by other workers, is the so-called reticuloendothelial nodules of Miescher. According to Miescher (12, 13), this finding indicates that the classical erythema nodosum is an infective (virus?) condition, and that the infections (particularly tuberculosis) which often occur with it are only provoking factors which play a role comparable to that of malaria or pneumonia in relation to herpes simplex. In cases of erythema nodosum due to sulfathiazole, the Miescher bodies were also found.

In our cases of P.N.L. in the lepromatous form of leprosy we were unable to find the Miescher bodies. This we feel is another point against the identity of the two conditions. We therefore propose the term panniculitis nodosa leprosa as a substitute for erythema nodosum leprosum.

Erythema induratum (Bazin).—In this condition there may be areas of ulceration and necrosis of the epidermis. The lower third of the cutis

¹ It should be remembered that there are various combinations of signs in this syndrome. Although the original patients of Weber and Christian showed no suppurative lesions, cases have since been described with suppuration and with or without depression of the healed lesions.

usually shows caseation necrosis and diffuse infiltration by lymphocytes. Caseation necrosis is also evident in the septa and fat lobules of the subcutis, and these areas of necrosis are surrounded by epithelioid cells, giant cells and lymphocytes. "Wucheratrophie" is frequently present. A very prominent feature of this condition is the presence of obliterative thrombotic vasculitis.

Sarcoid of Darier and Roussy.—There is no unanimity over this syndrome. The term panniculitis is rarely used in the French literature, but cases with this type of change are described under the title of sarcoid of Darier and Roussy. Pautrier (14) describes the histological picture thus:

The hypodermal lesions are of two varieties; on the one hand there may be banal inflammatory lesions of the adipose tissue; on the other hand there may be tuberculoid formations or nodules having all the characteristics of frank tuberculosis.

German writers generally consider this condition together with erythema induratum of Bazin, as a form of tuberculosis cutis indurativa; and American and English authors often classify it as a hypodermal variety of the Besnier-Boeck-Schaumann sarcoidosis.

Polyarteritis nodosa.—In the cutaneous form of polyarteritis nodosa the typical features are fibrinoid necrosis of the intima, media and adventitia of the arteries, and a massive neutrophil leucocytic infiltrate with much leukocytoclasia.

COMMENTS AND CONCLUSIONS

Although the individual lesions of acute panniculitis nodosa leprosa (P.N.L.) may often resemble those of classical erythema nodosum and occasionally, in the cases of longer duration those of erythema induratum, sarcoid of Darier and Roussy or the cutaneous forms of polyarteritis nodosa, the histological pictures in those conditions are easily distinguishable. Confirmation of our findings comes in articles by Birrell (3, 4), who originally published as Weber-Christian nonsuppurative panniculitis a case which he eventually found to be one of leprosy (probably P.N.L.).

The cause of P.N.L. is obscure. Although it occurs most commonly in treated cases it cannot be classified simply as an allergic reaction to a medicament. The existence of the lepromatous state is essential for its development. As it does not occur in tuberculoid leprosy, it may well be that the presence of many bacilli is necessary for its development. The incidence of the reaction seems to be in direct proportion to the effectiveness of the medicament used for treatment of the disease. It may therefore be a reaction of the fat against the products of degeneration of lepra bacilli (bacterial allergide) in treated or untreated cases. Against this is the fact that the lepromin test is usually negative in cases with P.N.L.

It could also be postulated, as Miescher has done in classical erythema nodosum, that a mechanism of biotropism is involved, and that the

lepromatous state or the medicaments may only act as facilitating factors for some unknown organism.

P.N.L. might also be a manifestation of the Shwartzman or Arthus phenomenon, or a combination of the two.

SUMMARY

The histological features of 20 specimens of acute panniculitis nodosa leprosa (erythema nodosum leprosum) are studied. The most important feature is shown to be a panniculitis.

The histological picture in P.N.L. is shown to be distinct from those of classical erythema nodosum, erythema induratum, sarcoid of Darier and Roussy, and the cutaneous form of polyarteritis nodosa, all of which conditions may bear a clinical resemblance to P.N.L.

Although P.N.L. occurs most frequently in treated cases, the lepromatous state is essential for its development.

It is suggested that the term "panniculitis nodosa leprosa" describes more accurately the lesion now known as erythema nodosum leprosum.

SUMARIO

Estudiadas las características histológicas de 20 ejemplares de paniculitis nudosa leprosa aguda (eritema nudoso leproso), la más importante resultó ser una paniculitis.

El cuadro histológico en la P. N. L. se mostró distinto de los cuadros del eritema nudoso clásico, del eritema indurado, del sarcoide de Darier y Roussy y de la forma cutánea de la poliarteritis nudosa, dolencias todas éstas que pueden guardar semejanza clínica con la P. N. L.

Aunque la P. N. L. aparece más frecuentemente en los casos tratados, el estado lepromatoso es indispensable para su aparición.

Apúntase que el término de "panniculitis nudosa leprosa" describe más exactamente la lesión hoy día denominada eritema nudoso leproso.

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DESCRIPTION OF PLATE

PLATE (3)

FIG. 1. Acute panniculitis nodosa leprosa, showing areas of acute panniculitis and abscess formation. Hematoxylin and eosin, 30X.

FIG. 2. Acute panniculitis nodosa leprosa, showing panarteritis and edema of the artery wall. Hematoxylin and eosin, 120X.

FIG. 3. Erythema nodosum, showing involvement of septal tissue by the inflammatory process. Hematoxylin and eosin, 120X.

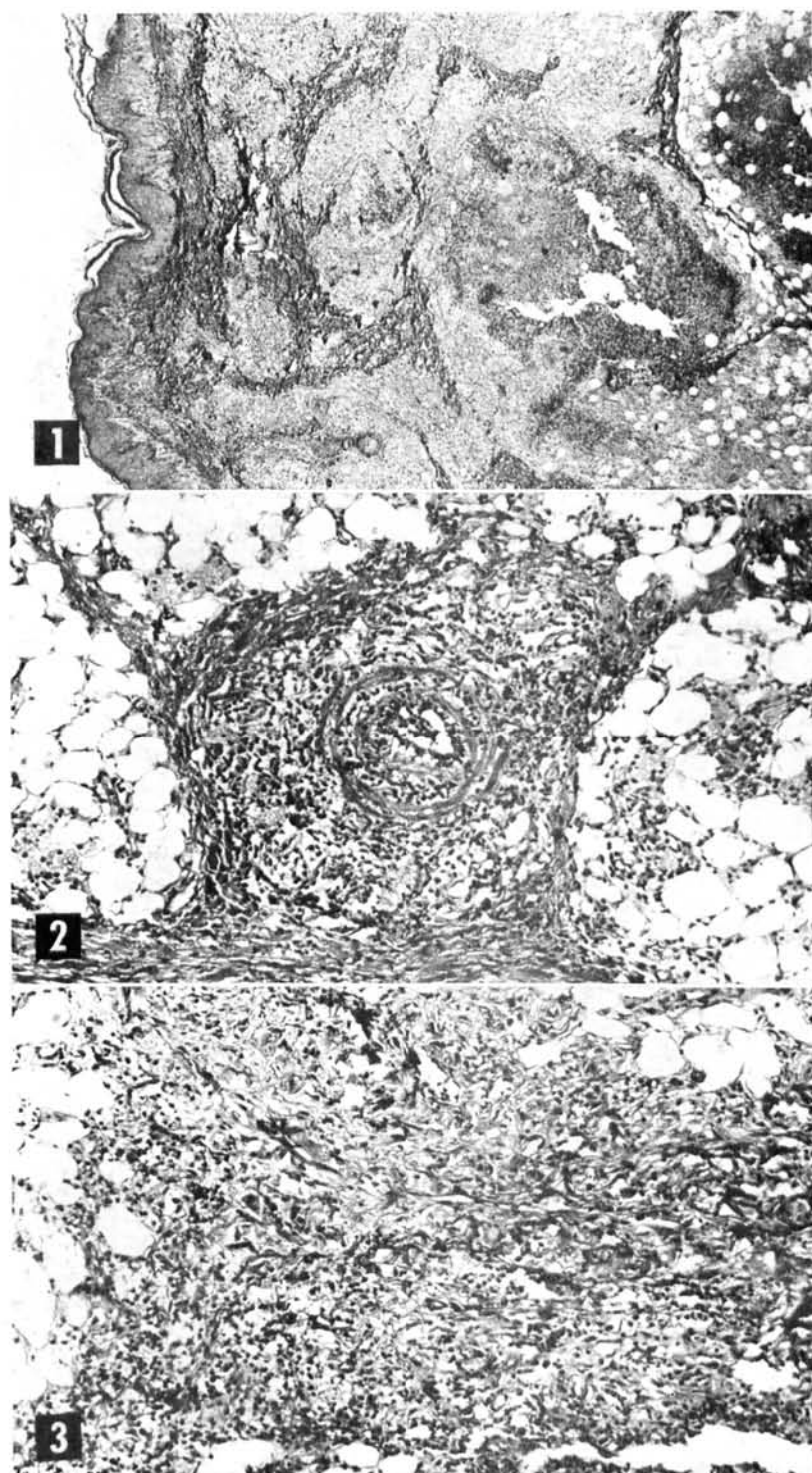


PLATE 3.