

# Hypopigmented Skin Lesions with Doubtful/Minimal Sensory Impairment: A Histopathology-Based Analysis

## Abstract

**Background:** Cardinal criteria proposed by the World Health Organisation (WHO) lack sensitivity to diagnose indeterminate leprosy. **Aims:** To estimate the frequency of hypopigmented skin lesions with doubtful/minimal sensory impairment showing histopathology features of indeterminate leprosy. To compare between the histopathology findings noted in specimens showing features suggestive of indeterminate leprosy and those showing a non-specific dermatitis pattern. **Materials and Methods:** Data on patients who attended our department with hypopigmented patches with doubtful/minimal sensory impairment from January 2018 to December 2019 and who underwent a skin biopsy were collected. A pathologist blinded to the clinical findings reviewed the histopathology specimens using a pre-set questionnaire. **Results:** We studied sixteen biopsy specimens from 14 patients. Eight specimens (50%) showed histopathology suggestive of indeterminate leprosy and the remaining eight showed a non-specific dermatitis pattern. A higher percentage of patients with indeterminate pattern showed mast cells (87.5% vs 25%) and fibrosis around nerve twig or sweat duct (75% vs 12.5%) when compared to those who showed a non-specific dermatitis pattern. **Limitations:** Small sample size and retrospective study design were the limitations. **Conclusions:** We found histopathology features of indeterminate leprosy in 50% of the skin biopsy specimens from hypopigmented lesions with doubtful/minimal sensory impairment. The present study highlights the need to improve the diagnostic definition of indeterminate leprosy.

**Keywords:** *Histopathology, indeterminate leprosy, indeterminate pattern, nonspecific dermatitis*

## Introduction

Indeterminate leprosy is the early lesion of the disease before the body is able to mount a granulomatous response. The usual presentation is 1 or 2 hypopigmented macules with minimal or doubtful sensory impairment.<sup>[1]</sup> As per the cardinal criteria for leprosy proposed by the World Health Organization, a skin lesion should either show a definite sensory impairment or acid-fast bacilli in skin smear to make a diagnosis of leprosy<sup>[2]</sup>; in other words, the World Health Organization criteria is not sensitive to diagnose indeterminate leprosy.

A hypopigmented patch with doubtful/minimal sensory impairment is diagnosed as indeterminate leprosy when the histopathology is supportive. Indeterminate histopathology in leprosy refers to perivascular, periadnexal, and perineural lymphocytic infiltration without any granulomas.<sup>[1,3]</sup> Among these, nerve infiltration is considered as the most

specific for histopathologic suspicion of leprosy. Lymphocytic infiltration of arrector pilorum muscle is less specific followed by infiltration of eccrine glands and ducts. Though the presence of acid-fast bacilli in the histopathology specimen can confirm the diagnosis, many authors have reported this finding to be a rarity in indeterminate leprosy.<sup>[4]</sup>

Previous authors have noted that a nonspecific histopathology of perivascular lymphocytic infiltrate mimicking chronic dermatitis is not rare in indeterminate leprosy. The same may occasionally be seen in maculoanesthetic lesions of leprosy.<sup>[4]</sup> A nonspecific histopathology may not be of much significance in maculoanesthetic cases since they manifest definite sensory impairment, and thus can be diagnosed by the cardinal criteria. On the contrary, diagnosing indeterminate leprosy is difficult in the absence of supportive histopathology. This becomes significant, as

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30% of indeterminate leprosy cases progress to a definite granulomatous form with two-thirds of them advancing to lepromatous spectrum, if left untreated.<sup>[1]</sup>

In this setting, we did a retrospective descriptive study on patients who attended our referral center with hypopigmented patches with doubtful/minimal sensory impairment. The study aimed to estimate the frequency of hypopigmented skin lesions with doubtful/minimal sensory impairment that showed histopathologic features of indeterminate leprosy and to compare between the histopathology findings observed in specimens showing indeterminate pathology and a nonspecific dermatitis pattern.

## Materials and Methods

We reviewed the case records of patients who attended our department with hypopigmented patches with doubtful/minimal sensory impairment from January 2018 to December 2019 and underwent a skin biopsy for the same. Case sheets with insufficient data were excluded.

As per institutional policy, sensory perception in a skin lesion is tested by cotton wool (to assess perception of fine touch), sterile needle prick (to assess perception of pain), and warm (42°C) and cold (25°C) water in 10 mm Cresil glass test tubes (to assess perception of temperature sensation). We assess sensory perception by checking the normal skin on the opposite side to the leprosy lesion, then nearby normal skin, and finally the lesion itself and document the sensory deficit in comparison to contralateral and nearby normal skin.

With a preset proforma, we collected information on patient characteristics, clinical profile, treatment received, and follow-up from previous case records.

A pathologist blinded to the clinical findings reviewed fresh slides (stained by hematoxylin and eosin) prepared from archived specimens using a preset questionnaire. Atrophy of epidermis, intercellular edema, exocytosis, basal cell vacuolation, density and components of inflammatory infiltrate, and distribution of inflammatory infiltrate (perivascular, around sweat ducts, around arrector pilorum muscle, and perineural) were looked for. We documented the density of inflammatory infiltrate as percentage of dermis occupied by the infiltrate. Presence of fibrosis around sweat glands, arrector pilorum muscle, and perineurium was noted. Specimens stained by modified Zeihl Neelsen technique were studied for acid-fast bacilli. Mean number of mast cells (in toluidine blue stained specimens) per high-power field (LEICA ICC50 HD microscope) was noted after examining 5 high-power fields.

We made a histopathologic diagnosis of indeterminate leprosy when the specimens showed peri/intra neural lymphocyte infiltration or acid-fast bacilli without granulomas. Nonspecific histopathology was defined as

sparse, superficial, perivascular, and/or periappendageal lymphocytic infiltrate.

The data were entered in Microsoft Excel and analyzed with SPSS version 18. The study was approved by the ethics committee of the institution.

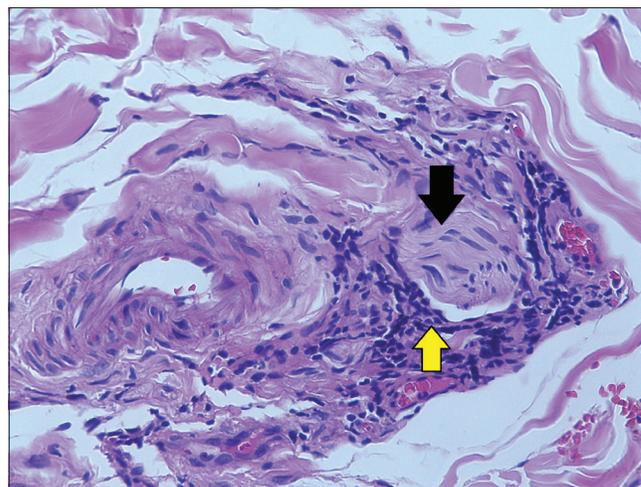
## Results

During the 2-year study period, 136 patients underwent skin biopsy with a clinical diagnosis or suspicion of leprosy. Among these, 14 patients (10.3%) presented with hypopigmented patches with minimal or doubtful sensory impairment.

The study participants included 10 females and 4 males. Age ranged from 8 to 55 years (mean age and standard deviation - 29.9 ± 13.7 years). All except 2 patients had single skin lesion. One patient had 2 and another had 3 skin lesions (case numbers 4 and 14, Table 1). Among the 17 skin lesions (1 each in 12 patients, 2 lesions in 1 patient, and 3 in another) examined, we noted a minimal sensory impairment in 14 lesions (14/17, 82.4%) and a doubtful sensory impairment in 3 (3/17, 17.6%). One patient with 2 skin lesions (case no. 4, Table 1), and another with a lesion on the back of trunk (case number 13, Table 1) had doubtful sensory impairment.

Total 16 biopsies were taken from 14 patients [Table 1]. Both lesions were biopsied in patient number 4 [Table 1], who had 1 lesion on leg and another on forearm. The other patient with multiple lesions had 1 lesion on the forehead and 2 on the left forearm. Representative lesions from both body sites (forehead lesion as well as one forearm lesion) were biopsied.

Eight lesions from 7 patients showed indeterminate histopathology [Figures 1, 2a and b] and 8 lesions from the remaining 7 showed a nonspecific dermatitis



**Figure 1:** Skin biopsy from a hypopigmented lesion with minimal sensory impairment showing perineural lymphohistiocytic inflammatory infiltrate (hematoxylin and eosin, ×400). Black arrow denotes the nerve twig and yellow arrow denotes the inflammatory infiltrate

**Table 1: Histopathology findings in patients presenting with hypopigmented skin lesions with doubtful/minimal sensory impairment**

Age (years), gender	Site of biopsy	Changes in epidermis	Histopathology findings							
			Inflammatory infiltrate		Histopathology diagnosis	Mean number of mast cells/HPF*	Fibrosis			
			Distribution	Composition			% of dermis occupied by infiltrate	Around hair follicle	Around sweat duct	Around nerve twig
19, M	Right leg	Nil	P/A and P/V, more P/A	Lymphocytes and histiocytes	<5%	Nonspecific dermatitis	3	Yes	Nil	Nil
20, F	Right forearm	Nil	P/V	Lymphocytes	<5%	Nonspecific dermatitis	0	Yes	Nil	Nil
55, F	Upper back	Nil	P/V and P/N, More P/N	Lymphocytes and histiocytes	5%	Indeterminate leprosy	3-4	Yes	Nil	Yes
22, F	Right forearm	Nil	P/V, P/N, More P/N	Lymphocytes and histiocytes	5%-10%	Indeterminate leprosy	4	Nil	Nil	Yes
	Right leg	Nil	P/V, P/N, More P/N	Lymphocytes and histiocytes	<5%	Indeterminate leprosy	4	Nil	Nil	Yes
46, M	Right elbow	Nil	P/V, P/N, More P/N	Lymphocytes and histiocytes	<5%	Indeterminate leprosy	0	Nil	Yes	Nil
39, F	Right ankle	Nil	P/V	Lymphocytes	<5%	Nonspecific dermatitis	0	Nil	Yes	Nil
35, F	Left hand	Nil	P/V and P/N, P/N more	Lymphocytes and histiocytes	5%-10%	Indeterminate leprosy	2-3	Nil	Yes	Nil
22, F	Left mammary area	Nil	P/V and P/N, P/N more	Lymphocytes and histiocytes	<5%	Indeterminate leprosy	5-6	Yes	Nil	Nil
15, F	Right hand	Minimal spongiosis	P/V and P/N, P/N- more P/N	Lymphocytes and histiocytes	<5%	Indeterminate leprosy	<1	Nil	Yes	Nil
36, M	Abdomen	Nil	P/V	Lymphocytes	<5%	Nonspecific dermatitis	0	Nil	Nil	Nil
8, F	Right leg	Nil	P/V and P/A, more P/V	Lymphocytes	<5%	Nonspecific dermatitis	0	Yes	Nil	Nil
47, F	Right thigh	Nil	P/V, P/A, P/N- more P/N	Lymphocytes, histiocytes	<5%	Indeterminate leprosy	1-2	Nil	Nil	Nil
32, F	Back of trunk	Nil	P/V, P/A-more P/V	Lymphocytes and histiocytes	<5%	Nonspecific dermatitis	1-2	Yes	Nil	Nil
23, M	Forehead	Nil	P/V	Lymphocytes and histiocytes	<5%	Nonspecific dermatitis	0	Nil	Nil	Nil
	Left forearm	Focal mild spongiosis with lymphocytic exocytosis	P/V and P/A, more P/V	Lymphocytes and histiocytes	5%-10%	Nonspecific dermatitis	0	Nil	Nil	Nil

M=male, F=female, P/V=perivascular, P/N=perineural, P/A=periappendageal, HPF=high-power field. \*Mean number of mast cells per high power field calculated after examining 5 high power fields

pattern [Figure 3]. Two of the 3 lesions (2/3, 66.7%) with doubtful sensory impairment showed indeterminate histopathology. Thirteen out of the 14 lesions (13/14, 92.9%) with minimal sensory impairment were biopsied. Six out of the 13 showed indeterminate histopathology (6/13, 46.2%).

Histopathology revealed epidermal changes (spongiosis and lymphocytic exocytosis) in 2 of the 16 specimens (12.5%). One of them showed minimal spongiosis and had histopathology features suggestive of indeterminate leprosy, while the other showed minimal spongiosis and exocytosis and a nonspecific dermatitis pattern.

The inflammatory cells noted were lymphocytes and histiocytes (12/16, 75%) or lymphocytes alone (4/16, 25%). All specimens with histopathologic features of indeterminate leprosy showed lymphocytes and histiocytes, while the inflammatory infiltrate was composed of lymphocytes alone in 50% (4/8) of the specimens with nonspecific dermatitis pattern.

Inflammatory infiltrate occupied <5% of the dermis in 13 specimens (13/16, 81.3%) and 5% to 10% of the dermis in 3 (3/16, 18.8%).

Seven of the 8 specimens (87.5%) that showed indeterminate histopathology and 2 of the 8 specimens (25%) that showed nonspecific pattern had mast cells [Figure 4].

Fibrosis around sweat duct [Figure 5a] was more frequent in specimens with indeterminate histopathology (3/8, 37.5%) in comparison to specimens with nonspecific pattern (1/8, 12.5%). Fibrosis around hair follicle [Figure 5b] was more frequent in specimens with nonspecific pattern (4/8, 50%) in comparison to specimens with indeterminate histopathology (2/8, 25%). Fibrosis around nerve twigs [Figure 5c] was seen exclusively in specimens that showed indeterminate histopathology (3/8, 37.5%),

The 7 patients who showed indeterminate histopathology received paucibacillary multidrug therapy (MDT).<sup>[1]</sup> The

7 patients who showed nonspecific dermatitis pattern were kept under follow-up.

One of the 7 patients (14.3%) who showed the histopathology of indeterminate leprosy, developed type 1 lepra reaction (manifested as erythema, edema, and tenderness of skin lesion) 3 months after starting MDT.

## Discussion

Intraneural lymphocytic infiltration and/or presence of acid-fast bacilli, which are considered as conclusive evidence of indeterminate leprosy were not seen in any of the specimens and literature also report them as less frequent findings in indeterminate leprosy.<sup>[1,3]</sup> We made a diagnosis of indeterminate leprosy in 50% of cases since in the setting of a hypopigmented patch with minimal or doubtful sensory impairment, perineural lymphocytic infiltration is highly suggestive of the former. At the same time, we cannot rule out the possibility of indeterminate leprosy in 50% of our study participants who showed a nonspecific dermatitis pattern. An earlier study on indeterminate leprosy, demonstrated mycobacterial antigen by immunoperoxidase technique in 60% of cases with a nonspecific histopathology.<sup>[5]</sup>

A comparison between the specimens with an indeterminate histopathology and a nonspecific dermatitis pattern revealed that a higher percentage of patients with indeterminate pattern showed mast cells (87.5% vs 25%) and fibrosis around nerve twig or sweat duct (75% vs 12.5%). Previous authors have suggested mast cell as a diagnostic clue in indeterminate leprosy.<sup>[6]</sup> Apart from their role in immediate hypersensitivity reactions, mast cells are known to take part in delayed hypersensitivity reaction as well. They are located at the entry point of external antigens to host body (skin, gastrointestinal tract, and respiratory epithelium).<sup>[7]</sup> On activation, the cells become elongated

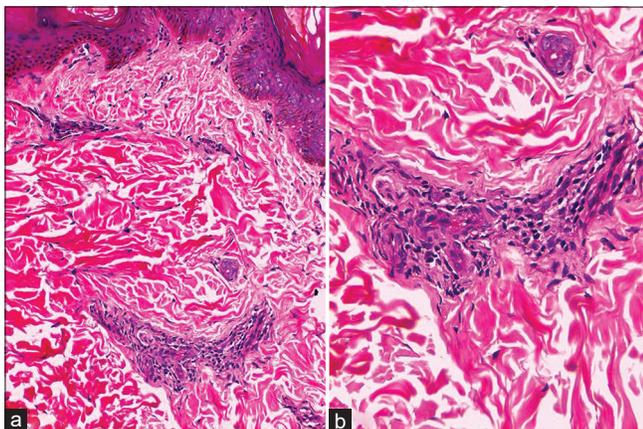


Figure 2: (a) Skin biopsy from a hypopigmented lesion with minimal sensory impairment showing lymphohistiocytic inflammatory infiltrate along a neurovascular bundle (hematoxylin and eosin, ×200); (b) higher magnification of 2 a (hematoxylin and eosin, ×400)

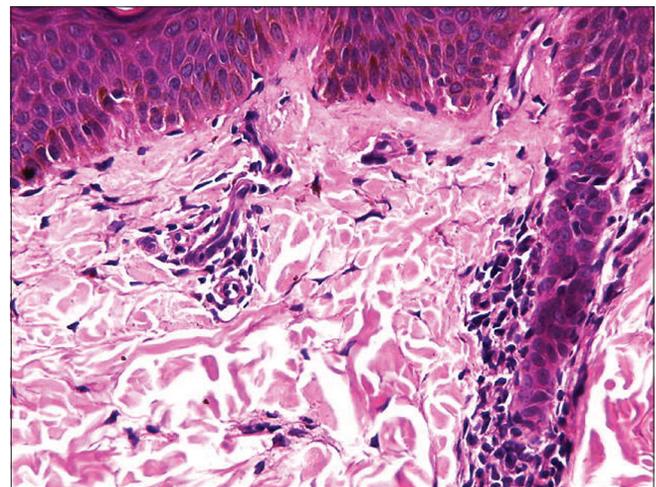


Figure 3: Skin biopsy from another patient with hypopigmented lesion with minimal sensory impairment showing perivascular and periappendageal lymphohistiocytic infiltrate (hematoxylin and eosin, ×400)

to discharge granules that contain heparin, histamine, proteases, and various cytokines.<sup>[6]</sup> Previous authors have reported fibrosis around sweat ducts in indeterminate leprosy and attributed it to the proximity of sweat gland to dermal nerves.<sup>[6,8]</sup> Individually these findings lack specificity. However, their role as diagnostic indicators, when seen in an appropriate setting, deserves further evaluation.

Whether the female predilection noted by us (which was contrary to the male predilection seen in leprosy) indicates a higher risk for females to manifest indeterminate leprosy or is a reflection of the tendency of women to notice and seek medical aid for asymptomatic skin lesions needs analysis in future studies.<sup>[9]</sup>

We did not find any difference in the histopathology findings between lesions with minimal and those with doubtful sensory impairment, as 2 of the 3 patients (66.7%)

with doubtful sensory impairment showed indeterminate histopathology.

Only 2 of the 16 (12.5%) specimens (one each with histopathology features of indeterminate leprosy and nonspecific dermatitis) showed epidermal changes. A previous study of 20 cases of indeterminate leprosy showed epidermal changes in 25% of specimens, which included spongiosis (10%), vacuolar formation (15%), and basal cell liquefaction (10%).<sup>[8]</sup> In our study, the specimens that showed spongiosis were taken from lesions on the dorsal aspect of hand and forearm, respectively (trauma prone sites). Whether unrecognized trauma, especially in the setting of a minimal sensory deficit, contributed to the epidermal change remains unclear.

None of the specimens showed inflammation involving more than 10% of dermis, which was consistent with literature.<sup>[8]</sup>

The type 1 lepra reaction noted in one of the patients who received paucibacillary MDT could be due to immune stimulation and granuloma formation following antileprosy treatment. Previous authors have noted patients with indeterminate leprosy manifesting granulomas after completion of treatment.<sup>[10,11]</sup> The possible explanations put forth are the treatment-induced immune activation or an inability of MDT to alter the natural course of the disease in at least some of the patients.<sup>[10]</sup>

### Limitations

Small sample size and retrospective design were the major limitations of the study. Lack of information on polymerase chain reaction test for antigens of *Mycobacterium leprae* on formalin-preserved specimens was another limitation.

Future prospective studies designed to follow-up clinically suspected cases of indeterminate leprosy that show a nonspecific dermatitis pattern of histopathology and perform serial biopsies of persistent lesions at regular intervals may give us more information on the evolution of these lesions.

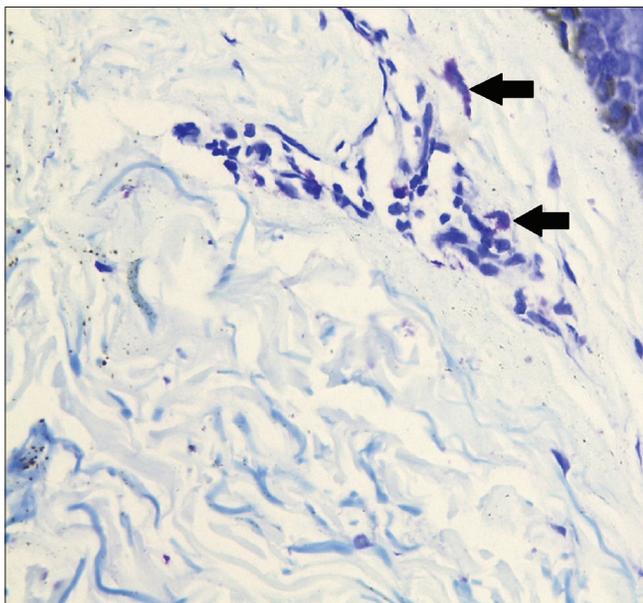


Figure 4: Lesional biopsy of a hypopigmented skin lesion with minimal sensory impairment showing (black arrows) mast cells (Toluidine blue, ×400)

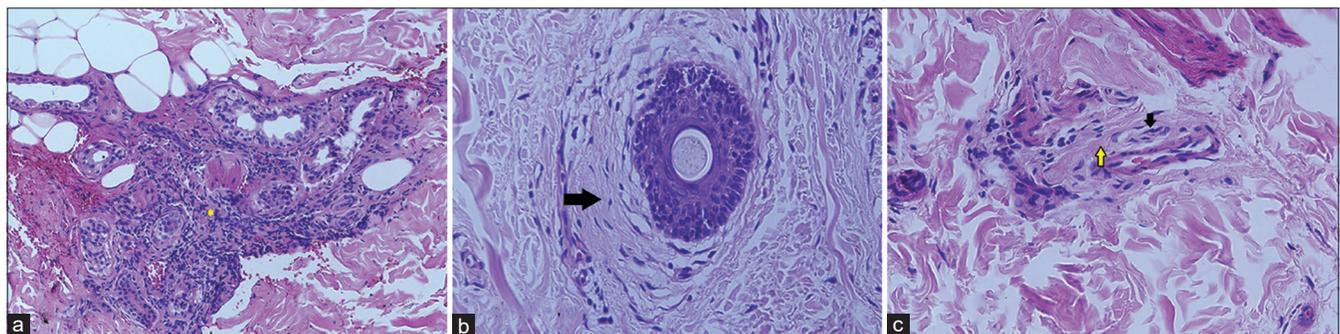


Figure 5: (a) Lesional biopsy of a hypopigmented skin lesion with minimal sensory impairment showing fibrosis (denoted by yellow star) around sweat glands (hematoxylin and eosin, ×400); (b) Lesional biopsy from a hypopigmented skin lesion with minimal sensory impairment showing concentric fibrosis (black arrow) around a hair follicle (hematoxylin and eosin, ×400); (c) Lesional biopsy of a hypopigmented skin lesion with minimal sensory impairment showing fibrosis around a neurovascular bundle (hematoxylin and eosin, ×400). Black arrow denotes the nerve twig and yellow arrow denotes the fibrosis

The present study reiterates the limitation of histopathology in diagnosing indeterminate leprosy and highlights the need to improve the diagnostic definition of the same by incorporating advanced diagnostic techniques.

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### **Conflicts of interest**

There are no conflicts of interest.

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