Successful Treatment of Topical Tretinoin Cream in a Patient with Unilateral Nevoid Hyperkeratosis of Nipple and Areola

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CASE REPORT

A 53-year-old man presented with a 20-year history of asymptomatic, progressive pigmented thickening of his left nipple and areola. He denied having any chronic illness. However, a diagnosis of glioblastoma multiforme had recently been made, and he had received three years of combination therapies, including subtotal excision, radiotherapy, chemotherapy, and photodynamic therapy, without any documented subsequent endocrine abnormality.

Physical examination revealed a blackish verrucous plaque blanketing the left areola, and extending up the base of the left nipple (Fig. 1A, 1C). On palpation, the involved skin was neither indurated nor tender nor adherent to the underlying structures. There was no discharge from the nipple, and no regional lymphadenopathy, associated warts, ichthyosis, epidermal nevus, or acanthosis nigricans was noted. No family member had similar lesions.

Histopathologic examination of a specimen from the left areola showed extensive and marked elongations of rete ridges of the epidermis, inducing filiform acanthosis and papillomatosis, orthokeratotic invaginating hyperkeratosis, and occasional keratic plug (Fig. 2). In addition, some anastomosing strands of elongated ridges and ectopic sebaceous glands were seen. The ectopic sebaceous glands were thought to be an accidental finding. The basal layer of the epidermis was hyperpigmented, but there was no melanocytic proliferation. The elongated papillary dermis was mildly edematous, and a sparse perivascular lymphocytic inflammatory infiltrate was found in the dermis. The histopathologic picture was compatible with a diagnosis of nevoid hyperkeratosis of nipple and areola.

The patient received tretinoin cream per night topically use for a period of two months. The lesion improved significantly in pigmentation and minimally in thickness (Fig. 1B, 1D). No relapse has been observed during 6 months’ follow-up after discontinuation of topical agent.

DISCUSSION

Hyperkeratosis of the nipple and areola was first described by Tauber in 1923. Then, Levy-Francel classified hyperkeratosis of the nipples and areola (HNA) into three categories. Type 1 is hyperkeratosis that occurs as an extension of an epidermal nevus. Type 2 is hyperkeratosis associated with other dermatoses, such as acanthosis nigricans, ichthyosis, lymphoma, chronic eczema, seborrheic keratoses, or Darier’s disease. Type 3, which is described in this case, is nevoid...
hyperkeratosis of the nipple and/or areola (NHNA), without association with epidermal nevi or other dermatoses. To date, only approximately 70 cases of NHNA have been reported in the literature.

Typically, NHNA presents as hyperkeratotic, hyperpigmented, and occasionally verrucous plaques on the nipple and/or areola. It is generally asymptomatic and is considered bothersome and cosmetically unsightly. The lesions are often bilateral; however, there have been several reported cases of unilateral involvement. When Kubota et al. reviewed 45 cases of nevoid hyperkeratosis, 17% of cases involved the nipple, 25% of cases involved the areola, and the remaining 58% of cases involved both the areola and the nipple.

NHNA is a diagnosis of exclusion. The differential diagnosis includes: HNA types 1 and 2, Paget’s disease, superficial basal cell carcinoma, dermatophytosis, Bowen’s disease, and seborrheic keratosis. These disorders can be differentiated from NHNA by correlating the clinical and histologic features. Common histopathologic features of NHNA include prominent orthokeratotic hyperkeratosis, mild acanthosis, and papillomatosis with a striking filiform pattern. The keratotic plugging represents an associated finding, which is the result of the exaggerated undulation of the surface. Baykal et al. stressed that the very prominent surface undulation was the main differentiating feature between NHNA and epidermal nevus or acanthosis nigricans. Anastomosing rete ridges and the striking filiform nature of papillomatosis and acanthosis are also important clues.

We have presented a case of unilateral NHNA in a middle-aged male patient. When Obayashi et al. reviewed 45 reported cases of HNA in the literature, they found that 36 (80%) of the lesions were idiopathic or nevoid. The lesions were mostly reported among females (80%), and tended to appear during the second and third decades of life. In males, the age of onset is much more variable. Two of the seven reported male patients were elderly and had received estrogen therapy for prostatic adenocarcinomas. As a result, although the exact etiology of NHNA remains unknown, it has been postulated that some cases may be due to alterations in estrogen levels. Additional support for this theory comes from reports of patients whose lesions began with puberty, or with pregnancy, or changed from a unilateral to a bilateral distribution with pregnancy. However, this theory fails to explain the numerous cases of nevoid hyperkeratosis in men and in women that are not associated with hormonal changes. For example, our case showed persisted lesion for over twenty years without endocrine abnormalities noticed, despite history....
Nevoid Hyperkeratosis of Nipple and Areola

Various therapeutic modalities, such as salicylic acid gel, lactic acid lotion, corticosteroid gel, topical retinoic acid, and cryotherapy, have been used for NHNA patients, with differing rates of success. Topical retinoic acid has been reported to produce good cosmetic effects with no relapse when used continuously for two months, then intermittently thereafter. Two Taiwanese case reports had shown good treatment responses to the topical regimens of urea (12.5%) plus corticosteroid and urea (10%) only, by taking the advantage of keratolytic effect of urea under the high concentration. Ablative procedures with carbon dioxide, radiofrequency surgical unit, and skin graft reconstruction have all been documented with successful results. Vitamin D analogues, calcipotriol and calcitriol, have both been shown their beneficial effects toward NHNA lesions. Recently, a case of HNA was reported with a longest documented remission period of 2 years under the combination therapies of low-dose acitretin and topical calcipotriol. Our case showed similar positive response to continuous topical retinoic acid for two months as previous literatures did. However, the possibility of recurrence should be kept in mind and lesions should be followed up since the treatment was discontinued.

The case is presented due to the following points. First, the case is a man without underlying endocrinological abnormalities, and this is rarely seen in NHNA previous reports. Second, the case presented with unilateral lesion, which is also a less-frequent encountered circumstance, since most of the nevoid variants are bilaterally involved. If we further combine the above two characters together, only two case reports were found in the English literatures. From the etiological point of view, it seems that the unilateral involvement of skin lesions in an otherwise healthy male does not favor the endocrine theory for NHNA. Therefore, in addition to highlighting the possibility of diagnosing NHNA in an unilaterally involved male patient, it is hoped that through this report, this rare condition of rarely documented entity will become more recognizable and more thoroughly discussed, leading ultimately to further studies of its pathogenesis and treatment.

REFERENCES
5. Obayashi H, Tsuchida T, Ikeda S: [Hyperkeratosis of nipple and areola]. [Japanese] Rinsho Derma-