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Case Report

A MALE WITH HYPERKERATOSIS OF AREOLA ASSOCIATED WITH CHRONIC ECZEMA

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ABSTRACT
Hyperkeratosis of the nipple and areola (HNA) is a rare disorder characterized by verrucous thickening and brown pigmentation of the nipple and areola. HNA is very rarely seen in men and generally has been reported to be related to hormonal therapy. Here, we report a male patient who developed verrucous brown pigmentation on his areola for the last two years and who had no association with hormonal therapy but with chronic eczema.

Key words: Hyperkeratosis, nipple, areola, eczema, obesity

ÖZET
Meme başı ve areolanın hiperkeratozu (MAH) nadir rastlanan ve nedeni bilinmeyen bir hastalık olup meme başı ve areolada verrüköz kalınlaşma ve kahverengi pigmentasyon ile karakterizedir. Genellikle erkeklerde görülmektedir. Erkeklerde MAH prostat karsinomu için verilen östrojen tedavisi gibi hormonal tedavilerle ilişkilendirilmiştir. Ancak literatürde herhangi bir ilaç kullanım öyküsü olmayan erkek hastalar da bildirilmektedir. Bu erkek hastalarda ya eşlik eden bir hastalık bulunmakta ya da MAH lezyonları nevoid tipte (idiyopatik) görülmektedir. Burada 5 yıldır kronik egzeması olan ve son iki yılda areola üzerinde kahverengi pigmentasyon gelişen bir erkek hasta sunduk. Ayrıca erkek MAH hastalarında bildirilmiş eşlik eden hastalıkları kısaca tartıştık.

Anahtar kelimeler: Hiperkeratoz, meme, areola, ekzema, obezite

INTRODUCTION

Hyperkeratosis of the nipple and areola (HNA) is an unusual disease which presents as brown and verrucous thickening of the nipple and/or areola.[1] Although the etiology has not been clarified yet, hormonal factors have been suggested to have a role in its pathogenesis.[2,3,4]

HNA lesions are usually bilateral but unilateral presentation is also seen. Although some patients might report mild pruritus, it is generally asymptomatic. In case of excessive nipple involvement breast feeding may be problematic. It is generally seen in females in the second or third decade of life.[5]

HNA is clinically classified into three types. Type I is an extension of an epidermal nevus and seen unilaterally. Type II is associated with various dermatoses including ichthyosis, lymphoma, acanthosis nigricans (AN), chronic eczema and Darier's disease. Type III is the idiopathic form and also referred to as nevoid hyperkeratosis which is seen usually bilaterally in women in the second or third decade of life.[2,6,7]

Drug induced forms have been reported and proposed to represent a distinct type of disease.[8] In a meta-analysis, 80% of the HNA cases were reported to be type III.[5] Other authors have classified HNA as idiopathic (nevoid) or secondary. As the name implies, the secondary type is associated with underlying diseases and it is further divided into local or systemic. Local type is associated with acanthosis nigricans (AN), verrucous nevus and seborrheic keratosis and the systemic type is associated with ichthyosis, malignant lymphomas, Darier's disease, chronic eczemas and medications.[9]

To the best of our knowledge, less than 100 cases of HNA have been reported to date most of the cases being female.[1] Male patients with HNA, as reportedly, mostly associates with hormone therapy.[5] Here, we report a man with HNA whose lesions are not associated with hormone therapy but with chronic eczema.

CASE REPORT

62 years old man presented with bilateral verrucous keratosis on his areola with brown yellow pigmentation sparing the nipple for the last two years. Informed consent has been obtained from the patient to use his pictures (Figure 1 a, b).

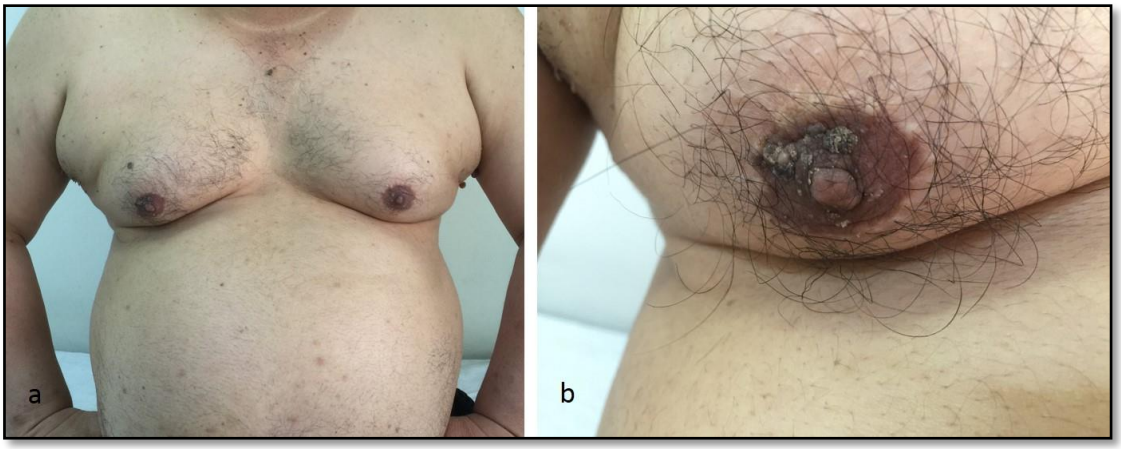

Figure 1. a) Bilaterally involvement of areola with hyperpigmented verrucous lesions b) Close-up view of the right areola

Lesions were not adherent to the underlying structures. There was no discharge from the nipples and the patient had no signs of AN. It was learned that he had not taken any hormone containing drugs. He had chronic eczema on his hands, arms and body for 5 years which had worsen for the last year. He had been treated with only various topical emollients before. No family member had similar lesions. The body mass index (BMI) of the patient was 31.2 (30≤ accepted as obese). His complete blood count, sedimentation rate, biochemical tests including plasma glucose level and electrolytes, oral glucose tolerance test, tumor markers, endocrinological investigations including thyroid and sex hormones, abdominal ultrasonography were entirely normal. The history, physical and laboratory examination revealed no signs of underlying endocrinopathy or malignancy. A biopsy was taken from the right areola. Histopathological examination revealed papillomatoses and hyperkeratotic changes of stratified squamous epithelium (Figure 2a, b).

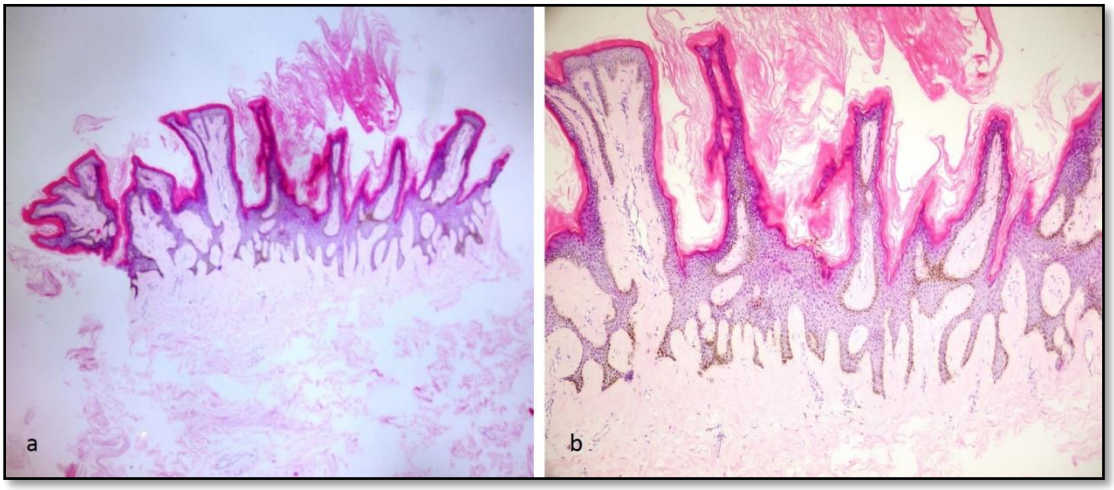

Figure 2. a) Papillomatosis and hyperkeratosis in epidermis (HE x 40), b) Papillomatosis and marked pigmentation at the basal layer (HEx100).

According to these pathological findings the diagnosis of HNA was made. The patient didn't demand treatment for his HNA lesions. Soon after, the patient's eczema worsened. He had tried several topical preparations for his eczema with no relief before and he could not tolerate narrow-band UVB. After confirming the diagnosis of eczema by multiple biopsies, excluding mycosis fungoides (MF), the patient was commenced cyclosporine (CsA) 3mg/kg/day. Only after two weeks a pronounced response was seen in his eczema lesions. Interestingly his HNA

lesions were partially improved after 1 month cyclosporine therapy without any topical treatment (Figure 3a, b). The patient stopped taking CsA treatment himself after two months as his eczema was treated.

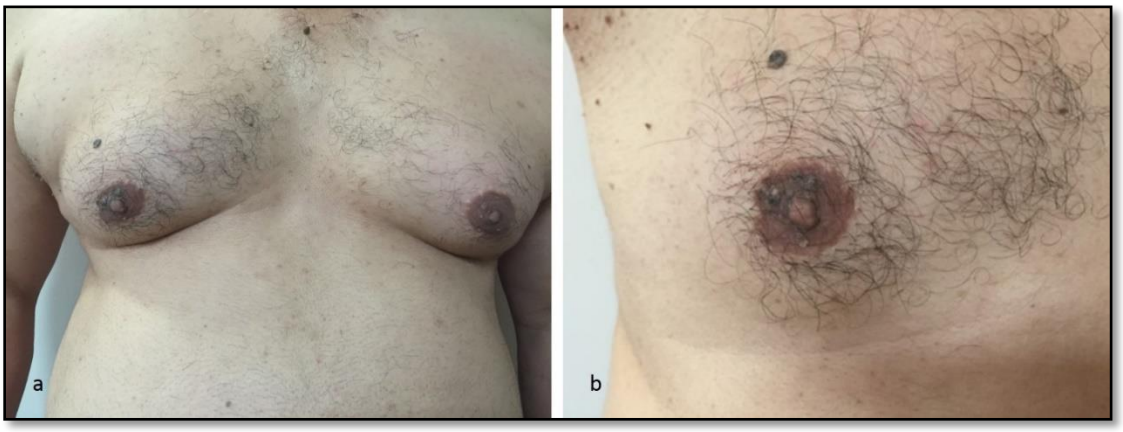

Figure 3. a) One month after cyclosporine therapy, b) Close up view after one month cyclosporine therapy

DISCUSSION

HNA is an unusual dermatosis characterized by dark brown verrucous thickening of nipple and/or areola with a marked female preponderance.[1] Hormonal factors have been suggested to play a role in the etiopathogenesis.[2,3,4]

It is rarely seen in males, and if seen, it is reported to be usually associated with hormonal therapy including estrogen containing drugs for prostate carcinoma.[4,5,10,11] However, men with HNA without history of hormone therapy have also been reported.[6,12] Male patients with HNA without an association of a dermatosis or systemic disease, namely nevoid type HNA have also been reported.[13 -15] Additionally, drug-induced HNA forms in male patients after use of vemurafenib and sorafenib (BRAF inhibitors) have been reported.[8,16,17]

Allegue et al.[18] have described a man with HNA who also has cutaneous T-cell lymphoma. Subsequently, Ahn et al.[19] have reported a male patient who had HNA lesions with histopathologic features of cutaneous T-cell lymphoma. There are further reports present in the literature suggesting an association of HNA and MF.[20-23] However, some of the patients showed the histopathological findings of MF while others did not.[20-23]

Male HNA patients with other associated diseases have also been described. Guevara-Gutiérrez et al.[24] have reported a

male patient with unilateral HNA with pruritic dermatosis on the ipsilateral breast. Tsai et al.[25] reported a male patient with unilateral HNA for twenty years who was diagnosed to have glioblastoma multiforme and took anti-tumor treatment afterwards. One of the three patients in the study of Mixtelena et al.[14] had benign prostate hyperplasia. Kavak et al.[26] described a male HNA patient with chronic mucocutaneous candidiasis. The association between AN and HNA has been well-known for years and AN-associated HNA is classified as type II.[2] Also, there are authors that accept HNA as a cutaneous sign of AN that is localized to the nipple and areola region.[4] Lee HW et al.[27] reported a female patient who has developed AN and bilateral hyperkeratotic nipple lesions consecutively after gaining 10 kg over 3 months, though her endocrinological test results were normal. The association between high BMI and insulin resistance as well as the association between insulin resistance and AN have been well established.[7,28] In men, HNA can be observed either unilaterally or bilaterally.[14] Some authors suggested that the bilateral occurrence of HNA in male patients favors an underlying endocrinologic etiology.[25] Our patient did not have an endocrinological laboratory abnormality although he had high BMI. HNA can also be associated with acanthosis nigricans maligna (ANM). A female patient with gastric adenocarcinoma has been reported to have secondary HNA lesions associated with AN.[29] Recently, a male patient who also have gastric adenocarcinoma has been described with HNA, ANM, tripe palms and florid cutaneous papillomatosis (FCP) that further reinforces the above mentioned association.[7]

Our patient had chronic eczema for long years before the HNA lesions appeared. According to the classification of the disease, the patient was accepted as having 'type II' and Pérez-Izquierdo[9] as 'secondary' HNA. Chronic scratching because of pruritic dermatosis has been suggested to trigger the hyperkeratosis in a male case.[6] However, the etiologic relation between the chronic dermatosis and HNA remains to be explored as the associated dermatosis were not co-localized with HNA lesions in our patient. Considering the extent of involvement, male patients with HNA have the lesions either on the areola [6,15,16] or on both areola and the nipple.[12,26] The lesions of our patient spared the nipples.

There is no effective treatment for HNA and often the therapeutic options are

accompanied with variable success. Treatment options in the literature include topical retinoids, topical calcipotriol, topical steroids, keratolytics such as salicylic acid, emollients with urea, cryotherapy, systemic acitretin and surgery.[1,8] As our patient had no symptoms he did not demand treatment for HNA lesions. CsA was commenced to treat his worsened chronic eczema which resulted partial improvement of the lesions. CsA has potent immunosuppressive properties, reflecting its ability to block the transcription of cytokine genes in activated T cells and have not been used to treat HNA before. CsA has been found to be effective in dermatosis such as atopic dermatitis characterized by lymphocytic infiltration by reducing the inflammatory cells attacking the skin.[30] In some HNA cases, perivascular lymphocytic inflammatory infiltrate were observed.[2] Furthermore, HNA lesions that harbour intraepidermal lymphocytes have been reported.[21,22] Although lymphocytic infiltration was not observed histologically in our case, inflammatory feature that might be seen in HNA as reported in above mentioned studies, may be involved in the response to CsA. However, further studies are warranted to clarify this association.

CONCLUSION

Considering the rare occurrence of HNA in men, we suggest that extending the number of male cases published in the literature will provide insight into etiology of HNA.

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