Bilateral nipple neoformations

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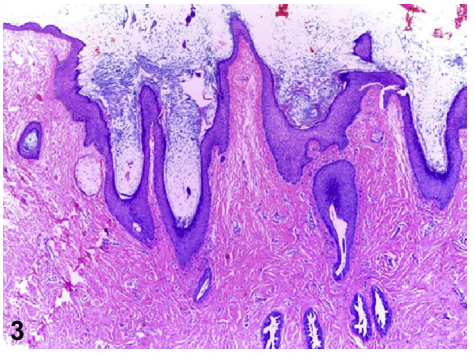

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An 11-year-old woman, with a 1-year history of bilateral, symmetric, and slightly pruritic dermatitis located on the breasts, presented for dermatologic evaluation. On physical examination, brown inverted verrucous papules were observed on both nipples. The surrounding skin and areolae were covered in a speckled, hyperpigmented plaque with pinpoint adherent scale (Figs 1 and 2). Histopathology reported abundant orthokeratosis; epidermis with papillomatosis, as well as a marked, irregular acanthosis. The papillary dermis contained a mild lymphohistiocytic inflammatory infiltrate (Fig 3).

Question 1: What is the most likely diagnosis?

A. Ichthyosis vulgaris

B. Nevoid hyperkeratosis of the nipple and areola (NHNA) and dermatitis neglecta

C. Darier disease

D. Paget disease of the breast

E. Chronic nipple eczema and dermatitis neglecta

Answer:

A. Ichthyosis vulgaris—Incorrect. Ichthyosis vulgaris is an inherited autosomal dominant disease. It is clinically characterized by xerosis, hyperkeratosis, excess scaling, and palmar and plantar hyperlinearity.[1]

B. NHNA and dermatitis neglecta—Correct. NHNA is a benign condition, affecting both sexes. It can affect the nipple, areola, or both uni- or bilaterally. NHNA presents as hyperpigmented wart-like papules, which may resemble hyperkeratosis or have a tumor-like appearance. Skin lesions are frequently asymptomatic, without exudate, or associated lymphadenopathy; some patients may experience pruritus. The associated dermatitis neglecta is related to a lack of hygiene in the affected areas, resulting in hyperpigmented and adherent scales.[2]

C. Darier disease—Incorrect. Darier disease is an autosomal dominant genodermatosis. Clinical symptoms typically appear in childhood and include erythematous or tan hyperkeratotic papules varying in size from 1-3 mm, which are present in a seborrheic distribution.[3]

D. Paget disease of the breast—Incorrect. Paget disease of the breast is a disorder of the nipple-areola complex. It is often associated with underlying ductal carcinoma *in situ* and/or invasive ductal carcinoma. It occurs most commonly in postmenopausal women. The clinical appearance of Paget disease is usually a thickened, sometimes pigmented, eczematoid, erythematous weeping or crusted lesion with irregular borders. Usually, the lesion is limited to the nipple or extended to the areola; in chronic cases, it may also involve the surrounding skin.[4]

E. Chronic nipple eczema and dermatitis neglecta—Incorrect. It is considered a minor manifestation of atopic dermatitis. It is known to predominate in adolescent girls and characterized by erythema, scaling, crusting, fissures, vesicles, erosions, and lichenification. Both nipples are commonly involved.

Question 2: Which factors are most related to the etiology of this dermatosis?

A. Puberty and pregnancy

B. Viral DNA

C. Filaggrin mutation

D. Mutations in the *ATP2A2* gene

E. Oncoprotein Her-2

Answer:

A. Puberty and pregnancy—Correct. Although the etiology of NHNA is unknown, most of the cases occur in women in the second or third decades of life. An exacerbation during pregnancy has been commonly reported in female patients. Cases among males receiving estrogen therapy for prostate cancer have been reported; therefore, a hormonal role has been suggested as a possible etiological explanation of the condition.[2]

B. Viral DNA—Incorrect. Despite the warty appearance that NHNA may have, no viral DNA has been found in the lesions of this dermatosis.

C. Filaggrin mutation—Incorrect. Filaggrin mutations are associated with dermatosis-like atopic dermatitis[1] and ichthyosis vulgaris, causing disorganization and immaturity of the lamellar bilayers, an elevated skin surface pH, and increased transepidermal water loss. According to the Levy-Franckel classification, type 2 NHNA may be associated with ichthyosis. However, type 2 NHNA is uncommon.[5]

D. Mutations in the *ATP2A2* gene—Incorrect. Darier disease is an autosomal dominant condition caused by mutations in the *ATP2A2* gene. A more recent classification divides NHNA into two principal types: 1) primary or idiopathic type and 2) secondary type associated with another skin

condition (*e.g.*, Darier disease). Primary or idiopathic NHNA is the most commonly reported type.[3]

E. Oncoprotein Her-2—Incorrect. The Her-2 Oncoprotein is one of many proteins expressed in Paget disease of the breast, a malignant disease that can be a differential diagnosis of NHNA. The clinical appearance of Paget mammary disease can function as a guide to achieve a correct diagnosis.[4]

Question 3: Which of the following therapeutic options has been used as a safe first-line treatment for this dermatosis?

A. Corticosteroids

B. Keratolytic agents

C. Surgical and ablative procedures

D. Retinoids

E. Vitamin D analogs

Answer:

A. Corticosteroids—Incorrect. Topical corticosteroids are only helpful in reducing pruritus in this dermatosis.

B. Keratolytic agents—Correct. Keratolytic agents such as urea, salicylic acid, or lactic acid have been used as first-line treatments because of their safety and efficacy in the treatment of NHNA, improving hyperkeratosis by producing lysis of the stratum corneum. Recurrence of the lesions has been reported after cessation.[2]

C. Surgical and ablative procedures—Incorrect. Surgical procedures (shaving, excision, curettage, removal of the affected area with subsequent reconstruction) and ablative procedures (cryotherapy, resurfacing laser) have been used as NHNA treatments in a few cases. However, some of these treatments may result in permanent structural and functional damage of the nipple-areola complex; therefore, they should not be considered as first-line treatments.[2]

D. Retinoids—Incorrect. Topical and systemic retinoids (tretinoin, etretinate, and acitretin) have been used to treat NHNA, considering their application and usage in hyperkeratotic conditions like psoriasis. Systemic etretinate was ineffective in one case. Tretinoin and acitretin have shown variable results, but nothing certain.

E. Vitamin D analogs—Incorrect. Vitamin D analogs are known by their inhibitory effect on cellular proliferation and the induction of keratinocyte differentiation; therefore, there are many reports on their role in hyperkeratotic and hyperproliferative dermatosis-like NHNA. Although there are cases with improvements, long-lasting results remain to be reported.

Abbreviation used:

NHNA: nevoid hyperkeratosis of the nipple and areola

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