

## Case Report

# Cytokeratin 7- and human epidermal growth factor receptor 2-negative Paget disease of the nipple: a case report and review of the literature

Lanqing Cao, Min Yao, Pingli Sun, Hongwen Gao

Department of Pathology, The Second Hospital of Jilin University, Changchun, Jilin, China

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**Abstract:** Cytokeratin 7 (CK7)- and human epidermal growth factor receptor 2 (HER2)-negative Paget disease is a very rare variant of breast carcinoma, and presents a major diagnostic challenge for pathologists. We report a case of CK7- and HER2-negative Paget disease in a 43-year-old woman. Histological examination of the biopsy specimen revealed neoplastic cells within the epidermis, with abundant pale cytoplasm and large nuclei. In addition, an intermediate-grade ductal carcinoma *in situ* was found upon a subsequent surgical excision. Immunohistochemical analysis revealed tumor cells with positive immunoreactivity for GATA3, CAM5.2, estrogen receptor, and progesterone receptor. Negative immunoreactivity was found for CK7, HER2, S-100, CK5/6, GCDFP-15, and neuroendocrine makers. CK7- and HER2-negative Paget disease of the nipple is extremely rare. The importance of recognizing this rare variant of Paget disease lies in avoiding misdiagnosis. Thus, in such cases, GATA3, CAM5.2, estrogen receptor, and progesterone receptor immunohistochemistry will be valuable for the differential diagnosis. Owing to the possibility of small underlying carcinomas, simple mastectomy is a suitable treatment for patients with Paget disease, even if physical examination and ultrasonography reveal no underlying lesion.

**Keywords:** Paget disease, breast cancer, CK7, HER2

## Introduction

Paget disease (PD) of the nipple is characterized by the presence of malignant glandular epithelial cells within the squamous epithelium of the nipple and accounts for 1-4% of all breast cancers [1, 2]. In addition, PD of the breast is nearly always associated with an underlying carcinoma, which may be intraductal or invasive. In rare cases, PD invades the dermis and can be associated with axillary lymph node metastases [3, 4]. Paget cells have a characteristic immunophenotype: almost always positive for cytokeratin 7 (CK7) and positive for human epidermal growth factor receptor 2 (HER2) in 80-90% of cases [5, 6]. Estrogen receptors (ER) and progesterone receptors (PR) are expressed in 40% and 30% of cases [1, 2], respectively. The morphologic appearance of the lesion on hematoxylin and eosin (H&E)-stained sections coupled with CK7 and HER2 immunoreactivity are commonly used for the diagnosis of PD. Thus, confirmation

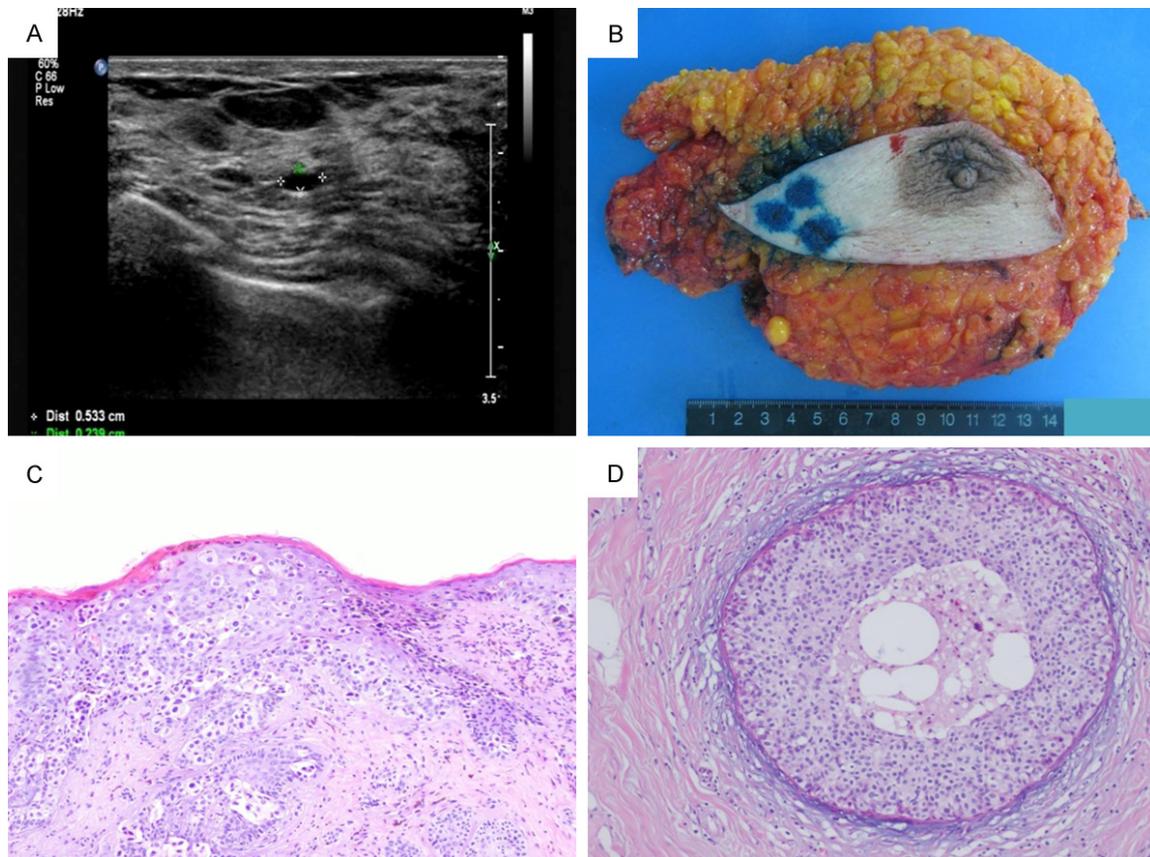
of PD diagnosis relies on the appearance of the lesion on H&E stains, and diagnosis is confirmed when the neoplastic cells show negative staining for CK7 and HER2. To the best of our knowledge, only one patient with CK7- and HER2-negative PD has been reported to date. However, this first reported case involved only immunohistochemical analysis and presented limited clinicopathological information.

Herein, we present a case of PD with negative results for CK7 and HER2. We describe the clinical features of CK7- and HER2-negative PD, the findings from a formalin-fixed macroscopic examination, a spectrum of histopathologic findings, and the complete clinical course of the disease.

## Case report

A 43-year-old woman presented to the Dermatology Clinic of our hospital with an eczematous lesion in the left nipple-areola com-

## CK7- and HER2-negative Paget disease



**Figure 1.** Imaging and histopathological characteristics of the CK7- and HER2-negative Paget disease of the nipple. (A) Ultrasound image of the left breast did not reveal any underlying lesion. (B) A white brownish area of skin over the nipple was identified on mastectomy specimen. (C) Paget cells were seen as clusters predominantly in the basal epidermis. (D) Intermediate-grade ductal carcinoma *in situ* with periductal fibrosis and lymphocytic infiltrates (C, D original magnification  $\times 100$ ).

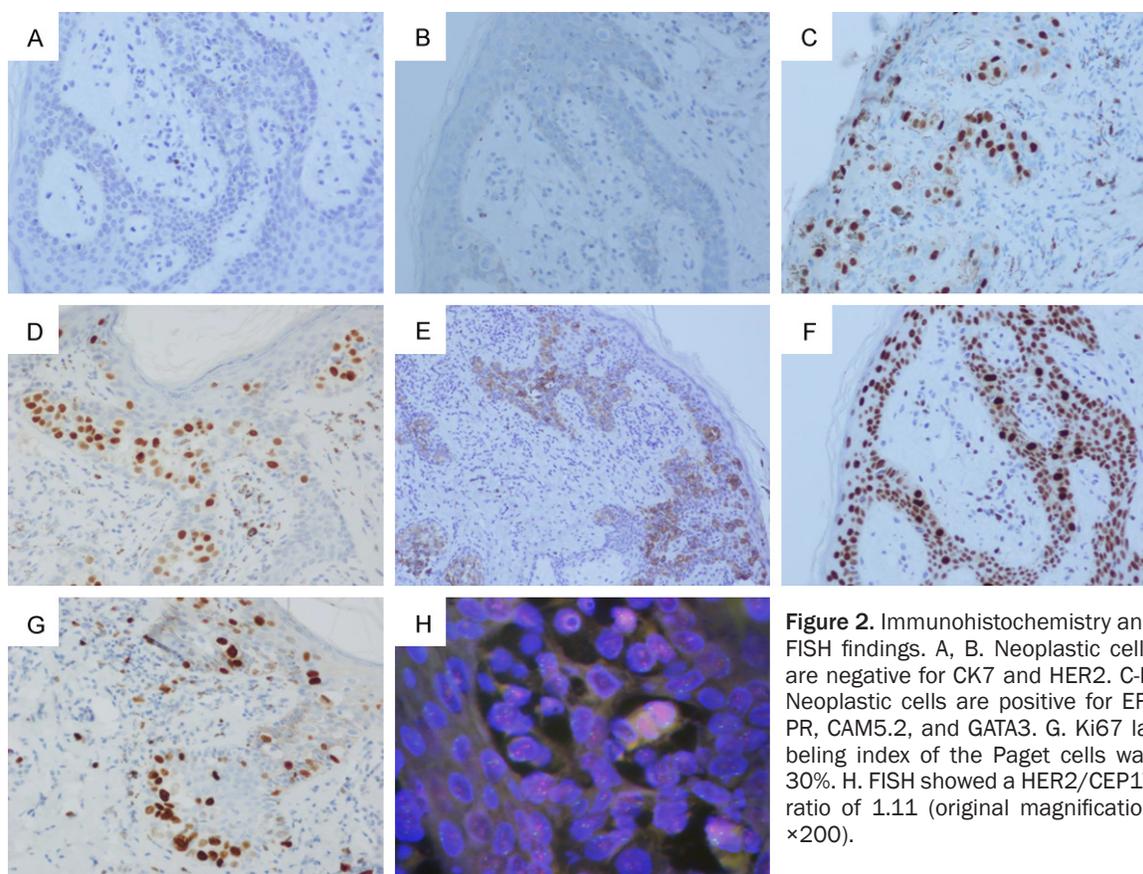
plex measuring 1 cm across the largest diameter. The patient reported that the lesion was present for 2 years and had enlarged over the past few months. Physical examination revealed no abnormality in the size and shape of the breast and no nipple discharge, bleeding, ulceration, or inversion. Ultrasonography did not reveal any underlying lesion (**Figure 1A**). Moreover, no enlarged axillary lymph nodes were noted. The patient reported no family history of breast cancer. We suspected PD of the nipple, and therefore, the patient was referred to the Department of Breast Surgery. A biopsy of the left nipple-areola complex was performed; pathologic examination showed the presence of malignant cells within the squamous epithelium. The patient was referred for surgery and the lesion was completely resected. Subsequently, the patient underwent a simple mastectomy and sentinel lymph node biopsy.

### *Pathological findings*

The mastectomy specimen measured 14 $\times$ 12 $\times$ 8 cm, and the nipple was elevated by 1 cm (**Figure 1B**). During the macroscopic examination, a white brownish area of skin over the nipple was identified, along with a rubbery grey area in the cut surface of the specimen that had a diameter of 2 cm. The specimen was subsequently submitted for histologic examination.

Histopathologic examination (**Figure 1C**) revealed abnormal cells, with abundant pale cytoplasm and large nuclei with prominent nucleoli, within the epidermis. These Paget-like cells were arranged singly and clustered. The epidermis contained large pale tumor cells that formed a continuous layer along the epidermal basement membrane. No other specific findings were identified when examining the sub-nipple/areola duct. However, sclerosing adeno-

## CK7- and HER2-negative Paget disease



**Figure 2.** Immunohistochemistry and FISH findings. A, B. Neoplastic cells are negative for CK7 and HER2. C-F. Neoplastic cells are positive for ER, PR, CAM5.2, and GATA3. G. Ki67 labeling index of the Paget cells was 30%. H. FISH showed a HER2/CEP17 ratio of 1.11 (original magnification  $\times 200$ ).

sis and small foci of intermediate-grade ductal carcinoma in situ (DCIS) were detected 5 cm far from the nipple, with the largest diameter measuring 2 mm (**Figure 1D**). No lymph node metastasis was detected during the sentinel lymph node biopsy.

Immunohistochemistry of breast markers (ER, PR, HER2, GATA3, and GCDFP-15), glandular markers (CK7 and CAM5.2), neuroendocrine markers (CD56, CgA, and Syn), S-100, CK5/6, and Ki67 was performed to confirm the diagnosis. The neoplastic cells were negative for CK7, HER2 (**Figure 2A, 2B**), S-100, CK5/6, CD56, CgA, Syn, and GCDFP-15, but positive for ER, PR, CAM5.2, and GATA3 (**Figure 2C-F**). The antigen Ki67 labeling index of the Paget cells was 30% (**Figure 2G**). Immunohistochemical examination of the DCIS tissue was attempted; however, the lesion was not visible on the immunostained slides. Fluorescence *in situ* hybridization was performed to screen for HER2 amplification (**Figure 2H**) and the test yielded a HER2/CEP17 ratio of 1.11 (HER2 = 2.5 and CEP17 = 2.25). The final pathologic diagnosis was CK7- and HER-negative PD.

### Discussion

The pathological diagnosis of classic PD is usually easy to establish on the basis of the typical morphologic appearance of the lesion on H&E sections coupled with CK7 and HER2 immunoreactivity. Developing CK7- and HER2-negative PD is extremely rare. Although CK7 and HER2 negativity does not support the diagnosis of PD, typical morphologic appearances and positive GATA3, CAM5.2, ER, and PR expression can be used to establish the diagnosis.

The first case of CK7- and HER2-negative PD was reported by Yao and in that case, the patient had an underlying invasive ductal carcinoma that was also CK7 and HER2 negative [7]. However, clinical features such as ER, PR, and GATA3 immunoreactivity were not reported. A previous study revealed that GATA3 was a useful immunohistochemical marker to confirm PD, even CK-negative PD [8]. The findings of our case confirm these results. Moreover, the ER and PR overexpression in neoplastic cells indicated primary PD of the breast.

The etiology of PD of the nipple has two main theories. The first postulates that Paget cells originate in underlying or intraepidermal lactiferous or deeper ducts and then migrate into the epidermis. The second theory implicates Toker cells as precursors of Paget cells [9], particularly in cases without an underlying DCIS. Moreover, both cases of CK7- and HER2-negative PD were associated with an underlying carcinoma, which is consistent with the first hypothesis referred to above. As already indicated, the majority of PD cases are associated with underlying high-grade invasive carcinoma or high-grade DCIS. The underlying carcinoma usually has the same immunoprofile as PD. Although no DCIS or other neoplastic lesions were detected in the sub-nipple/areola duct, foci of intermediate-grade DCIS lesions were found in the subsequent surgical excision specimen. Unfortunately, the sample was too small to allow for immunoprofiling. Therefore, we recommend simple mastectomy for patients with PD, even if ultrasonography has not revealed any underlying lesion.

The differential diagnoses for PD includes malignant melanoma, Bowen's disease of the skin, and Toker cells. In our case, S-100 and HMB45 negativity excluded the possibility of malignant melanoma. Negative CK5/6 and P63 expression excluded Bowen's disease of the skin, while a high Ki67 index excluded Toker cells.

In conclusion, CK7- and HER2-negative PD of the nipple is extremely rare. The main reason for the need to recognize this rare variant of PD lies in avoiding misdiagnosis. Immunoreactivity of GATA3, CAM5.2, ER, and PR will be valuable in such cases for the differential diagnosis, particularly CK7 and HER2 negativity. Owing to the possibility of a small underlying carcinoma, simple mastectomy is a suitable treatment for patients with PD, even when physical examination and ultrasonography reveal no underlying lesions.

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### Disclosure of conflict of interest

None.

**Address correspondence to:** Drs. Hongwen Gao and Min Yao, Department of Pathology, The Second Hospital of Jilin University, 218 Ziqiang Road, Changchun 130041, Jilin, China. Tel: +86-431-88796933; Fax: +86-431-88796933; E-mail: gaohongwen@jlu.edu.com (HWG); Tel: +86-431-88796833; Fax: +86-431-88796833; E-mail: yaomin902@sina.com (MY)

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