

## Hyperkeratosis of the Nipple Associated with Chronic Graft versus Host Disease after Allogeneic Haematopoietic Cell Transplantation

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Sir,

Hyperkeratosis of the nipple and the areola (HNA) is a rare, benign condition characterized by asymptomatic hyperkeratosis and hyperpigmentation affecting the nipples and/or the areolae mammae (1–3). It may be idiopathic or associated with diseases such as ichthyosis, acanthosis nigricans, Darier's disease or endocrinopathies. A few cases have also been reported related to internal malignancies, cutaneous T-cell lymphoma, or use of drugs (oestrogen and spironolactone) (4–7). We report here a case of HNA that developed during chronic cutaneous graft versus host disease (GVHD) following allogeneic peripheral blood stem cell transplantation.

### CASE REPORT

A 35-year-old woman diagnosed with acute myeloid leukaemia in July 2000 received an allogeneic peripheral blood stem cell transplant from an HLA-matched sibling donor in November 2001. After transplantation, cyclosporin A and corticosteroid were initiated for graft versus host prophylaxis.

At day 30 post-transplantation, she developed abdominal pain, vomiting and diarrhoea. Gastric and duodenal biopsies showed acute GVHD. Within a few weeks, axillary and inguinal hyperpigmentation and desquamation appeared and a skin biopsy confirmed acute GVHD. Two months later she developed severe xerosis, generalized

violaceous papules and plaques on the trunk and extremities and white reticular lesions on both buccal mucosae, despite therapy with cyclosporin A and corticosteroids. A skin biopsy showed findings compatible with chronic lichenoid GVHD. Mycophenolat mofetil was added and the lichenoid papules regressed, leaving postinflammatory hyperpigmentation and xerosis. She also complained of progressive thickening, desquamation and brown discoloration of both nipples (Fig. 1). A biopsy revealed orthokeratotic hyperkeratosis forming occasional keratotic plugging, acanthosis, papillomatosis and hypergranulosis in the epidermis and slight fibrosis in the upper dermis consistent with hyperkeratosis of the nipple (Fig. 2). No change in systemic therapy was undertaken, but emollients for xerosis and topical tretinoin for hyperkeratosis of the nipple were initiated with clinical improvement.

### DISCUSSION

HNA is a rare condition usually affecting women. Although it is an asymptomatic condition it may cause cosmetic disturbance and may hinder breast-feeding (3–5, 8).

It was first described in association with ichthyosis vulgaris by Tauber in 1923 (9) and the initial classification of the disease was made by Levy-Frankel (10) in 1938. Type 1 HNA is an extension of an epidermal naevus, Type 2 HNA is related to ichthyosis, acanthosis nigricans, Darier's disease or chronic eczema, Type 3 HNA is an



Fig. 1. Hyperkeratosis and brown discoloration of the nipple.

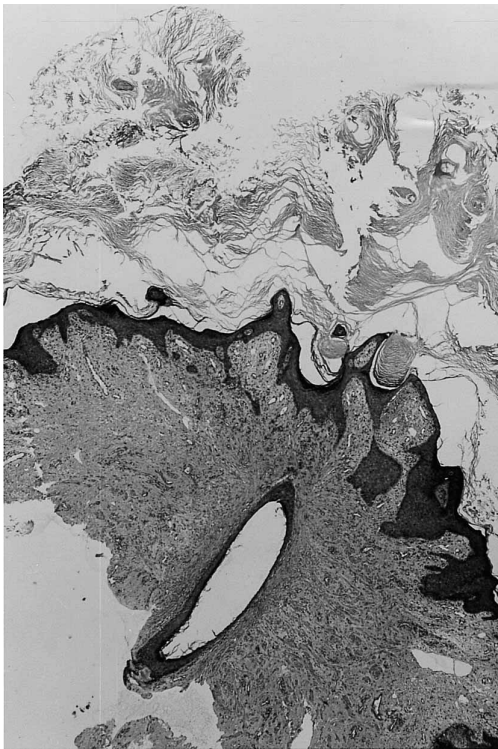


Fig. 2. Hyperkeratosis, acanthosis, papillomatosis and keratotic plugging (HE  $\times 40$ ).

isolated naevoid form. In 2001, Mehanna et al. (11) reported that type 1 according to Levy-Frankel's classification is an epidermal naevus, which involves the nipple and the areola, and that it should not be considered as hyperkeratosis of the nipple. They proposed an alternative classification including three variants: Type 1 primary HNA occurring coincidentally with other skin diseases such as ichthyosis, acanthosis nigricans or Darier's disease; Type 2 secondary HNA occurring secondary to hormonal changes, internal malignancies or lymphoma; and Type 3 idiopathic HNA. Our patient probably belongs to the first group of this classification,

since hyperkeratosis of the nipple occurred during the course of chronic cutaneous GVHD in association with severe xerosis. The possibility of a relation with leukaemia was excluded as she was in complete chimeric status and in sustained remission.

Skin is the most frequently affected target organ in chronic many other VHD. In addition to the classical cutaneous findings, manifestations such as keratinization disorders, including acquired ichthyosis, have been described in these patients (12, 13). Currently, 70 patients with chronic cutaneous GVHD are under continuous observation in our clinic. Although xerosis is a relatively frequent finding in these patients, this patient was the first to develop hyperkeratosis of the nipple. To the best of our knowledge the association of GVHD and HNA has not been reported until now. Since the condition is asymptomatic and causes only cosmetic problems, it probably does not arouse much medical attention. We believe, however, that HNA may not be so infrequent in patients with cutaneous GVHD who experience severe xerosis, and chronic GVHD should be considered within the spectrum of diseases associated with HNA.

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