

***Malassezia* associated hyperkeratosis of the nipple in young females: Report of three cases**

Sir,

Hyperkeratosis of the nipple and/or areola (HNA) is an unusual condition characterized by hyperpigmented, verrucous, keratotic thickening of the nipple and/or areola.^[1] We report three cases of hyperkeratosis of the nipple associated with *Malassezia*.

CASE 1

A 21-year-old woman had suffered a recurrent papule and effusion on her right nipple [Figure 1a] for more than 15 years. There was no pain, and the papule was not itchy. The patient had taken advice from a gynecologist and had been followed up for 7 years. However, since no improvement was noted, the gynecologist did a biopsy of the nipple considering breast cancer. Her family history was negative, and the patient had no history of ichthyosis or eczema. A skin examination showed crusting and effusion on the right nipple.

CASE 2

A 19-year-old woman with asymptomatic verrucous lesions on both nipples for 3 years was referred to the clinic. The lesions consisted of a round, rough plaque, 2 cm in diameter, on each nipple. They showed dark-brown discoloration and a cobbled hyperkeratotic appearance [Figure 1b]. The patient was otherwise healthy and had no other skin lesions.

CASE 3

A 16-year-old girl presented with a 1-year history of brown patches associated with pain and itching on her nipples. On examination, we found brown, waxy scales on both nipples [Figure 1c]. The patient's nipples were inverted. There was no history of eczema, Darier's disease, or ichthyosis.

Biopsies performed in patients 1 and 3 revealed papillomatous elongation of the epidermis with hyperkeratosis. A number of budding yeast cells were detected in the stratum corneum by periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) staining [Figure 2].

Direct methylene blue staining of scrapings revealed yeast cells in all three patients [Figure 3]. Scales were cultured and the colonies examined under a microscope, which revealed yeast cells. Three strains recovered from the medium were identified as *Malassezia* species. Fungal DNA was extracted from paraffin-embedded tissues of patients 1 and 3, and from scales of patient 2, according to the method of Sugita *et al.*^[2] Overall colonization by all *Malassezia* species and colonization by *M. globosa* and *M. restricta* were determined by real-time polymerase chain reaction (PCR) analysis of the samples, performed

according to the method of Sugita *et al.*^[2] All samples were analyzed in triplicate. *M. globosa* was detected in the samples from patients 1, 2, and 3 in all three cases. *M. restricta* was detected in patient 2.

The first patient was treated with oral itraconazole (0.2 g, twice a day) and topical povidone-iodine for 16 days [Figure 4a]. The other two patients finally improved after treatment with oral itraconazole (0.2 g, twice a day), topical 1% naftifine-0.25% ketoconazole cream, and washing with 2% ketoconazole lotion for 14 days [Figure 4b and c], and no yeasts were found by direct mycological examination. No recurrence has been observed in any of the three patients till date.

The three patients were female, in the age group 16-21 years. None of them had pityriasis versicolor or seborrheic dermatitis. Females in this age range often have high levels of estrogen secretion, but endocrinological investigations showed that the levels of female hormones in the three patients were within normal limits. Doppler ultrasonograms of the breasts

were normal. We found no evidence that the cases we reported were connected with the endocrine system. While terra firma-forme dermatosis and dermatosis neglecta have similar clinical manifestations, such pigmented plaques could be easily removed using isopropyl alcohol.^[3] In contrast, repeated efforts to scrub the affected area with different types of soaps and cleaners, as well as isopropyl alcohol, failed to improve the condition. It is rare that hyperkeratosis of the nipple is associated with *Malassezia* infection. *Malassezia* sp. are lipophilic yeasts of the cutaneous microbiota and have been implicated in various diseases, including pityriasis versicolor, seborrheic dermatitis, *Malassezia* folliculitis, atopic dermatitis, and psoriasis.^[4] Taizo *et al.* reported a case of confluent and reticulate papillomatosis with *Malassezia* sp. in the lesion.^[5] Tamraz *et al.* reviewed 10 cases of confluent and reticulated papillomatosis, and observed *Malassezia* yeast in six cases. An improper keratinizing response to *Malassezia* has been hypothesized as underlying the pathological keratinization.^[6] A similar improper

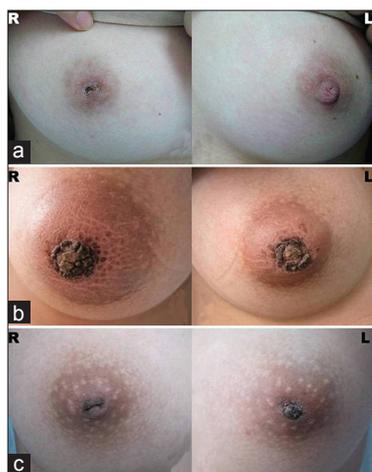


Figure 1: Lesions on the right nipple of patient 1 (a) and on both nipples in patients 2 and 3 (b and c)

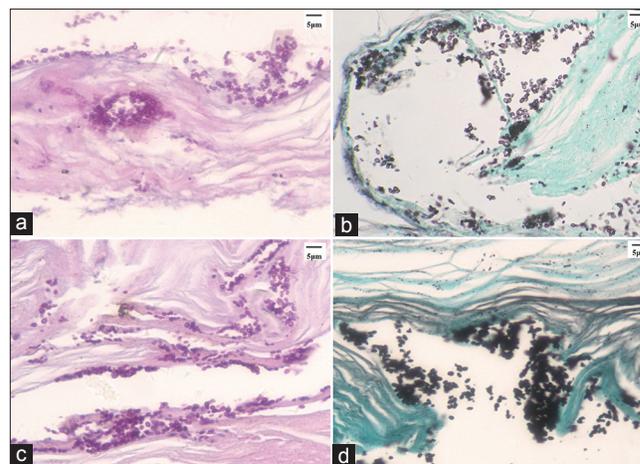


Figure 2: Budding yeast cells were detected in the stratum corneum in cases 1 (a and b, ×400) and 3 (c and d, ×400) by using periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) staining

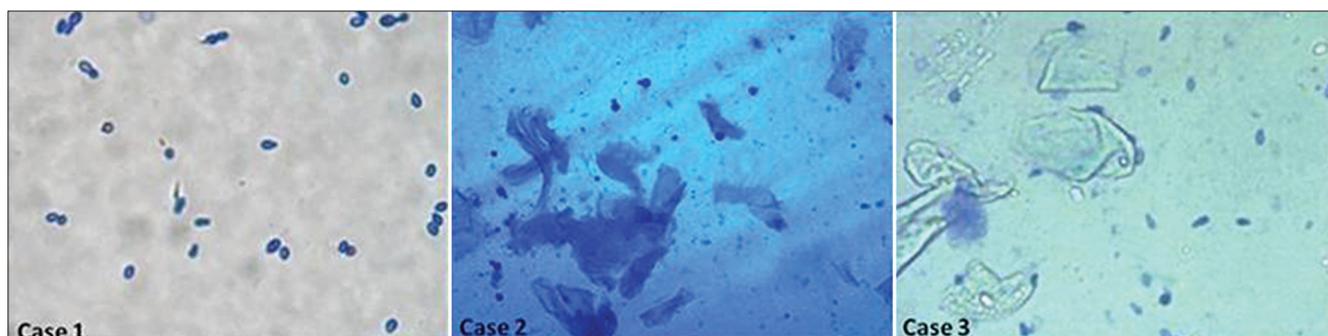


Figure 3: Direct methylene blue staining of scrapings revealed yeast cells in all three patients



Figure 4: All three patients improved after treatment for 14 days

keratinizing process may be underlying the three cases reported here. Boralevi *et al.* reported two cases of hyperkeratotic head and neck *Malassezia* dermatosis; *M. globosa* and *M. sympodialis* were identified from the scrapings.^[7] In the three cases reported here, *M. globosa* were dominant in cases 1 and 3, but *M. restricta* was detected in case 2. It is still unclear whether the different species are related to body regions or ethnic or geographic background.

In conclusion, *Malassezia* yeasts were detected in the lesion and antifungal therapy was effective in all these patients; therefore, we consider that *Malassezia* might be a new factor associated with hyperkeratosis of the nipple. Although it is still unsettled whether *Malassezia* is the direct cause, antifungal therapy could be considered besides keratolytic therapy, cryotherapy, and retinoid therapy in patients with hyperkeratosis of the nipple.

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