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Published In/Presented At

Soro, L. A., Gust, A. J., & Purcell, S. M. (2013). Inflammatory vitiligo versus hypopigmented mycosis fungoides in a 58-year-old Indian female. *Indian dermatology online journal*, *4*(4), 321–325. https://doi.org/10.4103/2229-5178.120662

Inflammatory vitiligo versus hypopigmented mycosis fungoides in a 58-year-old Indian female

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Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.120662

Quick Response Code:

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ABSTRACT

Vitiligo, particularly the rarer inflammatory variant, may be difficult to distinguish from hypopigmented mycosis fungoides (MF) clinically. Complicating the distinction is that when biopsies are taken from the periphery of early vitiliginous lesions or from lesions with an inflammatory border (inflammatory vitiligo), a dermal lymphocytic infiltrate, exocytosis, interface dermatitis, and mild spongiosis may be seen, all resembling the findings seen in hypopigmented MF. We present a case demonstrating the difficulty in differentiating between these two diseases and examine some characteristic clinical and histopathological features of each. Often, a conclusive diagnosis cannot be made, necessitating close follow-up of the patient and monitoring for progression of their disease over time.

Key words: Cutaneous T-cell lymphoma, hypopigmented mycosis fungoides, inflammatory vitiligo

CASE REPORT

A 58-year-old Indian female presented to our office complaining of a 3-year history of white patches on her face, neck, trunk, and extremities. New lesions were continuing to develop, with the left anterior leg and right wrist being the most recently affected sites. Past medical history was significant only for osteoporosis and the patient denied taking any medications. She admitted to a trip to India several years prior but had no other recent travel. A review of systems was negative, with the patient denying pain, pruritus, dysesthesia, peripheral neuropathy, and alopecia of the scalp or eyebrows.

On physical examination, speckled, depigmented macules and patches on the eyelids, forehead, cheeks, neck, and hands were appreciated. In addition, hypopigmented patches with scaly, raised, erythematous borders were observed on the back, abdomen, legs, thighs, and buttocks [Figures 1-4]. No hypoesthesia or dysesthesia of the patches was noted. There was no loss of hot or cold sensation within or surrounding the patches.

An in-office KOH was negative for fungal organisms. A punch biopsy was taken from the right lower back at the margin of a hypopigmented patch that was surrounded by erythema [Figure 2]. This revealed: "spongiosis, a superficial perivascular and interstitial scattering of lymphocytes in a papillary dermis of altered collagen, scattered single necrotic keratinocytes, multifocal vacuolar alteration of the junction, and mounds of parakeratosis" [Figures 5 and 6]. A second biopsy taken from the right medial buttock [Figure 4] showed "superficial perivascular and sparse interstitial infiltrate of lymphocytes with a rare eosinophil, wiry bundles of collagen in the papillary dermis, mild spongiosis, lymphocytes sprinkled within the epidermis, and mounds of parakeratosis [Figure 7]. CD4 and CD8 stains demonstrated a helper: suppressor ratio of greater than 5:1 [Figure 8a and b]. A CD7 stain demonstrated staining of approximately 30% of lymphocytes [Figure 9]. Further staining with Melan-A demonstrated a marked reduction of melanocytes but not complete absence [Figure 10]. Given the patient's previous report of travel to India, leprosy had been a consideration clinically but neither granulomas, foamy macrophages, nor perineural inflammation were identified histopathogically. A Fite-Faraco stain was also negative. With some worrisome features for mycosis fungoides, including wiry

bundles of collagen, inflammatory infiltrate, and mild exocytosis, a polymerase chain reaction (PCR) assay for rearranged T-cell receptor gamma genes was obtained. This showed polyclonality, with the intensity of peak not consistent with that seen in clonal neoplasms.

Given the clinical findings of several classic appearing depigmented patches on the forehead, eyelids, and dorsal hands, the inflammatory nature of the lesions from which the biopsies were taken, the near-total loss of melanocytes evident with Melan-A staining, and PCR findings demonstrating a lack of monoclonality, the diagnosis of inflammatory vitiligo was favored. However, hypopigmented MF could not be definitively ruled out and the coexistence of two separate disease processes remained a possibility. Therefore, close follow-up of this patient remains important.

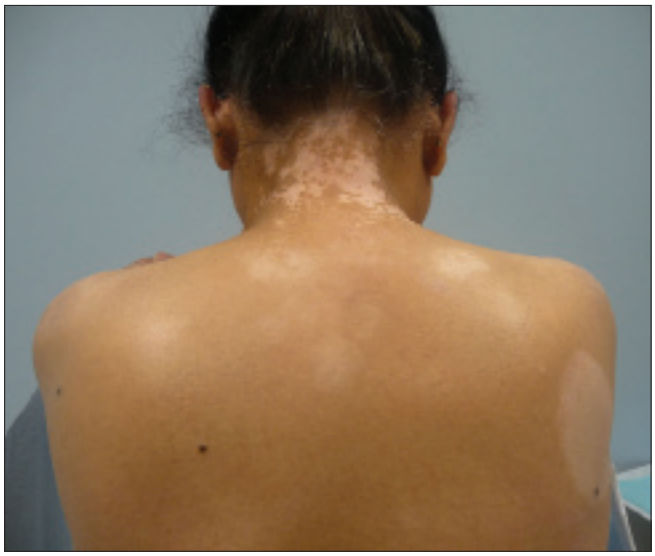

Figure 1: Speckled depigmented patches on the posterior neck. Hypopigmented patches on the back

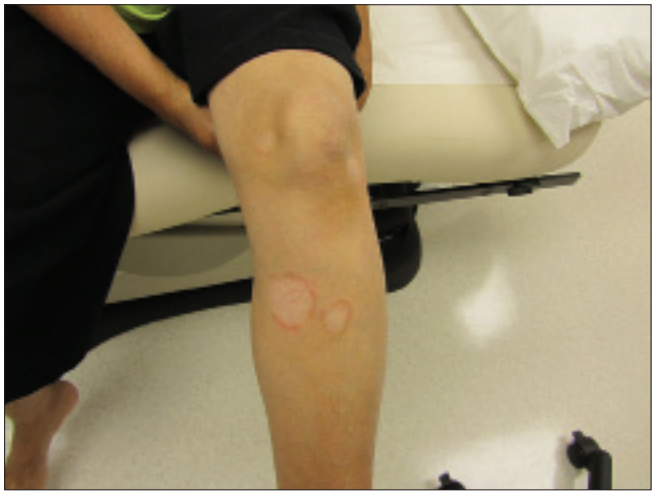

Figure 3: Hypopigmented patches with raised erythematous borders

DISCUSSION

Vitiligo is an idiopathic disorder characterized by the disappearance of melanocytes in lesional skin resulting in sharply demarcated depigmented macules and patches. Affecting 0.5-2% of the population worldwide, it can begin at any age, and affects all races. The classically affected areas include the face, dorsal hands, axillae, and groin, among other regions. Although often fairly distinct clinically, the differential diagnosis includes postinflammatory hypopigmentation, tinea versicolor, pityriasis alba, and, less commonly, hypopigmented mycosis fungoides (MF) and leprosy, among other entities. Lesions of vitiligo surrounded by a raised erythematous border represent the uncommon variant of inflammatory vitiligo, which is estimated to occur in less than 5% of cases. In the relatively few published reports of this variant, it is seen to occur at any age and affects both sexes equally, with some reports identifying its presentation in patients with a history of atopic dermatitis, hepatitis C, and Sjogren's syndrome.[1-3]

In contrast to its suggestive clinical presentation, vitiligo typically demonstrates unremarkable histopathological changes other

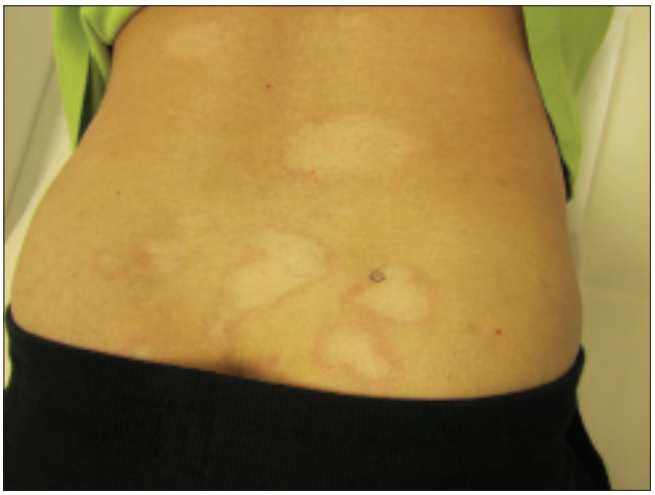

Figure 2: Hypopigmented patches with erythematous borders

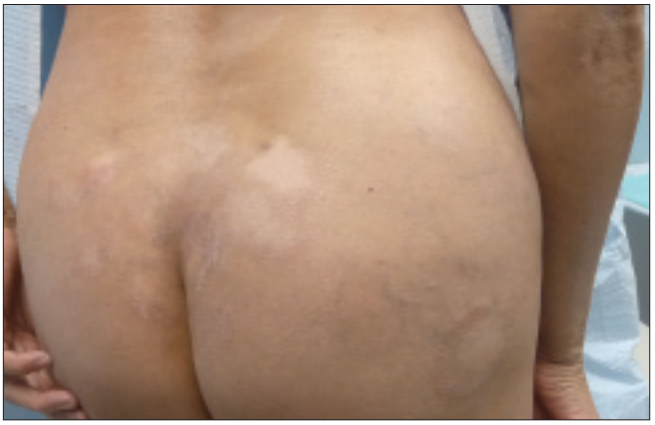

Figure 4: Hypopigmented patches with scaly erythematous borders

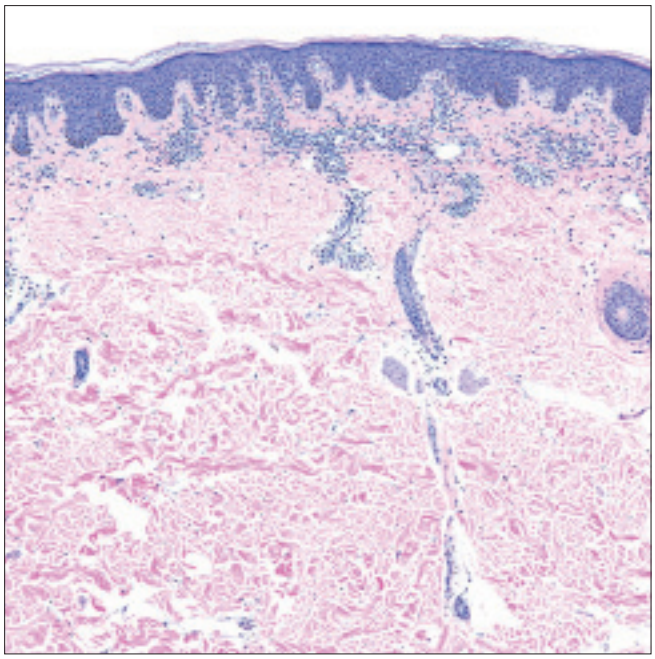

Figure 5: Punch biopsy – back [H & E, 40x]

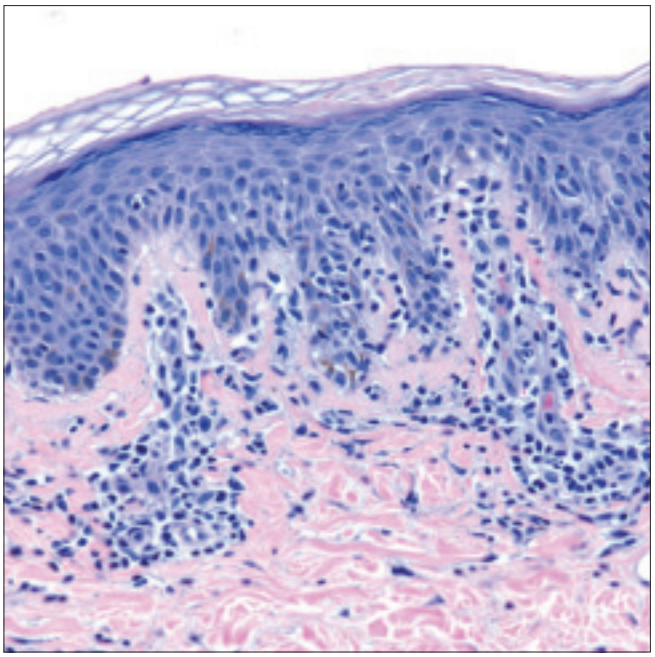

Figure 6: Punch biopsy – back [H & E, 400x]

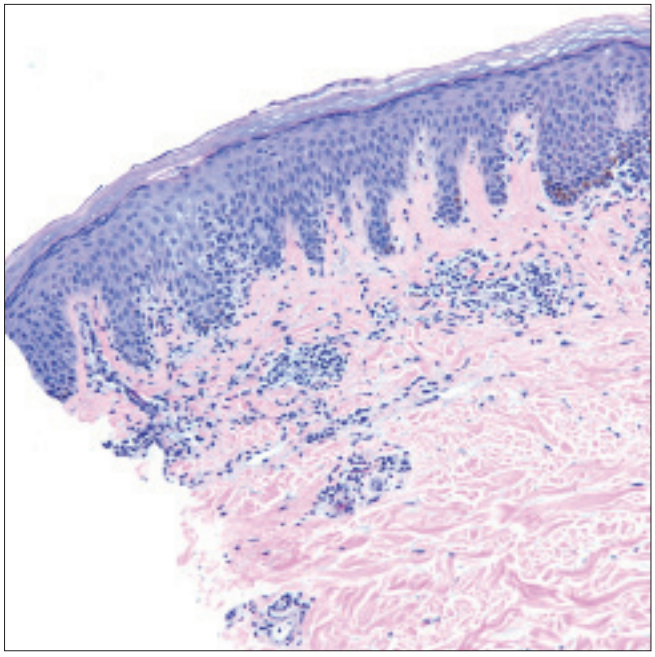

Figure 7: Punch biopsy – buttock [H & E, 200x]

than an absence of melanocytes. However, when biopsies are taken from the periphery of early depigmented lesions or from lesions with an inflammatory border, a dermal lymphocytic infiltrate, exocytosis, interface dermatitis, and mild spongiosis may be seen. CD4+ and CD8+ T-cells are both present in the dermal infiltrate, usually with an increased CD8/CD4 ratio, although a CD4 predominant infiltrate has also been reported.[4]

Mycosis fungoides, on the other hand, is the result of intraepidermal and superficial dermal infiltration by malignant T-cells. Hypopigmented MF is a rare variant of patch-stage MF and is most frequently reported in dark-skinned individuals, likely because of the lesions' contrast with surrounding skin. Unlike classic MF, hypopigmented MF is reported to manifest in younger populations from the first to third decade of life. This variant follows a similar clinical course and prognosis as classic MF.

On histopathology, early patch stage MF and hypopigmented MF tend to show a band-like lymphocytic infiltrate in the papillary dermis with coarse wiry fibrosis. Epidermotropism may present in a variety of patterns, including a linear accumulation of lymphocytes along the basement membrane zone, a single cell pattern, or a clustered pattern (Pautrier microabscesses). The epidermotropism is seen with a disproportionately small amount of spongiosis, with the epidermis described as having a passive appearance, allowing the accumulation of atypical lympocytes between keratinocytes. There are some differences between classic MF and hypopigmented MF seen with immunohistochemistry studiesin that the infiltrate in classic MF shows a predominance of CD4+ lymphocytes while hypopigmented MF tends to be made up of predominantly CD8+ cells, similar to vitiligo. One recent publication on hypopigmented MF in India reported that 80% (8/10) of the cases showed predominant CD8 positivity, while the other two showed no evidence of CD8+ or CD4+ lymphocytic infiltrate.[5] There are reports of hypopigmented MF demonstrating a CD4+ predominance, however.

A 2006 study by El-Darouti *et al*. sought to identify some defining histopathological features of each to aid in differentiating the two entities. They compared biopsy

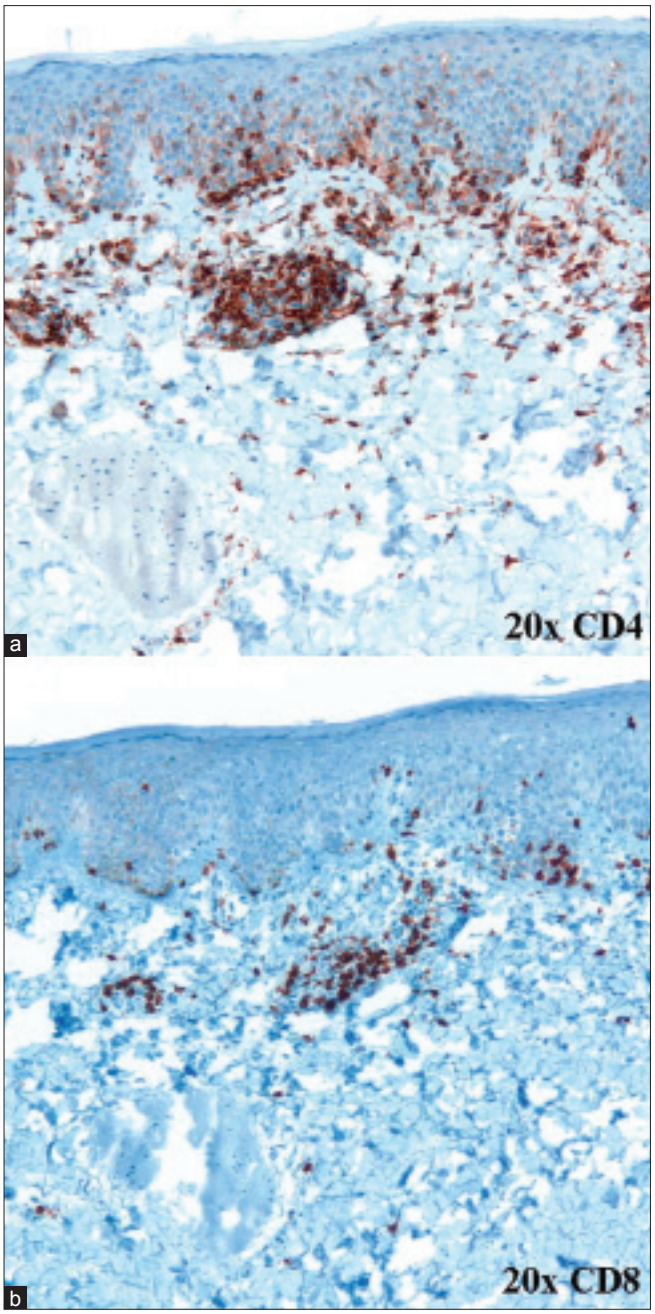

Figure 8: (**a**) Punch biopsy – buttock. CD4+ (a) to CD8+ (b) ratio approximately 5:1

specimens of 26 patients with vitiligo to 28 patients with hypopigmented MF, and determined several statistically significant differences [Table 1]. None of these features were 100% specific however. Immunohistochemistry comparisons of CD3, CD4, and CD8 revealed no statistically significant differences between the two groups as both tended to show CD8+ T cell predominance.

In addition to the histopathological differences, T-cell receptor gene rearrangement study with PCR can be useful for detecting hypopigmented MF. However, only 50% of patch-stage MF lesions are reported to demonstrate monoclonality. Similarly,

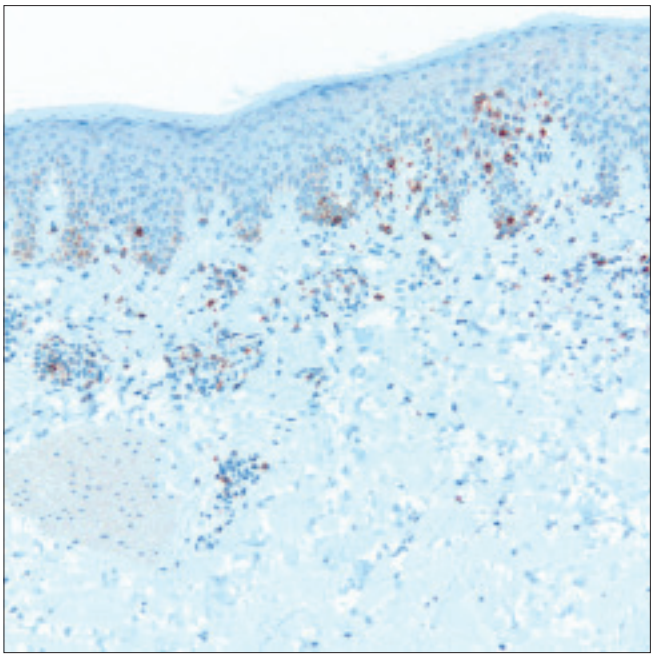

Figure 9: CD7 stain positive in approximately 30% of lymphocytes

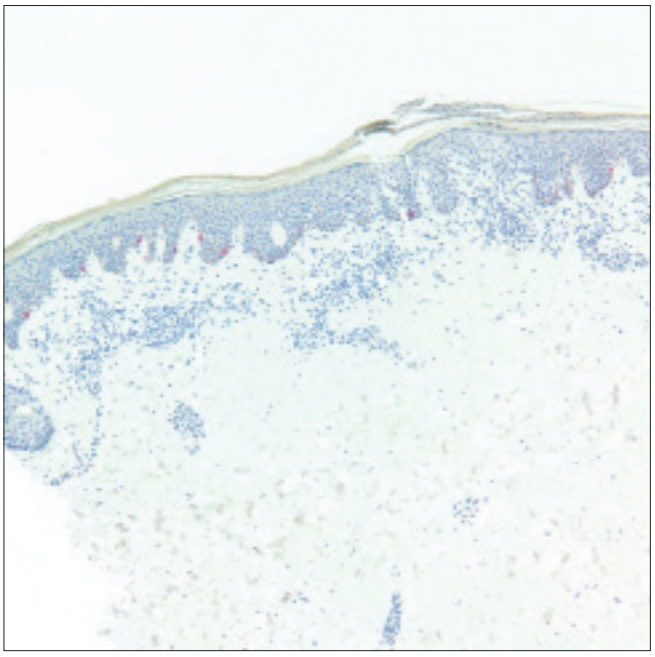

Figure 10: Melan-A. Markedly reduced number of melanocytes

monoclonality may also be seen in benign disorders, including inflammatory vitiligo. Therefore, hypopigmented MF cannot be definitively ruled out based on T-cell receptor gene rearrangement. Nevertheless, despite its cost, this test can be a helpful clue.

From a clinical standpoint, some authors offer that if erythematous lesions coexist with the hypopigmented lesions at the time of presentation or develop at a later stage, it is suggestive of MF. As noted by El-Darouti *et al*., however, of their

Table 1: Histopathological distinctions between vitiligo and hypopigmented MF

	Vitiligo	Hypopigmented MF
Melanocytes	Total loss	Partial (focal) loss
Hydropic degeneration	Rare	More frequent
BM thickening	More frequent	Rare
Lymphocytes in papillary dermis	Less common	More frequent
Dermal infiltrate	Less common (lower density)	More frequent (higher density)
Dermal wiry fibrosis	Less common	More frequent

Adopted from El-Darouti *et al.*

28 patients with hypopigmented MF, none presented with any accompanying erythematous lesions, making this clue helpful only in rare instances. The presence of surface changes like scaling or poikiloderma have also been mentioned as factors that favor a diagnosis of MF.[5]

Several other case reports discussing similar diagnostic dilemmas between these two entities include a 2003 paper by Petit *et al*. who reported two cases of hypopigmented macules with sharp, raised erythematous borders.[6] In the first case, a biopsy taken from the red border showed a dense superficial infiltrate and marked lymphocytic exocytosis. The infiltrate was composed of 80% CD8+ cells. HMB45 immunostaining revealed an absence of melanocytes and a PCR for monoclonality was negative, leading the authors to favor inflammatory vitiligo. The second case had similar hypopigmented lesions with erythematous raised borders, the largest being 17 cm in diameter. A biopsy showed a band-like epidermotropic infiltrate of predominantly CD3+ lymphocytes. HMB45 also showed loss of melanocytes. PCR was negative for a dominant T-cell clone. Inflammatory vitiligo was also favored in this case based on the total absence of melanocytes, CD3+/CD8+ lymphocytic infiltrate, and absence of monoclonality on T-cell clonal rearrangement.

In conclusion, in a patient presenting with hypopigmented lesions demonstrating a lymphocytic infiltrate, exocytosis, and interface dermatitis on biopsy, both vitiligo and hypopigmented MF should be included in the differential diagnosis. Clinicopathologic correlation is essential in differentiating the two. The presence of coexisting erythematous lesions, scaling, or poikiloderma favors hypopigmented MF. Distinguishing histopathological features of vitiligo include near-complete absence of melanocytes, basement membrane thickening, and focal as opposed to diffuse epidermotropism.[7,8] Hypopigmented MF is more likely to demonstrate a relative decrease (<50%) of melanocytes, vacuolar degeneration, and a dermal wiry fibrosis, among other features. Lastly, a T-cell gene rearrangement study may be helpful in the event of monoclonality, which favors MF, but is only approximately 50% sensitive and not entirely specific. Often, a conclusive diagnosis cannot be made, necessitating close follow-up of the patient and monitoring for progression of their disease over time.

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Cite this article as: Soro LA, Gust AJ, Purcell SM. Inflammatory vitiligo versus hypopigmented mycosis fungoides in a 58-year-old Indian female. Indian Dermatol Online J 2013;4:321-5.

Source of Support: Nil, **Conflict of Interest:** None declared.