

# Case Letter

## Acantholytic Anaplastic Paget Disease

To the Editor:

Acantholytic anaplastic Paget disease is a subset of classic Paget disease with distinctive histologic features that may be a diagnostic challenge.<sup>1</sup> We report a case of this rare variant of Paget disease and briefly review its characteristics.

An 81-year-old woman presented with an asymptomatic lesion on her left nipple of 2 years' duration. Physical examination revealed enlargement of the left nipple with an erythematous, eroded, exudative, and lightly crusted surface (Figure 1). The areola was unaffected. On physical examination a poorly defined, tough but lightly mobile mass was observed on the upper and inner quadrant of the ipsilateral breast. There were no lymphadenopathies. A skin biopsy specimen showed an eroded hyperplastic surface epithelium with an overlying scaly crust and full-thickness atypia, preservation of the basal layer, and focal acantholysis. Nuclei were pleomorphic and mitotic figures were frequent. Tumoral



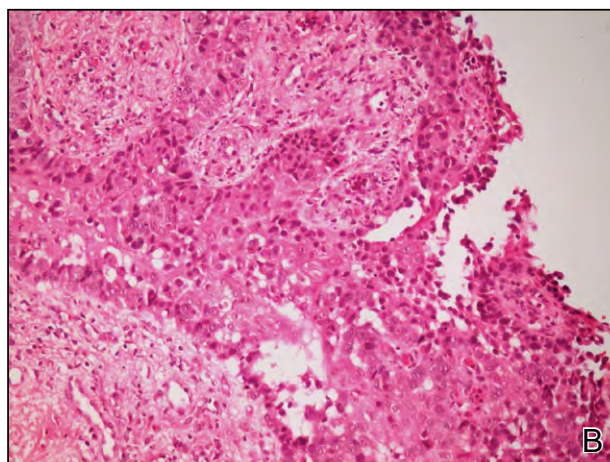
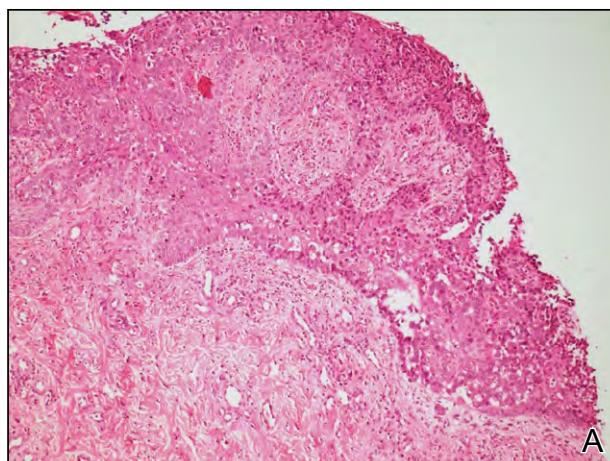
**Figure 1.** Erythema, erosions, exudation, and thin desquamation on the left nipple.

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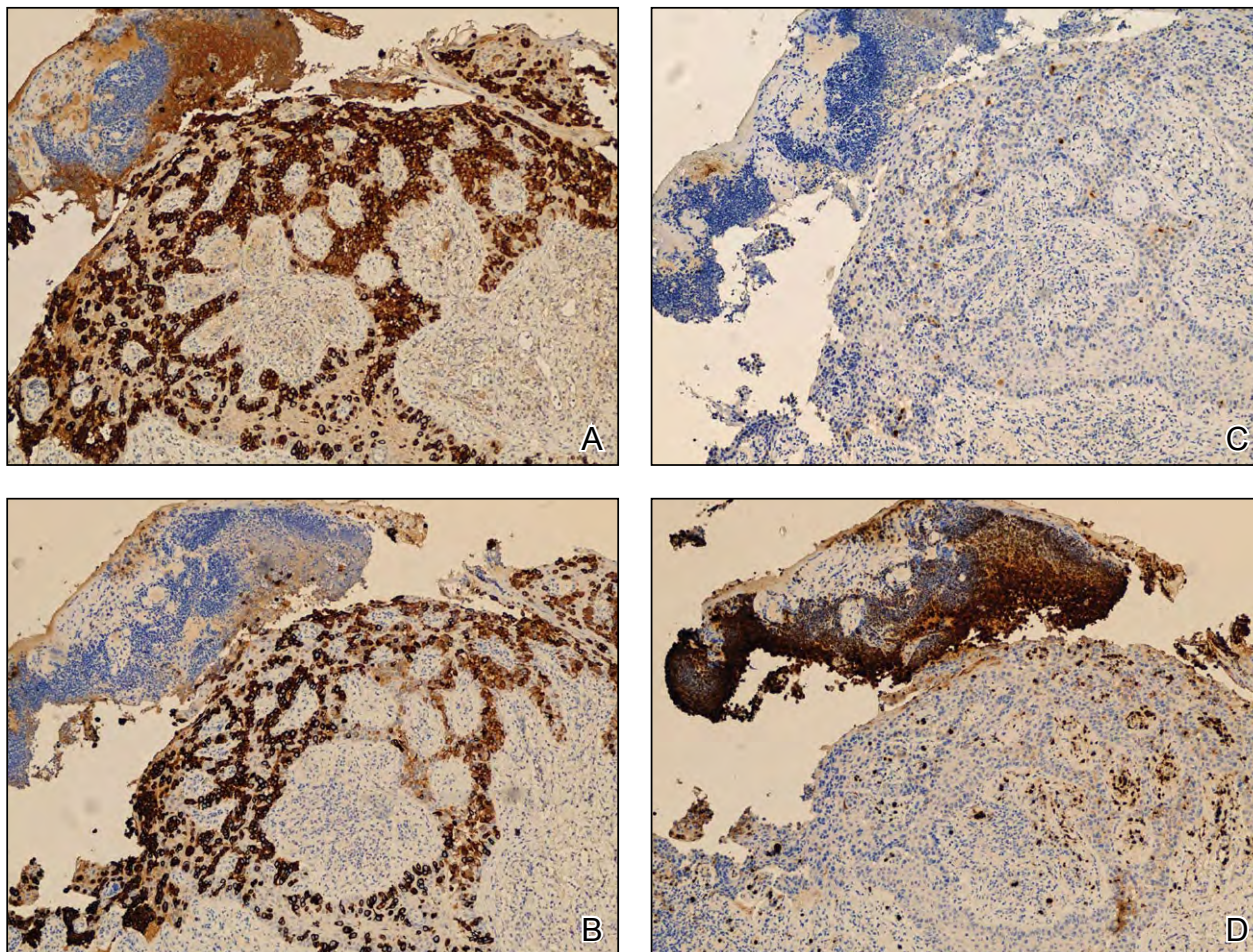
The authors report no conflict of interest.

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pagetoid spread within the epidermis was not present (Figure 2). Immunohistochemical techniques were positive for cell adhesion molecule 5.2 (CAM5.2), epithelial membrane antigen, cytokeratin (CK) 7, Ki-67, and E-cadherin; partially positive for carcinoembryonic antigen (CEA); and negative for gross cystic disease fluid protein (GCDFP) 15, CK20, and estrogen and progesterone receptors (Figure 3). A diagnosis of acantholytic anaplastic Paget disease



**Figure 2.** Biopsy revealed an eroded hyperplastic surface epithelium with full-thickness atypia, acantholysis, and basal layer preservation (A)(H&E, original magnification ×100). Acantholysis did not disrupt the basal layer (B)(H&E, original magnification ×200).



**Figure 3.** Immunohistochemical techniques were positive for cell adhesion molecule 5.2 (A) and cytokeratin 7 (B), negative for gross cystic disease fluid protein 15 (C), and partially positive for carcinoembryonic antigen (D)(all original magnification  $\times 100$ ).

was made. Mammography confirmed the presence of underlying disease that was classified as category 5 (highly suggestive of malignancy), according to the American College of Radiology Breast Imaging, Reporting and Data System (BI-RADS) atlas.<sup>2</sup> Surgical removal was performed.

Paget disease of the nipple and/or areola is a clinicopathologic entity that often is associated with an underlying in situ or invasive carcinoma in the breast parenchyma in up to 82% to 98% of cases, and it comprises less than 5% of all breast cancers.<sup>3-7</sup> Histologically, classic Paget disease is characterized by the presence of Paget cells within the epidermis.<sup>6,8</sup>

Acantholytic anaplastic Paget disease is a rare subtype of classic Paget disease that is characterized by full-thickness atypia of the epidermis, fissurations, loss of the normal contacts among the cells of the acanthoid layer, dyskeratotic cells, prominent mitotic figures, and preservation of the basal layer.<sup>1,5,6</sup>

Immunohistochemical techniques in classic and acantholytic anaplastic Paget disease are positive for cytokeratin AE1/AE3 (pan-cytokeratin), CAM5.2, and CK7; negative for mucin and GCDFP-15; and negative or hardly positive for CEA.<sup>1</sup> It has been suggested that acantholytic anaplastic Paget disease may not react with the standard immunohistochemical markers due to a poor differentiation that might be characteristic of the anaplastic variant.<sup>5</sup>

When an eczematous lesion on the nipple or areola is present, the primary clinical differential diagnoses include nipple eczema, psoriasis, irritant contact dermatitis, and Paget disease. Drug eruptions, nevroid hyperkeratosis of the nipple, and malignant melanoma also must be included.<sup>5,7</sup>

In cases of acantholytic anaplastic Paget disease, Bowen disease may be regarded as one of the main histologic differential diagnoses. Although Bowen disease more frequently affects genitalia, which always

includes extramammary Paget disease in the differential diagnosis, there are a few reported cases in the literature of Bowen disease on the nipple or areola.<sup>1</sup>

Bowen disease may be a potential diagnostic pitfall, especially in superficial shave biopsies, due to the bowenoid appearance of acantholytic anaplastic Paget disease. Therefore, it is important to obtain a deeper specimen.<sup>1</sup> Features such as full-thickness epidermal atypia, loss of nuclear polarity, and cytologic anaplasia resemble Bowen disease, while intraepidermal acantholysis, absence of dyskeratotic cells, and persistence of the basal layer are features against Bowen disease.<sup>5</sup> In addition, acantholytic anaplastic Paget disease and Bowen disease share the negative immunohistochemical stain for mucin, CEA, and GCDFP-15, but the former stains positively for CK7 and CAM5.2.<sup>1</sup>

In this variant of Paget disease, acantholysis is a constant finding, but anaplasia may be subtle. Therefore, other acantholytic dermatoses must be considered in the differential diagnosis.<sup>8</sup> We consider Hailey-Hailey disease as the main differential diagnosis in this group of acantholytic dermatoses because of its clinical (solitary lesions) and histologic (variable or full-thickness epidermal cleavage) appearance.

Acantholysis is a primary histopathologic feature of well-known dermatologic diseases, but in acantholytic anaplastic Paget disease it could be a secondary feature due to anaplastic changes in the lower layers of the epidermis. Secondary acantholysis also has been reported in other dermatologic pathologies such as basal cell carcinoma, squamous cell carcinoma, solar keratosis, or malignant melanoma.<sup>8,9</sup>

Prognosis of Paget disease is related to the presence or absence of a palpable invasive breast tumor or axillary node metastases.<sup>8</sup> The anaplastic variant does not imply a change in prognosis, as it has not been related with a better or worse prognosis.<sup>5</sup> In our case,

a poor prognosis was expected due to the presence of an underlying mass.

We reported a case of an infrequent variant of Paget disease to expand the awareness of this entity to avoid misdiagnosis and a possible associated underlying breast tumor.

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