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CASE REPORT

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Paget's disease versus Toker cell hyperplasia in a supernumerary nipple

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Abstract We report the second case of mammary Paget's disease arising in a supernumerary nipple of a 29-year-old woman. The epithelium of the nipple was infiltrated by large cells with abundant and pale-staining cytoplasm. The nuclei had a vesicular chromatin pattern and identifiable nucleoli. The cells were strongly immunoreactive with KL1, CEA and EMA, but did not show reactivity with PS100, HMB45, or erb-B2. The pathogenesis of Paget cells is unclear. In our case, the lesion showed nearly all the clinical, histological and histochemical characteristics of Paget's disease, though without involvement of mammary gland epithelium and underlying carcinoma. The possibility of an intraepidermal origin, either by transformation from epidermal keratinocytes or by derivation from intraepidermal precursor cells, has to be considered. The differential diagnosis against Toker cell hyperplasia is also discussed.

Key words Paget's disease · Supernumerary nipple · Breast cancer

Introduction

Mammary Paget's disease (MPD) generally affects the nipple and the areola of adult women; it is associated with in situ or invasive carcinoma of the mammary gland in 96% of cases [3], which has led to the idea that MPD is a direct extension of such a carcinoma. Extramammary Paget's disease (EMPD) is an intraepithelial glandular neoplastic process associated with an underlying neoplasm in only 20% of cases [6], suggesting a different origin for Paget cells.

We report a case of Paget's disease arising in a supernumerary nipple of a 29-year-old woman and situated on the milk line, without an underlying carcinoma. It is the second case of this type to be described in the English language literature [6].

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Clinical history

The patient was a 29-year-old woman who presented with a solitary unilateral accessory nipple on the left. During her second pregnancy it became bigger, and she decided to have it removed 3 months later. Physical examination disclosed a small nipple 0.5 cm high, without any ulceration or eczematization, situated 5 cm below the normal left breast on the milk line. Physical examination of the two breasts did not show any gross abnormality, and mammography did not reveal a primary or metastatic carcinoma. Abdominal echography was normal.

Materials and methods

The initial exeresis fragment was 2 × 1 × 3 cm and the tissue removed at re-excision measured 5 × 2.5 cm. Both specimens were submitted in their entirety. The nipple was fixed in 10% neutral buffered formalin for 24 h. Blocks of fixed tissue were embedded in paraffin. Serial sections 6 μm thick prepared from the paraffin blocks were attached to silanized glass slides. All slices were processed and stained according to the usual procedures (haematoxylin–eosin and PAS).

The panel of antibodies used embraced: mouse monoclonal antibody to KL 1 (ImmunoTech, BP 177, Marseille, France), which recognizes cytokeratins CK 2 (65.5 kDa), CK 6 (56 kDa), CK 8 (52.5 kDa),CK 10, CK 11 (56 kDa), CK 18 (45 kDa), CK 19 (40 kDa) and, to a lesser extent, CK 5 (58 kDa) and CK 14/15 (50 kDa), diluted: 1:50; rabbit polyclonal antibody to carcinoembryonic antigen (Dako, Trappes, France) at a dilution of 1:1000; mouse monoclonal antibody to EMA, clone E 29 (Dako, Trappes, France) diluted 1:50; mouse monoclonal antibody to HMB 45 (Dako SA, Trappes, France) diluted 1:20; rabbit anti-cow polyclonal antibody to S100 (Dako, Trappes, France), which reacts strongly with human S100 protein A and B from brain, diluted 1:2000; Ab-3 rabbit monoclonal antibody for detection of the erb-B2 receptor protein (Dianova, Hamburg, Germany), diluted 1:100.

Immunochemical stains using avidin–biotinylated peroxidase methodology [2] were performed on paraffin sections.

Pathological findings

Sections from the initial biopsy revealed portions of skin with a slightly elevated lesion. The epidermis showed papillomatosis, diffuse hyperkeratosis and acanthosis. A few squamous epithelial islands and sebaceous glands were present in the superficial dermis. The epidermis was infiltrated by individual or small nests of Paget cells. These cells were characterized by a large amount of pale-staining cytoplasm with well-defined rounded cytoplasmic borders. The nuclei were centrally located and had a vesicular chromatin pattern and identifiable nucleoli. The Paget cells lacked intercellular bridges, and the loss of cohesion between the cells resulted in clefts and small spaces (Fig. 1).

After serial sectioning, the mammary ducts became visible with surrounding bundles of smooth muscle in the upper reticular dermis. The ducts revealed a focal hyperplastic epithelial change characterized by cells exhibiting an increased nuclear-to-cytoplasmic ratio, mild hyperchromasia with fine nuclear chromatin, inconspicuous nucleoli and no evidence of carcinoma in the underlying connective tissue. Staining with PAS yielded a negative result.

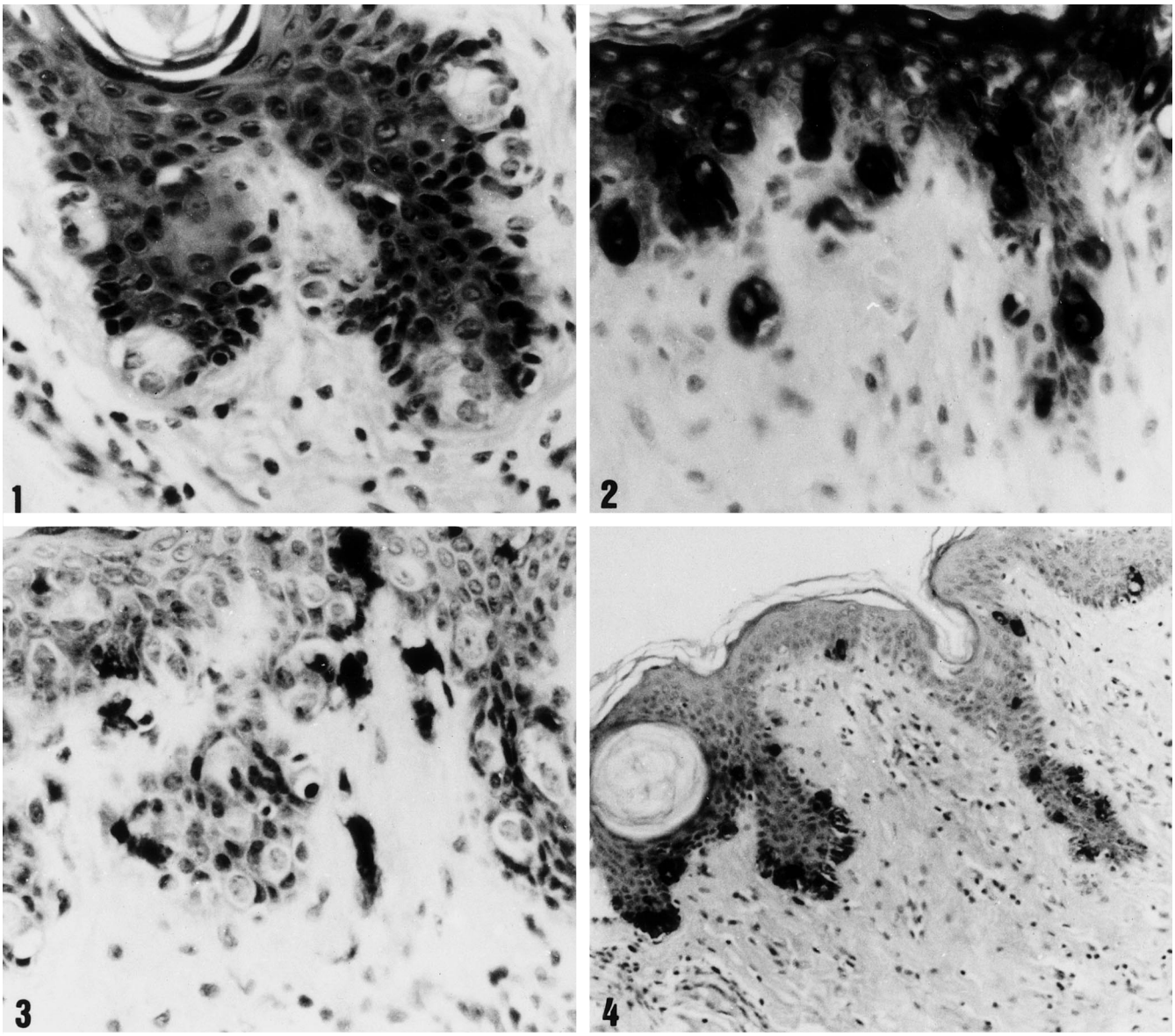
The Paget cells were strongly immunoreactive for KL1 (Fig. 2), CEA (Fig. 4), and EMA, but did not show reactivity with HMB45, protein S100 (Fig. 3) or erb-B2 (data not shown).

Fig. 1 The epidermis is infiltrated by individual or small nests of pagetoid cells. These cells are characterized by a large amount of pale-staining cytoplasm and a nuclei with a vesicular chromatin pattern and identifiable nucleoli. Haematoxylin and eosin, ×250

Fig. 2 Immunohistochemistry using KL1 antibodies, showing cytoplasmic and cell membrane immunoreactivity in pagetoid cells. ×250

Fig. 3 Pagetoid cells do not show reactivity with protein S-100. The intraepithelial Langerhans cells are positive. ×250

Fig. 4 Pagetoid cells positive for CEA in the basal part of a slightly broadened epidermis. ×63



Discussion

This case illustrates a rare occurrence of Paget's disease in a supernumerary nipple that was located on the milk line. Ectopic breast tissue may occur as any combination of or as any single element of the three components of the breast, the glandular acini, and the areola and/or nipple [1]. Accessory breasts containing ductal elements are subject to the same diseases as affect normal breasts.

The precise pathogenesis of MPD remains to be established. Almost all cases of MPD have an associated underlying ductal carcinoma, and the Paget cells are thought to be epidermotropic ductal carcinoma cells from direct migration or contiguous spreading. The origin of Paget cells in extramammary Paget's disease is uncertain. Various speculations can be found in the literature [5]. It has been suggested that tumour cells come from an adenocarcinoma originating in the pluripotential cells in the epidermis and then extend downward to adnexal structures; that they originate from the adnexal structures or adjacent organs and spread upward into the overlying epidermis and assume the appearance of adenocarcinoma cells; and that multicentric effects of unidentified carcinogenic stimuli are exerted on epidermis and underlying adnexal structures and adjacent organs, which means direct spread in either direction need not be involved.

In our case, the lesion of this supernumerary nipple showed nearly all the clinical, histological, histochemical characteristics of MPD [3, 6, 8, 9], except for erb-B2 expression and the lack of any involvement of mammary gland epithelium. In a series of 23 cases of MPD and 9 cases of extramammary Paget's disease (EPD), Meissner et al. [7] demonstrated that all MPDs were characterized by distinct membrane staining of tumour cells (by means of the monoclonal antibody 3B5 directed against amino residues 1242–1255 of the inner domain of the *neu* gene product) independently of the presence of ductal breast carcinomas found in 18 cases. In contrast, all EPDs were negative. Because of the negativity for c-erbB2, our case of EPD probably has a different pathogenesis from true Paget's disease.

The possibility of an intraepidermal origin either by way of transformation from epidermal keratinocytes, or by way of derivation from intraepidermal precursor cells must be considered. In this context, Toker's discovery of nonneoplastic cells resembling Paget cells in the epidermis of some normal nipples is of great interest [8, 9]. These cells were found in 34 nipples of 340 (10%) taken from surgical specimens and autopsies of male and female subjects, within the ampullae of the lactiferous ducts and the epidermis. These Toker cells are smaller in size than typical Paget cells. No large hyperchromatic nuclei were noted, and random staining with mucicarmine and PAS yielded negative results; melanin granules were frequently observed within the cytoplasm. The cells were concentrated in greatest numbers within the basal layer of the epidermis, but they were not confined to this stratum. They were organized mainly in small groups, although solitary elements were encountered. Small tubular structures were encountered within the cellular aggregates. The cytological aberrations so characteristic of Paget's disease were lacking in the clear-cell population under consideration [8]. These cells should not be confused with another type of "clear cell", namely epidermal keratinocytes with vacuolization of the cytoplasm; these have different histochemical and immunochemical characteristics [9].

In the light of Toker's work, our observation might correspond to hyperplasia of this type of cells, lacking the cytological stigmata of malignancy. However, it should be noted that they have been found in only a small number (10%) of examined nipples. In addition, our case concerns a malformed nipple, which might contain poorly differentiated pluripotential cells of adnexal origin having an immunohistochemical phenotype with positive CEA and EMA and negative erb-B2. The erb-B2 immunostaining is of great interest, because it is negative in these pagetoid cells, in contrast to the typical Paget cells of mammary Paget's disease [4].

The presence of in situ or underlying infiltrating carcinoma is not a mandatory feature of MPD, but the entity described by Toker calls in question the origin of this condition. Progress in immunohistochemistry, in particular the use of erb-B2 antibodies, apparently make it possible to differentiate between the two entities. In these cases without a clinically detectable tumour, a broad excision of the lesion with careful follow-up is the treatment of choice.

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