Neurofibromatosis 1 with Unusual Hypopigmentation Masquerading as Leprosy

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Abstract
A case of Neurofibromatosis 1 (NF1) occurring in association with symmetrical peripheral nerve enlargement and multiple hypopigmented macules strikingly limited to the neurofibromas, with normal to minimally reduced sensations, evoking a strong clinical suspicion of co-existent lepromatous leprosy, is being reported. Leprosy was ruled out by microbiological, histopathological and electrophysiological studies. The case is interesting in view of the hypopigmented macules overlying the neurofibromas, which is an unreported feature of NF1.

INTRODUCTION
Neurofibromatosis 1 (NF1) or von Recklinghausen’s disease is a common, autosomal dominant, nevoucutaneous disorder with an incidence of 1 in 3000 births. The diagnosis is based on a group of clinical stigmata, which include café-au-lait macules (CALM), neurofibromas and intertriginous freckling (axillary or inguinal). Peripheral nerve enlargement, although a well-known feature of this condition, has often posed diagnostic dilemma with leprosy. We report an interesting case of NF1, in whom symmetrical nerve enlargement in association with multiple, symmetrically distributed hypopigmented macules over the trunk and extremities and habitation in an endemic area for leprosy, led to strong clinical suspicion of concomitant lepromatous leprosy to the extent of initiating antileprosy treatment. We also seek to highlight unusual pattern of hypopigmentation in NF1, which was strikingly localized to the underlying neurofibromas.

CASE REPORT
A 20 years man, resident of Bihar, presented with multiple asymptomatic papules and nodules, which he had noticed since the age of six years. Since three years, he also noticed hypopigmentation over these lesions. There was no history of seizures or sensory loss. Family history was not significant. On examination, multiple, soft, ill-defined papules, plaques and nodules were present over the face, trunk and extremities with overlying hypopigmentation but no atrophy or sparing of appendages. The hypopigmentation also extended to adjacent apparently normal skin (Fig. 1).

Sensations over the hypopigmented patches varied from normo- to minimally hypoesthetic. Peripheral nerves including ulnar, radial cutaneous and common peroneal were symmetrically and uniformly thickened and non-tender. There was no glove and stocking anesthesia. In addition, there were multiple well-defined hyperpigmented macules over the trunk and extremities suggestive of CALM and axillary freckles. Systemic examination did not reveal any abnormality. Slit-lamp examination showed Lisch nodules in the iris. A clinical diagnosis of NF1 with a possibility of coexisting Hansen’s disease was made due to the presence of ill- to well defined hypopigmented macules with variable sensory loss and symmetrical nerve thickening. The patient was empirically started on multi-drug antileprosy therapy.

Multiple skin biopsies were obtained from hypopigmented nodule over the buttock and back and from hypopigmented macule overlying apparently normal skin, which revealed normal epidermis with normal number and melanization of melanocytes and dermis showing axial bundles of symmetrically arranged nerve fibers involving the upper and mid dermis, suggestive of neurofibroma. There was no evidence of leprosy on both hematoxylin and eosin and Ziehl Neelsen stain (Fig. 2). Slit skin smears for acid-fast bacilli were negative. Radial cutaneous nerve biopsy was suggestive of neurofibroma and nerve conduction study was normal.

Hence, a final diagnosis of NF1 was made with unusual pattern of hypopigmentation, which was predominantly overlying the neurofibromas and antileprosy treatment was prematurely terminated. Since such hypopigmentation has not been described in neurofibromatosis, we further investigated to find the possible etiology. Firm stroking of hypopigmented skin produced hyperaemia and histamine test (0.1ml of 1:10,000 histamine hydrochloride injected intradermally to elicit erythema, wheal and flare response) was positive on both the hypopigmented and normal skin,
which ruled out the possibility of increased stimulation of vasoconstrictor fibers of the arterioles in these areas, as seen in nevus anemicus. The possibility of decreased regional blood flow in the area of hypopigmentation was also dismissed on observing temperature difference of 1°C between the hypopigmented skin (showed higher temperature) and normal looking skin on contra lateral side, using a YSI Precision Thermistor probe (Colin BP-508) which has a range of 15°C-45°C and accuracy of ± 0.1°C.

DISCUSSION

There are several reports in the literature of leprosy misdiagnosed as neurofibroma or NF1 being confused with Hansen’s disease because of symmetrical peripheral nerve thickening.2,3 NF1 has also been reported to coexist with lepromatous and histoid leprosy in patients belonging to endemic areas for this disease.4 In our case, there was no doubt about the diagnosis of NF1. Interestingly, presence of multiple hypopigmented macules with variable sensory loss in association with symmetrical peripheral nerve thickening in an inmate of Bihar, a hyperendemic region for leprosy in India, aroused strong clinical suspicion of the co-existence of the two diseases. Leprosy was ruled out by detailed microbiological, histopathological and electrophysiological studies.

In NF1, both hyper- and hypopigmented macules occur. Hypopigmented macules are an uncommon presentation, two types of which have been described by Riccardi and subsequently by other authors.5 The first type, seen in 2 to 3% of cases, resemble ash-leaf macules, varying in size from 5 to 15 mm and are round to elliptical flat lesions with normal underlying skin. The second type is ‘pseudoatrophic macules’ with underlying depressed skin, that have been postulated to be due to replacement of dermal collagen by the neural tissue. Hypopigmented macules consistent with nevus anaemicus have also been described in NF1, which was ruled out in our case on the basis of negative histamine test.6

Hyperpigmented lesions such as café-au-lait macules (CALM), which are discrete, uniformly pale brown macules, are a cardinal feature of NF1, in which there are 6 or more macules > 0.5 cm in size under 5 years of age and > 1.5 cm in adults. In NF1, these macules are uniformly hyperpigmented with smooth borders resembling ‘coast of California’. They are also present in other conditions like McCune-Albright syndrome (polyostotic fibrous dysplasia, precocious puberty and pigmentary alterations), in which they tend to be very large, unilateral, with irregular and ragged borders like ‘coast of Maine’, and particularly involving the forehead, nuchal area, sacrum and buttocks. CALMs may also be associated with Bloom’s syndrome, Tuberous sclerosis, Silver-Russell syndrome or Watson syndrome.

In our NF1 patient, besides the classical hyperpigmented macules which included CALMs and freckles, hypopigmented macules were also present, the hypopigmentation being strikingly localized to neurofibromas, which is an unreported feature. Infact, histopathology from one of these lesions with no clinically discernable underlying neurofibroma also showed bundles of neuroid tissue in the dermis. Generally, hyperpigmentation with or without hypertrichosis overlying neurofibromas, especially plexiform neurofibromas, has been described, the pathogenic mechanism of which is unclear.5 Despite detailed evaluation, we were also unable to offer an appropriate, convincing explanation for the hypopigmented...
lesions in our patient.

In conclusion, it may be emphasized that our case of NF1 posed strong diagnostic challenge in excluding leprosy due to the rare manifestation of symmetrical hypopigmented macules that were strikingly localized to neurofibromas, the etiology of which is still obscure.

REFERENCES


Announcement

The Departments of Medicine and Pediatrics, JIPMER, Pondicherry are organizing an "International Allergy and Asthma Update 2005" on January 1st and 2nd 2005.

Salient features of the update include:

- Workshop on "Practical Procedures in Allergy Testing" (1st January, 2005) with extensive hands on training in allergy testing and interpretation of the results. The workshop will be conducted by reputed Allergy Specialists from USA and is limited to 25 participants.

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