Brief Report

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Pre-Paget cells: Evidence of keratinocyte origin of extramammary Paget's disease

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Summary **Extramammary Paget's disease (EMPD) is a carcinoma of the genital, perianal, and, rarely, axillary skin. The malignant Paget cells migrate extensively in the epidermis before invading the underlying dermis. Toker cells and keratinocytes have both been suggested as the cells of origin of EMPD. Paraffin sections of eight cases of EMPD were immunohistochemically stained for carcinoembryonic antigen, a known marker for Paget cells. The presence of carcinoembryonic antigen in some keratinocytes in all of the observed cases of EMPD suggests that EMPD originates from keratinocytes. Thus, keratinocytes containing carcinoembryonic antigen are pre-Paget cells.**

Keywords: EMPD, Paget cells, carcinoembryonic antigen, pre-Paget cells, keratinocytes

1. Introduction

Paget's disease of the skin is a carcinoma that occurs as isolated cells and groups of cells called Paget cells which migrate extensively in the epidermis before invading the dermis (*1,2*). Paget's disease is most common in the skin of the nipple where it usually originates by migration of cells from a ductal carcinoma (*3*). Extramammary Paget's disease occurs in the genital, perianal, and, rarely, axillary skin, usually in the absence of an associated cancer (*4,5*). There is considerable evidence that extramammary Paget's disease is not be the same disease as Paget's disease of the breast (*6,7*).

Paget cells are readily distinguished from keratinocytes by their larger cytoplasmic volume and even larger nuclei (*1,8*). Most Paget cells also contain biochemical markers that distinguish them from keratinocytes (*6,9-11*).

Toker cells are variably present benign epithelial cells that are morphologically similar to Paget cells (*12*). The reported frequency of Toker cells in the normal epithelium of the external genitalia does not exceeded 36% (*13*). It has been suggested that extramammary Paget's disease originates from Toker cells (*14-16*) although they are present in only a few cases of extramammary Paget's disease (*17*). Like Paget cells, Toker cells usually contain cytokeratin 7 (*18*) and epithelial membrane antigen (*19*). Unlike Paget cells, Toker cells are negative for carcinoembryonic antigen (*19*). The reaction of Toker cells with antibody to the progesterone receptor depends on the antibody chosen (*12,18*). Paget cells are only rarely positive for the progesterone receptor (*20,21*).

In 1975, Bussolati and Pich found β-casein, a marker for Paget cells, in keratinocytes near Paget cells in both mammary and extramammary Paget's disease (*22*). They called the keratinocytes with Paget cell markers "pre-Paget cells". In 2008, Smith et al. found epithelial membrane antigen, another marker for Paget cells, in keratinocytes in a case of extramammary Paget's disease (*23*). Unaware of the earlier paper, they called the keratinocytes with Paget cell markers "incipient Paget cells". The name "pre-Paget cells" has priority and is more easily found by search engines.

Carcinoembryonic antigen is a reliable marker for extramammary Paget's disease (*11,19*) that does not require unmasking after formalin fixation (*24,25*). Since carcinoembryonic antigen does not occur in Toker cells (*19*), it might be the best marker for pre-Paget cells.

2. Materials and Methods

The Cooperative Human Tissue Network provided

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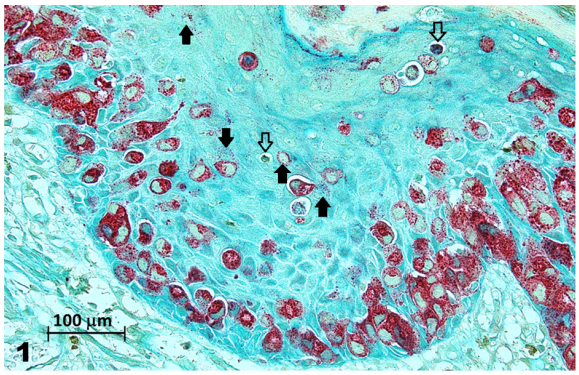

igure 1. Extramammary Paget's disease of the vulva stained for carcinoembryonic antigen with Vector Red and counterstained with fast green FCF. Several keratinocytes contain carcinoembryonic antigen (solid arrows), and two Paget cell do not (hollow arrows).

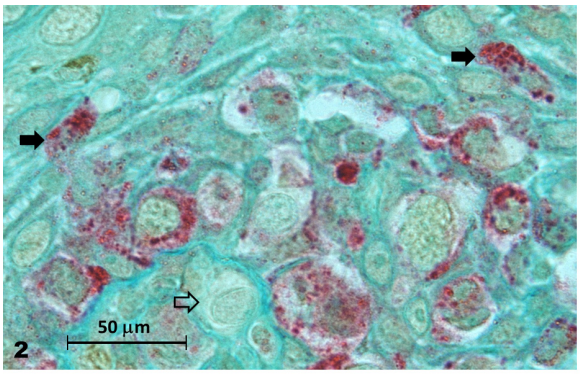

Figure 2. Extramammary Paget's disease of the vulva stained for carcinoembryonic antigen with Vector Red and counterstained with fast green FCF. Two keratinocytes contain carcinoembryonic antigen (solid arrows), and one Paget cell does not (hollow arrows).

unstained slides of formalin-fixed paraffin sections from 8 cases of extramammary Paget's carcinoma.

One slide from each case was incubated overnight at 4oC with 1/500 antibody to human carcinoembryonic antigen (Genetex rabbit polyclonal anti CD66e) followed by horse anti-rabbit IgG conjugated to calf intestine alkaline phosphatase via dextran ("ImmPressAP," Vector Labs), stained with Vector Red, and counterstained with 0.15% fast green FCF in 0.6% aqueous phosphomolybdic acid.

3. Results and Discussion

Carcinoembryonic antigen was present in all Paget cells in two cases and in most Paget cells in the other six cases (Figure 1 and Figure 2). Some keratinocytes in each case also showed staining for carcinoembryonic antigen (Figure 1 and Figure 2). There was no relation between the number of Paget cells in the section and the number of keratinocytes staining for carcinoembryonic antigen. In one case 15% of the cells staining for carcinoembryonic antigen were keratinocytes; in another case 10% were. In the other six cases 3% or fewer of the cells staining for carcinoembryonic antigen were keratinocytes.

Carcinoembryonic antigen is a reliable marker for Paget cells that is not found in normal keratinocytes. It follows that keratinocytes staining for carcinoembryonic antigen are pre-Paget cells.

The extreme variation in the ratio of pre-Paget cells to Paget cells is less surprising than it seems. The clinical course of EMPD is also extremely variable (*2,11,25*). Moreover, the response of EMPD to imiquimod varies from complete remission to complete resistance (*2,26*).

It is a priori unlikely that EMPD would originate from Toker cells which are usually absent in EMPD (*17*). For EMPD to have originated from Toker cells, all of the Toker cells in the tissue would have had to undergo malignant transformation at once.

The presence of a Paget cell protein in many keratinocytes in cases of EMPD strongly suggests that EMPD originates from keratinocytes. This also suggests that EMPD does not originate from Toker cells which do not contain carcinoembryonic antigen.

Paget cells often arrange themselves into a glandular pattern (*11*). They also share many antigens with the apocrine glands of the skin (*9,22,27*). EMPD may be a miscarried attempt to form apocrine glands.

The apparent presence of pre-Paget cells in EMPD suggests that this carcinoma does not originate from a single mutated cell, but from mutations in many cells. It further suggests that recruitment of new malignant cells is ongoing. Ongoing recruitment of malignant cells would explain other peculiarities of EMPD. EMPD has a high recurrence rate after apparent total excision (*4,5,11,25*). New foci of EMPD often appear at great distance from the original focus (*4,16,28,29*).

Acknowledgements

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Ethical Standards: The tissues in this study were removed in an effort to cure a life-threatening condition. Since the tissues were submitted to a tissue bank and sent to the author from the tissue bank, the author has no knowledge of the identity of the patients or the date of the surgery. The author knows only that the surgeries were performed in the eastern coastal states of the United States. This study was approved by Barry University's Institutional Review Board.

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