

SHORT REPORT

Diagnostic value of histopathology of the affected nerve versus overlying skin, in pure neural cases of leprosy

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Summary Proof of leprosy as a cause of ‘pure neural leprosy’ needs histological evidence, which is often sought in the affected peripheral nerves. Obtaining a nerve biopsy may not always be practicable. Thus in this study, the histopathology of the involved nerve and the overlying skin were compared in 32 cases of ‘pure neural leprosy’ in order to determine the utility of skin biopsy in diagnosing leprosy. Evidence of leprosy was present in all, except one nerve biopsy (97%) and in 14/32 (44%) skin biopsies from skin overlying the biopsied nerve. One noteworthy finding is that in nerves showing BL-LLs leprosy, which formed a major group (59%), only 26% of biopsies of the overlying skin showed evidence of leprosy. In nerves showing BT pathology, 67% of the biopsies of overlying skin showed evidence of leprosy. Conclusion: Histopathological examination of the overlying skin compares poorly with the affected cutaneous nerve and is of limited diagnostic value, particularly at the lepromatous end of the spectrum.

Keywords: Pure Neural leprosy diagnosis; Histopathology; cutaneous nerve biopsy; Skin overlying Nerve; leprosy; *Mycobacterium leprae*

Introduction

Pure neural leprosy (PNL) is reported in 5.5% to 18% of leprosy cases, and is more common in the Indian subcontinent compared to other countries of the world.^{1,2} Patients presenting with PNL have nerve impairments, enlargement of peripheral nerves with or without tenderness, in the absence of any skin manifestation or history of skin patches.^{3–7} There are no standard protocols to investigate the disease at the outpatient level of basic health facilities. Non-invasive tests like nerve conduction velocity and ultrasonography are useful in determining the type, site and extent of nerve involvement as well as in assessing the

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treatment outcomes, but do not provide an etiological diagnosis.⁸ A near confirmatory evidence of leprosy disease is usually obtained through histopathological examination of an involved cutaneous nerve. However, unlike skin, it may not always be practicable to obtain a nerve biopsy. Histopathological findings in the apparently normal skin and nasal mucosa suggested widespread leprosy pathology when the disease was clinically confined to a few nerves.^{9,10} In the present study, histological findings between biopsied cutaneous nerve and the skin overlying the biopsied nerve in patients with purely neural symptoms were compared with the aim of determining the diagnostic utility of the later.

Methods

STUDY SUBJECTS (TABLE 1)

Thirty two referred patients presenting with purely neural symptoms were included in the study. Twenty were males and 12 females with age ranging between 15 to 76 years. None of the patients had any visible skin lesions. None had any history of receiving anti-leprosy treatment and all were slit skin smear negative. Nerve biopsies obtained included 22 sural and 10 radial cutaneous nerves, all being either palpably thick or with impaired electrophysiology.

Using local anesthesia the nerve and the overlying skin from the incision site were biopsied after informed consent. Biopsies were fixed overnight in Formol Zenker, routinely processed and embedded in paraffin wax. Five micron thick, longitudinal and transverse sections of the nerve and sections of skin specimen, stained using Fite Ferraco were studied under the light microscope. Type of cellular infiltrate and the presence of acid fast bacilli (AFB) were recorded. Both nerve and overlying skin specimens were further classified using the Ridley-Jopling scale.¹¹ Type of leprosy specific cellular infiltrate, bacterial load in the nerve and overlying skin were compared.

Results

Histopathology findings in 32 nerves and overlying skin biopsies are described below and are summarised in Table 2.

Nineteen (59%) nerves showed Borderline Lepromatous leprosy (BL) or sub-polar lepromatous leprosy (LLs) pathology; characterised by the presence of varying density infiltrating cells comprising of macrophages, lymphocytes and a good number of plasma cells, largely in the endoneural area of the nerve. All the nerves scored positive for acid fast bacilli (AFB) with a Bacteriological Index (BI) ranging between 2+ to 5+. Acid fast

Table 1.

Total no. of Nerves	32 (includes 22 Sural and 10 Radial cutaneous)
No. of overlying Skin	32
Gender	Males = 20 & Females = 12
Age group	16 to 76 years
Clinical features	Involvement of one or more peripheral nerves. No visible skin lesions, no history of receiving anti-leprosy drug

Table 2. Summary of Histopathological findings in nerve vs overlying skin biopsy

Parameter	Nerve (n = 32)	Overlying Skin (n = 32)
Confirmed leprosy / number tested (%)	31/32 (97%)	14/32 (44%)
Leprosy class in Nerve vs overlying Skin	AFB +ve = 20 /32(63%)	AFB +ve = 0/14
	BL-LLs = 19 (59)	Indeterminate = 5 (36)
	AFB +ve = 19 (100%)	Non-specific infiltrate = 8 (42)
	BT = 8 (25%)	No abnormality = 6 (32)
	AFB +ve = 0	BT = 1
	BB = 4 (13)	Indeterminate = 4 (50)
	AFB +ve = 1	Non-specific infiltrate = 3 (38)
	Non-specific = 1	Indeterminate = 3 (75)
	AFB +ve = 0	Non-specific infiltrate = 1
		Indeterminate = 1

Key: BT- Borderline Tuberculoid, BB – Borderline Borderline, BL- Borderline Lepromatous, LLs- Lepromatous Leprosy, AFB – Acid Fast Bacilli.

bacilli were seen predominantly in the Schwann cells and macrophages. Perineural multi-layering was a characteristic feature of these nerves.

The overlying skin in these cases showed Indeterminate leprosy, characterised by the presence of a mainly lymphocytic infiltrate within and around the neurovascular bundle in the dermal area in five (26%) cases; in eight cases (42%) non-specific infiltrate (NS) in the form of macrophage infiltrate in the superficial dermis was seen; in six cases (32%) the skin had no abnormality (NA). None of the skin biopsies scored positive for AFB.

Eight (25%) nerves showed borderline tuberculoid (BT) leprosy pathology characterised by the presence of epithelioid type of macrophages, giant cells and a varying density of lymphocytes. All the nerves scored negative for AFB.

The overlying skin showed epithelioid cell granuloma depicting BT type of leprosy lesion in one case; indeterminate leprosy as described above in four (50%) cases and non-specific infiltrate in three (38%) cases.

Four (13%) nerves showed mid-borderline (BB) leprosy, characterised by the presence of a large number of lymphocytes and a mixture of epithelioid cells and macrophages within the endoneural area of the nerve. One nerve scored positive for AFB with BI = 1+. The overlying skin showed indeterminate leprosy as described above in three cases (75%) and non-specific infiltrate in one case.

In one case, the nerve showed involvement in the form of patchy fibre loss but no specific infiltrating cells or acid fast bacilli were seen. Thus the conclusion was no definite evidence of leprosy in the nerve; whereas the overlying skin showed indeterminate leprosy pathology.

Thus evidence of leprosy was present in skin overlying the nerve in 44% (14/32) of cases. A noteworthy finding is that in nerves showing BL-LLs leprosy, only 26% of the corresponding skin biopsies showed evidence of leprosy. In other words 74% of overlying skin showed no evidence of the disease. By contrast, in nerves showing BT pathology, 63% of the corresponding skin also showed evidence of leprosy. In one case it was the skin over the nerve that clinched the diagnosis.

As compared to nerve, inflammatory infiltrate seen in the overlying skin was of mild degree. In all except one case, the skin showed an indeterminate type of cellular infiltrate

mostly seen within and around the deep dermal nerves. None of the overlying skin biopsy specimens scored positive for AFB.

Discussion

Diagnosing leprosy relies on the identification of typical clinical and histopathological involvement of the skin and nerves. Proof of leprosy as a cause of 'pure neural leprosy' needs histological evidence, which is sought in affected peripheral nerves. As stated earlier, obtaining a nerve biopsy may not always be practicable, therefore in this study histopathology of the involved nerve and the overlying skin were compared in order to determine the utility of skin biopsy as a substitute.

Evidence of leprosy was present in all except one nerve biopsy (97%) and in 14/32 (44%) of skin biopsies. While 20/32 (63%) of nerve biopsies (all BL and LL cases and one BB case) scored positive for acid fast bacilli, none of the skin biopsies scored positive for AFB, which is in keeping with the general smear negativity usually observed with PNL cases.^{1,2}

One noteworthy finding in this study is that in nerves showing BL-LL leprosy, which formed a major group (59%), only 5/19 (26%) biopsies of the overlying skin showed evidence of leprosy. By contrast, in nerves showing BT pathology, 5/8 (63%) of the corresponding skin also showed evidence of leprosy. These findings show that patients with better cell mediated immunity (CMI) i.e. patients on the tuberculoid end of the spectrum are more likely to show changes in the adjacent dermal tissue. Indeed in one case, it was the skin over the nerve that clinched the diagnosis of indeterminate leprosy while the nerve showed nonspecific pathology. This could be a case of nerve sampling error. Histological studies of apparently normal skin obtained from clinically diagnosed pure neural cases of leprosy by two groups report leprosy specific changes in a highly varying (i.e. 32% to 65%) proportion of cases.^{9,12} Nerve biopsy reports were not available for comparison. If an inference can be drawn from the findings from our study, the vast difference noted between the two study findings could be a reflection of underlying leprosy type. Obtaining skin biopsies from multiple sites increases the likelihood of detecting leprosy specific changes to some extent.² One uniform finding across all the studies is that skin biopsies from PNL cases mostly showed indeterminate type of pathology, regardless of the underlying leprosy class.

Conclusion

It is concluded that histopathology of overlying skin compares poorly with the affected cutaneous nerve in cases of 'pure neural leprosy' and is of limited diagnostic value, particularly at the lepromatous end of the spectrum.

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