Mammary Paget Disease in Darier Disease: Beware the Wolf in Sheep’s Clothing

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Abstract: This case describes new onset mammary Paget disease arising in the background of Darier disease. Clinically and histologically, lesions of Darier disease can mask the lesions of mammary Paget disease. A high index of suspicion is necessary to diagnose Paget disease in a patient with Darier disease, for a potentially fatal disease could easily be missed.

Key Words: corps ronds, corps grains, Darier disease, endoplasmic reticulum, Hailey-Hailey disease, Paget disease, pemphigus, pityriasis rubra pilaris

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INTRODUCTION

Darier disease (aka Darier-White disease, Keratosis Follicularis, Dyskeratosis Follicularis) was simultaneously and independently reported in 1889 by Jean Darier in Paris and James C. White.1–16 Darier disease is inherited in an autosomal dominant fashion and is due to a mutation in ATP2A2 gene on chromosome 12q23-24.6 The resultant dysfunction of endoplasmic reticulum (ER) Ca\(^{2+}\) ATPase pump (SERCA2) leads to defects in calcium sequestration into the ER.6 This produces acantholysis by impairing normal processing of junctional proteins (desmoplakins).7

On histopathology, there is suprabasilar acantholysis and corps ronds and corps grains. Corps ronds are acantholytic enlarged keratinocytes with darkly staining and partially fragmented nuclei in the malpighian layer in the epidermis. The cytoplasm is clear and encircled by a bright ring of collapsed keratin bundles.10 Corps grains are small oval cells in the stratum corneum with intensely eosinophilic cytoplasm, collapsed keratin bundles, and shrunken parakeratotic nuclear remnants10 (Fig. 1).

Darier disease displays a chronic course with spontaneous remission.

In 1874, Sir James Paget first reported Mammary Paget disease. He reported this in association with underlying intraductal carcinoma of the breast.17 It occurs almost exclusively in women aged 22–84, with a mean age of 55. Approximately, 1%–4% of breast carcinomas are associated with Paget disease of the nipple, areola, and surrounding skin.2 Up to 100% of mammary Paget disease is associated with intraductal carcinoma (~10%) and infiltrating carcinoma (~90%).7

On histopathology, there are malignant Paget cells in the epidermis with abundant clear-pale staining eosinophilic cytoplasm and nucleoli with intracytoplasmic vacuoles.13 Paget cells stain positive for carcinoembryonic antigen and cytokeratin (CK7),13 and Her-2 Neu, MUC1, MUC2, MUC5AC, CAM 5.2, Ca 15-3, EMA, TP53, c-erb B-2, GCDFP-15.16

CASE REPORT

A 73-year-old female presented with a widespread skin eruption that was present for several weeks. On exam, she had diffuse, confluent, keratotic, crusted, papular lesions in seborrheic areas, including the scalp, forehead, back, and chest (Fig. 1). In addition, she had a lesion on her left nipple that was present for several months and unresponsive to topical corticosteroids. The left nipple also showed an erythematous, crusted plaque similar to the rest of her eruption. Her past medical history was unremarkable.

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FIGURE 1. Keratotic papules in seborrheic distribution.
Our differential diagnosis included seborrheic dermatitis, Darier disease, eczematous dermatitis, pemphigus group, pityriasis rubra pilaris, and Hailey–Hailey disease.

Biopsies were obtained from the scalp, abdomen, and left nipple. On routine histology, all biopsies showed suprabasilar acantholysis with scattered dyskeratotic keratinocytes (Corps ronds and grains) throughout the epidermis, consistent with Darier disease (Fig. 2). The biopsy from the abdomen was also submitted for direct immunofluorescence. This was negative which eliminated the pemphigus group as a diagnosis.

Additionally, the nipple biopsy showed rare atypical cells with pleomorphic nuclei in the epidermis (Fig. 3). These atypical cells were immunoreactive for carcinoembryonic antigen and CK7 (Fig. 4), confirming a diagnosis of Paget disease. The patient was referred to an oncologist who confirmed a diagnosis of underlying breast carcinoma. The patient subsequently underwent bilateral mastectomy and received chemotherapy and radiation treatment.

Upon further history and examination, the patient admitted to diffuse eruptions as a teenager and recalled the diagnosis of Darier disease. She denied knowledge of family members with the disease. She denied any history of nail and mucosal involvement throughout the course of her disease. Topical steroids were effective in resolving the cutaneous lesions.

**DISCUSSION**

A case of new onset mammary Paget disease arising in the background of Darier disease is described. To our knowledge, this is the first known case of these 2 diseases arising in 1 patient.

The most commonly associated conditions seen in Darier disease are infections, such as bacteria, fungi, and viruses—human papillomavirus and herpes simplex virus (Kaposi varicelliform eruption).

To date, there are only few reported malignancies occurring in Darier disease, including basal cell and squamous cell carcinomas. To our knowledge, the only malignancies described to occur in lesions of Darier disease are carcinomas of epidermal and adnexal origin.

We do not know what caused the Darier disease to erupt at this stage of the patient’s life. We could speculate that the onset of Paget disease was the trigger.

Clinically, the lesions of Darier disease can disguise the lesions of mammary Paget disease. Histologically, the presence of corps ronds typical for Darier disease can easily mask the presence of Paget cells. A high index of suspicion is necessary, both clinically and histologically, to diagnose Paget disease in a patient with Darier disease, for a potentially fatal disease could easily be missed.

**REFERENCES**

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