Interesting and unusual clinical presentations in leprosy at a referral center

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ABSTRACT

Background: Leprosy is a disease of declining global endemicity but is still an important health-care problem in India. Pure neural leprosy is an important subset of presentations of leprosy in India. Leprosy is a known disease of the skin and nerves, but cases of pure neural involvement are relatively less. We hereby present 10 cases of pure neural leprosy in which the diagnosis of leprosy was difficult with routine methods.

Materials and Methods: The study was conducted at the main referral center and satellite clinics of our organization. A retrospective analysis of patient records for the last four years was undertaken to identify patients presenting with predominantly neurological manifestations and uncommon presentations including those without skin lesions. The medical records of the patients were used as source of data. All the patients were subjected to a detailed clinical examination and bacteriological examination with slit-skin smears. Investigations like nerve biopsy, electromyography, and nerve conduction studies were done in patients with diagnostic difficulties.

Results: Patients presented with neurological symptoms like paresthesias (60%), diminished sensations (40%), nonhealing ulcers (30%), and blisters (20%). All except one had thickened nerves on clinical examination. Slit-skin smear was negative in all but one patient. Nerve biopsy confirmed the diagnosis of leprosy in seven cases.

Conclusion: Pure neural leprosy is difficult to diagnose with routine methods. The diagnosis should be considered, especially by neurologists and dermatologists, who are more likely to see such patients with predominant neural manifestations. The diagnosis should be confirmed with nerve biopsy to prevent delay in therapy and associated complications.

Key words: Interesting presentations, leprous neuropathy, nerve biopsy, pure neural leprosy

INTRODUCTION

Leprosy, a disease of high endemicity in India, is claimed to be showing a decline in mean prevalence in the country. However, the detection of new cases is relatively static and it has been observed that clinical manifestations of leprosy appear to be changing. This poses a great challenge for clinicians to diagnose leprosy in time and initiate therapy to prevent complications of untreated disease.

During the last four years, we have encountered cases presenting with predominantly neural manifestations with no or minimal cutaneous manifestations. We share our experience related to 10 such cases that we studied retrospectively in last few years which probably could have been difficult to detect in a field situation.

MATERIALS AND METHODS

The study was conducted at the main referral center and satellite clinics of our organization. The center carries out operational and clinical research along with providing outpatient management of both referred and self-reporting leprosy cases and reaction management. The patients seen are self-reporting as well as referred to the center from other hospitals, private clinics, and peripheral centers.

These cases were referred basically for diagnostic reasons and were selected for study in view of unusual presenting features which made the diagnosis of leprosy difficult with routine methods.

The medical records of the patients were used as the source of data. All patients were subjected to
a detailed clinical examination by trained medical officers and to a bacteriological examination with slit-skin smears. Higher investigations like electromyography (EMG)/nerve conduction studies (NCS) and nerve biopsy were done in seven patients. Profiles of two illustrative cases are given below.

Case 1
A 40-year-old female was referred with complaints of blisters on the right arm, forearm, and hand since two years. The patient had a history of tingling numbness in the right upper and lower extremity dating six years back. There was no history of hypopigmented patches or cutaneous lesions. There was no family history of leprosy or neuropathy. She was investigated with magnetic resonance imaging (MRI) of the spine and EMG/NCS three years before she was referred to our clinic. On examination, she was found to have a thickening of the right ulnar, median, and radial cutaneous nerves, and both posterior tibial nerves. Slit-skin smear was negative at multiple sites. Repeat EMG/NCS showed no sensory conduction in the right median, ulnar, radial, and both sural nerves, whereas amplitude and motor conduction velocity was reduced in the right median and both ulnar nerves. Laboratory investigations like hemogram, chest X-ray, urinalysis, liver function tests, renal function tests, and blood glucose levels were within normal limits. Finally, a biopsy of the left sural nerve was done which revealed three enlarged fascicles with a large number of infiltrating cells comprising lymphocytes, plasma cells, and macrophages in the endoneurium. Small clumps of acid-fast bacilli were seen in a good number of cells. A borderline lepromatous type of nerve lesion with evidence of type 1 reaction was diagnosed.

Case 2
A 38-year-old male, nondiabetic, was referred to our center for a slit-skin smear. The patient had a history of loss of sensation on the lateral aspect and heel of the left foot since three months. Past and family history was negative for neuropathy or leprosy. On examination, fine touch sensation was absent, whereas crude touch sensation was diminished in the left lower extremity. Left ulnar nerve, lateral peroneal, anterior tibial, and sural nerves were thickened. No hypopigmented patches were found. A diagnosis of leprosy was doubtful with such a short duration of complaints but EMG/NCS done before the patient was referred to us demonstrated left sural neuropathy. Therefore, a left sural nerve biopsy was done which showed granulomas comprising lymphocytes, macrophages, and epithelioid cells within and around fascicles. A borderline tuberculoid type of leprosy was diagnosed.

RESULTS
Of the 10 cases, six were males and four females, their age ranging from 11 to 63 years. Table 1 shows the demographics and details of individual cases. The histopathological findings of the nerve biopsy are shown in Table 2.
with skin involvement (ranging from 4 to 16%), their detection and treatment are vital in preventing deformities,[4-7] and if the classical diagnostic criteria are used for diagnosis of leprosy, then many cases are bound to be overlooked.[8]

According to the latest statistics of the World Health Organization (WHO) on leprosy, India is still the largest contributor to the global patient load of leprosy.[1] With elimination of leprosy being the aim, early diagnosis and prompt therapy of the patients holds the key. Any delay in diagnosis and initiation of appropriate therapy would potentially lead to disastrous results and disabilities. As leprosy is not being detected by the usual methods in a subset of patients, higher diagnostic tests such as nerve biopsy have to be used on a routine basis for such patients.

Nerve biopsy has proved to be a more sensitive and revealing test than skin biopsy alone. The efficacy of nerve biopsy as a diagnostic tool, especially when skin lesions are absent, has been proved previously.[9-12] The usefulness of nerve biopsy over skin biopsy in the diagnosis of leprosy has also been demonstrated earlier.[13] In cases of mononeuropathy without a known etiology and without skin changes suggestive of leprosy, de Freitas et al. recommended superficial nerve biopsy as a mandatory procedure to confirm leprosy mainly in developing countries where it is prevalent.[14] Kaur et al., in their study of 108 neuritic leprosy patients, have documented that nearly two-thirds of the patients had a moderate to heavy bacterial load within the nerves despite all the patients having a negative skin smear.[15] Gabelle et al. have documented a case in France which presented with a slowly progressive asymmetric axonal sensory-motor neuropathy, where the diagnosis was made after a delay of eight years with the help of a nerve biopsy.[16]
Table 1: Demographic, clinical, and laboratory features of patients

| Patients | 1     | 2     | 3     | 4     | 5     | 6     | 7     | 8     | 9     | 10    |
|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Age      | 63 (RP) | 40 (MG) | 28 (AK) | 40 (SW) | 11 (SM) | 48 (VT) | 38 (MJ) | 30 (BHC) | 46 (JK) | 50 (BG) |
| Sex      | Male | Female | Female | Male | No | Male | Male | Female | Male | Male |
| Paresthesias | Yes | Yes | Yes | Yes | No | Yes | No | Yes | No | No |
| Sensory loss | Yes | No | Yes | No | No | No | No | No | No | No |
| Motor loss | No | Yes | Yes | No | No | No | No | No | No | No |
| Thickened nerves | Rt ulnar, rt median, Rt radial cutaneous, bilateral popliteal | Rt ulnar, median and radial cutaneous, both posterior tibial | Rt ulnar, median and radial cutaneous, both posterior tibial | Left lateral peroneal, anter tibial, poster tibial | Right common peroneal | Left and right common peroneal | Left ulnar, lat peroneal, anter tibial, sural | Right ulnar | Right digital cutaneous |
| Slit-skin smear | –ve | –ve | –ve | –ve | –ve | –ve | –ve | –ve | –ve | +ve |
| EMG/NCS | Axonopathy + myelinopathy | Mononeuritis multiplex | Mononeuritis multiplex | No sensory conduction in both radial, sural nerves and in left common peroneal nerve | Mononeuritis multiplex affecting nerves of both lower limbs (right>left), could be compatible with leprosy | No sensory conduction in bilateral median, ulnar, radial, and sural nerves | Left sural neuropathy | Not done | Not done | Not done |
| Nerve biopsy | +ve | +ve | +ve [Ref: Figures 5 and 6] | Not done | +ve | ANA (+++) | +ve | +ve | +ve | Not done |
| Additional features and other investigations | USG nerve | USG nerve | USG nerve | USG nerve | USG nerve | USG nerve | USG nerve | USG nerve | USG nerve | USG nerve |
|             | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] | The ulnar nerves are enlarged bilaterally, there is mild enlargement of the left median nerve, no evidence of abscess noted [Ref: Figure 7] |

Rt: Right, postr: Posterior, ant: Anterior, –ve: Negative, +ve: Positive, EMG: Electromyography, NCS: Nerve conduction studies, USG: Ultrasonography, ANCA: Antineutrophil cytoplasmic antibodies, dsDNA: Double-stranded deoxyribonucleic acid, ANA: Antinuclear antibody.
Patients with complaints of predominantly neural manifestations such as tingling numbness, anesthesia, and nonhealing ulcers are more likely to visit neurologists and/or surgeons for treatment. Our study highlights that cases of neural leprosy are still very much present in the general population and therefore clinical suspicion of leprosy needs to be kept in mind. The diagnosis may be confirmed by a nerve biopsy, a relatively simple procedure with high diagnostic efficacy, which should be done promptly to establish the diagnosis and initiate the appropriate therapy without delay.

CONCLUSION

This study was done with the aim of bringing neural leprosy to the attention of neurologists, dermatologists, and leprologists alike. The interest in these cases was due to the fact that the diagnosis of leprosy on clinical grounds and routine testing was truly challenging and one had to resort to further investigations like nerve conduction studies and, nerve biopsies to confirm the diagnosis. India being an endemic region for leprosy, it is of paramount importance that differential diagnosis of leprosy be considered when faced with such cases in a busy outpatient neurology and dermatology setting. It is possible therefore, that many such patients with primary neurological complaints are likely to be seen and diagnosis either could be delayed or missed resulting in nerve damage and its consequences, if not thought of or investigated to confirm leprosy.

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Table 2: Nerve biopsy findings

| Patient | Biopsy findings |
|---------|-----------------|
| 1       | Papillary dermis shows collection of lymphocytes and epithelioid cells to form granulomas. At one place, such granuloma is seen to erode the basal layer of epidermis. Periappendageal infiltrate of lymphocytes and epithelioid cells seen. Subcutaneous tissues normal. No evidence of Acid Fast Bacilli. Perineural and endoneural infiltration of lymphocytes and epithelioid cells. Perineural influx of lymphocytes suggests active disease. Impression: Borderline tuberculoid leprosy |
| 2       | Three enlarged fascicles seen in transverse and longitudinal section. All are seen with a large number of infiltrating cells comprising lymphocytes (mostly perivascular), plasma cells, and macrophages in the endoneurium. Small clumps of acid-fast bacilli are seen in a good number of cells. Intercellular edema present (2+) Impression: Borderline lepromatous type of nerve lesion with evidence of type 1 reaction |
| 3       | LS and TS show multiple fascicles. There is lymphocytic infiltrate in the perineurium with epithelioid cells. Similar infiltrate is seen within all the fascicles. There is a moderate amount of fibrosis. There is no evidence of acid-fast bacilli. Impression: Borderline lepromatous type of disease in the nerve studied |
| 4       | Totally collagenized nerve and mild lymphocytic infiltration seen around blood vessels in the epineural area suggestive of a burnt-out case of tuberculoid type of nerve lesion |
| 6       | Aggregates of lymphocytes and macrophages seen around adnexa. Semithin, uniform, and extensive dropout of fibers (>80%). Impression: Borderline lepromatous type of leprosy lesion |
| 7       | Granulomas comprising lymphocytes, macrophages, and epithelioid cells seen within and around fascicles. Impression: Borderline tuberculoid type of leprosy |
| 8       | Indeterminate leprosy in skin over nerve. Nerve biopsy is inconclusive |

LS: Longitudinal section, TS: Transverse section

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