*Lepr Rev* (1988) **59,** 177–180

# Comparative histology of skin and nerve granulomas in leprosy patients

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Accepted for publication 16 September 1987

*Summary* Biopsies were taken from infiltrated lesions and thickened nerves in 23 patients with leprosy. The lesions were histologically graded and the histological features semiquantitated and compared at the 2 sites. No significant difference in the overall histological picture in the skin and the nerve was seen. Two features seen more in nerve granulomas were caseation and a higher granuloma fraction, neither of which was thought to have any significant bearing on the comparative immunohistological grading at the 2 sites.

## Introduction

The histological basis for classifying a leprosy patient along the immunohistological spectrum are the changes seen in the skin biopsy. The histologic grading thus arrived at correlates well with the clinical, bacteriological and immunological changes seen in most patients.

The criteria used for histologic grading also include changes in the dermal nerve twigs. Lesions in the larger nerves are however not considered for purposes of classification. The histological changes in the larger nerve trunks reveal a spectrum similar to that seen in the skin. Recent studies[1,5] further suggest that the immunological grading in the nerve is in fact lower than that in the skin in the same patient. This observation has serious implications with regard to classification, initial therapy and subsequent release from control of leprosy patients. A prospective study comparing the histological changes seen in the skin and in nerve lesions in leprosy patients across the spectrum was conducted with a view to examining this aspect of leprosy pathology in greater detail.

## Material and methods

Twenty-two patients were selected from the Leprosy Clinic at the Dermatology Department, Safdarjang Hospital, New Delhi. Only cases with thickened nerves and obvious skin lesions were selected as this would make it more likely that there would be well-developed lesions at both sites so that histological comparison could be properly made. The nerves biopsied were subcutaneous branches such as the superficial peroneal, sural, anterior branch of the ulnar cutaneous and index branch of the radial cutaneous nerve.

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In each case a 1·5-cm long segment of nerve and an incisional skin biopsy were taken for study. The tissues were fixed in 10% buffered formalin, processed for paraffin embedding and 5-micron thick sections cut and stained with H & E and Fite-Faraco stains.

The 22 patients were clinically classified as TT-2, BT-14, BB-1, BL-1, LL-3 and Indeterminate-1. The duration of the disease varied from 6 months to 15 years. Only 1 patient of BL leprosy had received specific therapy for leprosy with DDS for a period of 2 years while the remaining 21 patients did not give any history of past treatment with antileprotic drugs. No patient was in reaction at the time of biopsy.

## Results

Table 1 shows the concordance or discordance between skin and nerve lesions along the spectrum.

All 14 cases showing concordance at the 2 sites also had well-developed granulomas at both sites and the salient histopathological features in each case were semiquantitated and a comparison made between the lesions at the 2 sites. In the BT cases (Table 2), the nerve showed a higher granuloma fraction and more caseation and the skin showed a larger number of giant cells in the lesions while the other histological features were similar at both sites. In the LL and BL cases (Table 3), a higher BI was seen in 2 of the 4 cases while here too the histological features and the inflammatory cell types seen at both sites were similar.

Eight cases showed a discrepancy between the classification at the 2 sites. The breakdown of these cases (Table 4) shows features of indeterminate leprosy or nonspecific changes in 6 skin and 2 nerve lesions while the corresponding lesion in each case showed granuloma classifiable as BT, TT or BB.

**Table 1.** Distribution of cases along the spectrum with either concordance (Sk = N) or discordance (Sk = /N) between the skin and the nerve lesions

| Hist. Grading | TT | BT | BB | BL | LL | Ind. | Total |
|---|---|---|---|---|---|---|---|
| Skin = Nerve | 1 | 9 | 0 | 1 | 3 | 0 | 14 |
| Skin = /Nerve | 1 | 5 | 1 | 0 | 0 | 1 | 8 |

**Table 2.** Comparison of the salient histological features of the Skin/Nerve (S/N) granulomas in the BT cases with well-developed granulomas at both sites

| No. | GF | Epitheloid cell | Lymphocyte | Giant cell | Caseation | BI | Class |
|---|---|---|---|---|---|---|---|
| 1 | 2/5 | 5/5 | 5/4 | 5/0 | 0/0 | 1/1 | BT/BT |
| 2 | 2/4 | 5/5 | 5/4 | 0/0 | 0/5 | 0/0 | BT/BT |
| 3 | 2/5 | 5/5 | 4/4 | 3/0 | 0/3 | 0/0 | BT/BT |
| 4 | 2/5 | 5/5 | 4/4 | 3/3 | 0/3 | 0/0 | BT/BT |
| 5 | 2/4 | 5/5 | 3/3 | 3/0 | 0/4 | 0/0 | BT/BT |
| 6 | 3/4 | 5/5 | 5/5 | 4/4 | 0/5 | 0/0 | BT/BT |
| 7 | 1/3 | 5/5 | 4/2 | 2/2 | 0/0 | 0/0 | BT/BT |
| 8 | 4/4 | 5/5 | 4/4 | 3/0 | 0/3 | 0/0 | BT/BT |
| 9 | 3/5 | 5/5 | 4/4 | 4/3 | 0/3 | 0/0 | BT/BT |
| 10 | 3/4 | 5/5 | 5/5 | 3/3 | 0/3 | 0/0 | TT/TT |
| Total | 26/46 | 55/50 | 46/41 | 30/15 | 0/29 | 1/1 | |

**Table 3.** Comparison of salient histopathological features in the LL/BL group cases with well-developed granulomas at both sites.

| Case No. | GF | BI | Macrophage | Lymphocyte | Class |
|---|---|---|---|---|---|
| 1 | 1/1 | 4/4 | 1/0 | 2/2 | LL/LL |
| 2 | 3/3 | 2/5 | 5/5 | 1/1 | LL/LL |
| 3 | 2/3 | 4/4 | 5/5 | 1/1 | LL/LL |
| 4 | 1/2 | 3/5 | 2/4 | 2/1 | BL/BL |
| Total | 7/9 | 13/18 | 13/14 | 6/5 | |

**Table 4.** Comparative histopathological grading of skin and nerve lesions in the 7 cases showing discordance

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Skin | Ind | | Ind | | Ind | & | BT | | BT |
| Nerve | BT | | BT + Cas. | | BT | | Ind | | Ind |
| Skin | Ind. | & | Non-Spec. | | | & | Non-Spec | | |
| Nerve | TT | | BB | | | | Ind | | |

## Discussion

The histological features in the skin and in the nerve lesions in the same patient has been a point of interest for pathologists working with leprosy for some time now. While some workers in this field record a consistent discordance between lesions at the two sites with the nerve lesion showing more bacilli and a lower, i.e. towards LL, histological grading in most cases, others are of the opinion that the lesions are of similar histological grading at both sites. Thus, in one study[2] a significant discordance was found in 21 out of 36 patients with the nerve showing a lower grading in the majority of cases. Similarly, in a recent study[3] discordance in 35 out of 37 borderline cases was found with the nerve again showing a lower histological grading in most patients. On the other hand, in a study[4] of 153 nerve biopsies from Nepal it was observed that in the 133 cases where abnormal findings were seen in the nerve, the skin was also abnormal and that 'the type (classification) showed agreement at the two sites in every instance'.

Concordance in skin/nerve histology in 14 out of the 22 cases studied was seen in the study under report. It was further seen that well-developed granulomas were present at both sites in these 14 cases only. The remaining 8 cases where discordance was recorded between the skin and the nerve all had features of either indeterminate type disease or of nonspecific inflammation at either site.

Histological comparison of the granulomas at both sites in the first group of 14 cases brought out differences in the amount of caseation, number of giant cells, granuloma fraction and in the number of bacilli. The significance of these differences in terms of local immunity is however not clear. Caseation in leprosy lesions is known to occur almost exclusively in the nerve in TT and BT leprosy lesions. Anecdotal reports of caseation occurring in lepromatous nerves[5,6] have not been substantiated in any recent study. Again, immunologically speaking, caseation indicates a state of increased hypersensitivity and perhaps a higher immune status as is indicated by the larger number of giant cells. The higher GF in the nerve recorded in the present study has been described in a recent report[7] as the increased extent and severity of the nerve lesion. It is quite possible that both these features are caused by the anatomical differences in the target organs. Thus, while the tougher collagen of the dermis may limit the granuloma spread in the dermis, the relatively softer nerve

funiculi may allow easier spread of the granuloma up to the limits of the perineurium accounting for a higher GF. Similarly, caseation in the nerve may represent necrosis in the nerve after obliteration of the blood supply by the infiltrating granuloma. The higher BI in the nerve in 2 of the 4 multibacillary cases is also a well-established pathological observation. In both cases in the present study the histological picture at both sites showed concordance and no inference regarding a lower immunological state in the nerve could be drawn in this group either.

All 8 cases with discordance between the skin and nerve lesions did not show granuloma formation at either site in this study. In 6 of these patients the nerve showed well-developed granuloma formation and the skin had features of either indeterminate leprosy or of nonspecific inflammation, while in 2 cases BT granulomas were present in the skin and the nerve showed only inflammatory infiltrates without any bacilli. Thus, discordance was seen when incomplete granuloma formation at either site precluded proper classification along the histological spectrum. This difference could be explained by either slower granuloma development or quicker granuloma resolution at either of the 2 sites. Since both phenomena are related to the local immune response in the skin or in the nerve, the above observations do suggest a difference in the immune status between the 2 sites in this group of 8 cases. The difference, however, is not consistent, with the nerve being lower in 6 cases and higher in the remaining 2 cases.

The results of the present study show that there was complete agreement in the histological grading of the skin and the nerve lesion in the 14 cases with developed granulomas at both sites while discordance was seen in 8 cases where granuloma formation was not evident at one of the 2 sites. This is in contrast to earlier reports on the comparative morphology of the skin/nerve lesions which describe a greater degree of discordance with nerves showing a persistently lower immunological status. Since the site of nerve biopsy in both the earlier reports and the present one was the same, other explanations for this difference have to be looked for. The patients chosen for this study had infiltrated patches and thickened nerves and so they all had disease of a moderately advanced status. This in turn would suggest that with progression of the disease, granulomas of similar histological grading and BI are formed in the skin and in the nerve by the immunological mechanisms inspite of a heavier bacillary load or a lower histological grading at either site in the initial stages of the disease.

In conclusion, this study shows that in developed leprosy lesions the skin biopsy findings represents the histological grading in the nerve as well and still remains the most convenient and reliable means of classifying a patient along the immunohistological spectrum of the disease. In earlier lesions there appears to be a dichotomy between the immunohistological grading at the 2 sites which needs to be explored in greater detail in studies on a larger population of patients before the relevance of such a skin/nerve dichotomy to the overall immune status and prognosis of leprosy patients can be understood.

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