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Involvement of Subcutaneous Veins in Lepromatous Leprosy[1]

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Lepromatous leprosy (LL) is a multisystem disease with extensive involvement of the skin and peripheral nerves ([4, 8]). Bacteremia is observed quite frequently in the LL patient ([9, 10, 19, 27]) and acid-fast bacilli (AFB) have been demonstrated in the intimal cells of the smaller blood vessels of the skin ([5]), nerve ([6]), and testicles. Involvement of larger vessels by the lepromatous granuloma is still considered to be rare, however. Although described in the early studies on the pathology of leprosy ([1, 11, 12, 13, 20, 21, 25, 26]), only a few reports of vessel involvement are available in current literature.

Three years ago, we described six cases with lepromatous involvement of subcutaneous veins of the extremities ([22]). These present clinically as palpable subcutaneous cords, and are often confused with involved and thickened nerves. Subsequently, we have studied subcutaneous veins in LL patients, both with and without cord-like thickening, in order to assess the frequency of venous involvement in LL and to study the pattern of development of leprous phlebitis.

MATERIALS AND METHODS

Thirty-one patients attending the Central JALMA Institute Out Patient Department clinics were studied. By clinical and histopathological criteria, 29 patients had lepromatous leprosy (LL) and two had borderline lepromatous leprosy (BL). Four patients gave histories of previous erythema nodosum leprosum (ENL) reactions. No patient was in reaction at the time of biopsy. The patients ranged in age from 15 to 65 years with a mean of 42 years. Twenty-nine were males and two were females.

The duration of disease ranged from 1–19 years with 17 patients having had the disease for 1–5 years; six for 6–10 years, and eight for 11–19 years. Twenty-one patients had no history of previous treatment; six were on treatment with dapsone (DDS) in combination with rifampin or isoniazid (INH) and thiacetazone for an average period of six months; and four patients had histories of irregular treatment with DDS alone for an average period of three years.

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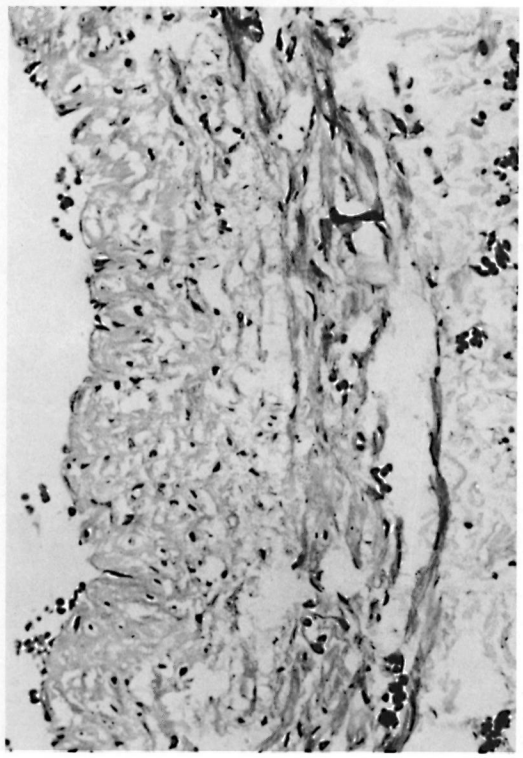

FIG. 1. Early lesion showing mild infiltration of inflammatory cells in the intima. Acid-fast bacilli (AFB) were present in the intimal layers (H & E ×80).

FIG. 2. Early lesion showing foamy cell transformation of the endothelial cells (H & E ×125).

Eleven cases presented with clinical evidence of leprous phlebitis in the form of subcutaneous, cord-like structures over the forearm and dorsum of the hand. These structures could be distinguished from thickened nerves by the criteria of a) continuity with visible veins, b) branching, and c) extension across limits of nerve supply, e.g., from the ulnar to the radial area. The remaining 18 cases had clinically normal venous networks over the extremities. Biopsies were taken from one of the involved veins in the former group and from one of the medium-sized tributaries in the latter. A 1.5 cm-long segment of vein was excised after ligating both ends. A skin biopsy for classification was taken from the same incision in each case.

The tissues were processed, paraffin embedded, cut at 5 μ, and stained by hematoxylin and eosin (H&E), the Fite-Faraco modification of the Ziehl-Neelsen, Masson trichrome, Verhoeff's, van Gieson's, and the phospho-tungstic acid hematoxylin (PTAH) stains.

THE TABLE. *Correlations between the observed grades or stages of leprous phlebitis and the duration of leprosy.*

Grade	Duration of disease (years)			Totals
	0–5	6–10	11–19	
1	9	3	1	13
2	3	2	3	8
3	4	1	3	8
No lesion	1	0	1	2

RESULTS

Of the 12 patients with venous thickening, 11 had histological evidence of leprous phlebitis; in the remaining case the lesion was nonspecific in nature. In the group with clinically normal venous networks, 18 out of 19 cases showed changes of leprous phlebitis; in the remaining case the vein was within normal limits.

Based on the percentage of lumen occlusion, the lesions could be divided into early

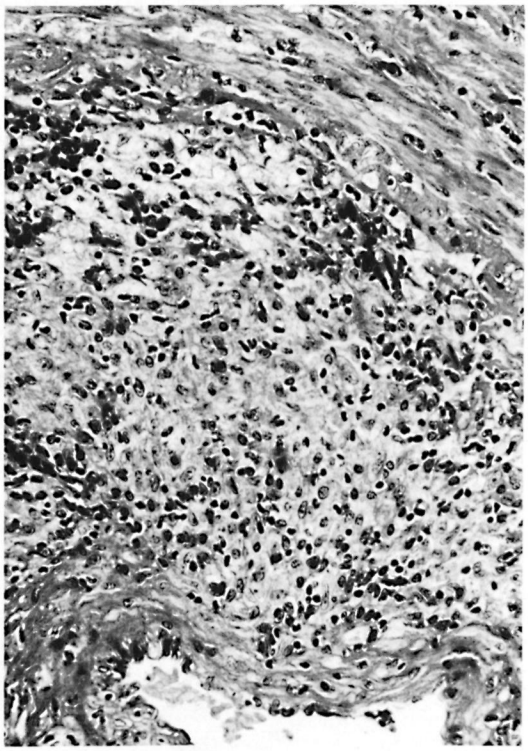

FIG. 3. Intima of intermediate lesion showing cell composition of the granuloma (H & E ×80).

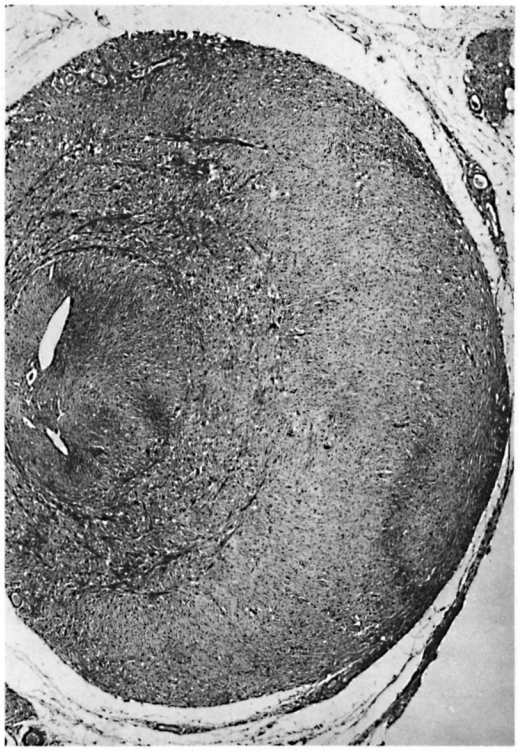

FIG. 4. Advanced lesion. The medial muscle fibers, although infiltrated are still seen as circularly running bundles (H & E ×8).

(0%–30%), intermediate (30%–60%), and advanced (60%–100%) stages. The Table shows the correlation of the stage of the lesion with the duration of disease. The shortest disease duration at which leprous phlebitis was observed was one year. No correlation with ENL reaction was observed.

The detailed histopathological findings were:

Intima. The earliest histological change was a mild inflammatory reaction in the intima (Fig. 1). No granuloma formation was seen at this stage, and the presence of acid-fast bacilli (AFB) in the endothelial and subendothelial layers was the only specific feature observed. More developed lesions in the early group showed transformation of the entire endothelial surface into a foamy cell layer (Fig. 2) and the presence of small granulomata consisting of foamy histiocytes, plasma cells, and lymphocytes at the base of the intima.

Lesions graded as intermediate showed well-developed lepromatous granulomata in the intima. The lumen was distorted and partially occluded. The immediate periluminal areas showed abundant deposition of collagen. The deeper tissue was cellular with foam cells, plasma cells, lymphocytes, neutrophils, and several newly formed, radially running vascular twigs (Fig. 3). Lesions graded as advanced had diffuse lepromatous granulomata replacing the whole intima and causing near total luminal occlusion with development of secondary luminal channels (Fig. 4). In some late lesions degeneration of the granuloma cells was seen. Neutrophils clustering around these sites suggested incipient abscess formation.

Media. The medial layer was the last to be involved. The muscle fibers remained totally free of granuloma in the early lesions. In the moderate group, granuloma cells could be seen compressing the muscle fibers without damaging them. In the advanced group, the muscle bundles were infiltrated and stretched into a thin but still recognizable layer (Fig. 4). The internal elastic lamina was seen as a discontinous, wavy layer

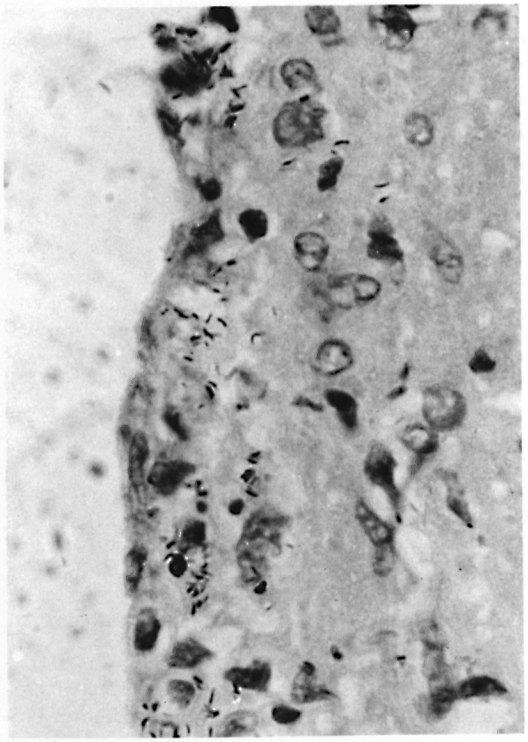

FIG. 5. Acid-fast bacilli in the intimal cells. This is another portion of the vein wall seen in Figure 2 (Fite-Faraco ×300).

in the first two grades, and as a stretched thin layer in the last.

Adventitia. In the early group no adventitial change was seen in the lesions with only intimal hyperplasia. Lesions with intimal granulomata had perivascular granulomata in the adventitia. In the group with moderate lesions, large crescentic granulomata extending around the adventitial circumference were seen; while advanced lesions showed total replacement by lepromatous granulomata (Fig. 4).

Acid-fast bacilli. Acid-fast organisms were present in large numbers in all biopsies. Lesions showing only intimal thickening without granuloma had several organisms in the subendothelial cells, present both singly and in small globi. Later cases showed heavy bacillation of the foam cells in the granulomata, the endothelial cells (Fig. 5), the medial smooth muscle cells, and the periadventitial nerve bundles. Two cases with early lesions which had only a few organisms in the intima had several small clusters of bacilli in the medial muscle cells. No significant morphological changes, e.g., vacuolation or inflammatory cell collections, were seen in or around these cells.

DISCUSSION

Leprous phlebitis was first described by Joelson in 1893 ([15]). Subsequent reports ([11, 12, 20]) describe this lesion as being seen occasionally in leprosy patients. Bernard ([1]) described a proliferative angiitis of veins among the various types of vasculitis seen in this disease. Our previous report ([22]) on this topic drew attention to the fact that this lesion could clinically be mistaken for a thickened nerve in a leprosy patient, and suggested that it may not be as rare as hitherto supposed. The results of the present study definitely show for the first time that a) venous involvement occurs in a very high percentage (96% in this series) of LL patients, and b) that it is seen in patients whose clinical disease is less than one year in duration.

The whole range of development of the lesion starting from infiltration of inflammatory cells with the presence of AFB in the intima to total destruction of the vein wall has been studied. The features suggest that the lesions begin with the entry of the organisms into the endothelial cells from the blood stream. The earliest tissue reaction at this stage is the presence of a few inflammatory cells in the intima. Subsequently, there is a foamy change in the endothelial cell cytoplasm and further infiltration of monocytes and other inflammatory cells from the blood and the medial vessels, causing the development of intimal granulomata. The intimal thickness is further added to by thrombosis caused by the narrow and irregular lumen, as shown by the abundant collagen deposits. A disturbance in the normal tonicity of the vascular system ([3]) in leprosy could also contribute to thrombosis at these sites. This is also the stage when the venous involvement begins to present clinically as a palpable, thickened, cord-like structure. The histological processes described above culminate in total occlusion of the vein by lepromatous granuloma, as seen in the advanced lesions.

The highly bacillated endothelial cells are ideal sites for the release of AFB into the circulation, and it is possible that they are responsible for the frequent bacteremia that

is seen in LL patients ([9, 10, 19, 27]). The consistent and early venous involvement also indicates that these vascular lesions may be of importance in the dissemination of the disease after the initial lesion in the nose or the skin has developed.

An important question that this study raises is whether or not similar infiltration of other components of the peripheral vascular system occurs. Nonspecific changes in the major vessels ([21, 25]) and various degrees of angiitis have been reported in leprosy ([1, 26]). Also, arteriographic studies ([2, 17]) have shown definite irregularities in the caliber and lumen outline in brachial vessels, but there is as yet no histological data available to prove that these lesions are specific in nature. Data from autopsy studies ([7, 14, 18, 23, 24]), however, do not describe any peripheral vascular lesions. This is possibly because the peripheral vascular system is not within the purview of the routine autopsy protocol.

Among the experimental animal models, leprous vasculitis has not been reported in infected armadillos although AFB are found in the endothelial cells. On the other hand, *Mycobacterium lepraemurium*-infected rats or mice show a predominately vascular disease distribution with lesions in major and minor blood vessels ([28]). Studies on murine leprosy ([16]) have also indicated that the vessel wall and particularly the endothelial cell may play a part in the defense mechanisms against the spread of *M. lepraemurium* after development of the initial lesion in the inoculated skin.

In conclusion, it may be said that peripheral venous system involvement frequently occurs in LL. Further studies to probe the involvement in nonlepromatous forms of leprosy are needed.

SUMMARY

Venous involvement in 31 patients with lepromatous leprosy has been studied in biopsies from clinically involved and clinically normal subcutaneous veins from the forearm. Twenty-nine of these showed histological evidence of leprous phlebitis. The earliest lesion was intimal cell hyperplasia with the presence of acid-fast bacilli in small groups in the intimal cells. This gradually progressed to total occlusion of the vein by lepromatous exudate. The results indicate much greater involvement of veins and possibly other components of the vascular system in patients with lepromatous leprosy than is generally accepted. The importance of such involvement in the pathogenesis of leprosy is also discussed.

RESUMEN

Se estudió el daño vascular en biopsias de venas subcutáneas clínicamente afectadas y en venas clínicamente normales del antebrazo do 31 pacientes con lepra lepromatosa. Veintinueve de éstas mostraron evidencias histológicas de flebitis leprosa. La lesión más temprana fue la hiperplasia de la íntima y la presencia de bacilos ácido-resistentes, en pequeños grupos, en las células de la íntima. Esto progresó gradualmente hasta la oclusión total de la vena por el exudado lepromatoso. Los resultados indican una afección de las venas (y posiblemente también de otros componentes del sistema vascular) mucho mayor de lo que generalmente se acepta. Se discute la importancia de tal afección venosa en la patogenia de la lepra.

RÉSUMÉ

On a étudié chez 31 malades atteints de lèpre lépromateuse l'atteinte des veines, dans des biopsies prélevées au niveau de veines sous-cutanées présentant une atteinte clinique ou cliniquement normale, dans l'avant-bras. Chez 29 de ces malades on a mis en évidence des signes histologiques de phlébite lépreuse. La lésion la plus fréquente consistait en une hyperplasie des cellules de l'intima, avec présence de bacilles acido-résistants en petits groupes dans les cellules de l'intima. Cette lésion progressait graduellement jusqu'à une occlusion complète de la veine par un exudat lépromateux. Ces résultats montrent que l'atteinte des veines, et peut-être d'autres constituants du système vasculaire, chez les malades de lèpre lépromateuse, est beaucoup plus prononcée qu'il n'est généralement accepté. L'importance d'une telle atteinte dans la pathogénie de la lèpre est également discutée.

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