Fibroepithelioma-like changes associated with anogenital epidermotropic mucinous carcinoma

Fibroepitheliomatous Paget phenomenon

We describe two patients with crusted perineal plaques that were biopsied and diagnosed as Paget's disease. Resection specimens of each contained a dermal mucinous carcinoma with extensive epidermotropism and coexistent epidermal basaloid proliferations closely resembling fibroepithelioma (Pinkus). The presence of the Paget phenomenon was supported by histochemical, immunohistochemical, and ultrastructural evidence. No other primary neoplasms were found in either patient. Followup at 2 1/2 and 3 1/2 years, respectively, has been negative. We conclude that either the fibroepitheliomatous changes may be induced by or may represent a collision (unlikely) with the epidermotropic mucinous carcinoma. It is proposed that the concept fibroepitheliomatous Paget phenomenon be used to stand for the histologic changes common to our cases as well as those previously reported.


In 1953, Pinkus (1) described an epithelial-stromal, basaloid, reticular tumor that was located primarily on the trunk. He noted the resemblance of the tumor to intracanalicular fibroadenoma of the breast, but because the cutaneous tumors lacked a ductal component, he regarded them as morphological variants of basal cell carcinoma ("epithelioma" in his terminology). "Fibroepithelial tumor" was the term he chose to represent the spectrum of these lesions.

Extramammary Paget’s disease is a concept that has evolved simultaneously with mammary Paget’s disease. It refers to a type of malignant tumor, usually found in the anogenital region, composed of randomly distributed individual cells, clustered cells, or both, existing within the epidermis. These cells exhibit phenotypic attributes of adenocarcinoma and may or may not be associated with a sweat gland or visceral carcinoma. Many authors have offered opinions to explain the microscopic findings responsible for the clinical changes of suspected (muco) cutaneous Paget’s disease of any type (mammary or extramammary). In retrospect, however, unrelated lesions such as superficial basal cell carcinoma (2), malignant melanoma (3), and spongiositic dermatitides (4) were previously diagnosed as such. The origin of the modern concept of the microscopic changes Paget’s disease of any type, as well as its proper clinicopathological context, began with Jacobaeus in 1904 (5). However, it was through the influence of authors such as Sekiguchi (6), Muir (7), Pautrier et al. (8), Weiner (9), and finally, Pinkus and Gould (10), that the clinical and histological changes, as we know them today, were objectively depicted. Pinkus and Gould proposed a special designation for the histological finding of the epidermal adenocarcinoma cells. They termed it the Paget phe-
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These three sections of the gross were adjacent. The white areas of epidermis (highlighted by arrows) correspond to the fibroepitheliomatous areas. A single mucin lake (arrowhead) is present in the lowest section.

This was done to distinguish it as a microscopic perceptual attribute, compared with the entire conceptual clinicopathological context of the breast, anogenital, or visceral tumors with which it might be associated in any individual case (10).

Mucinous carcinoma, occurring as a primary cutaneous malignancy, was first described by Leimox, Pearse, and Richards in 1952 (11). Of the cutaneous glandular adnexal carcinomas, it is usually located on the head or neck region (12), particularly the eyelid (13). Additionally, it is one of the more common morphological types of sweat gland carcinoma and, generally, is associated with a good prognosis. Although mucinous carcinomas of the anogenital region have been illustrated in the literature, many have differed from mucinous carcinomas of other regions. Specifically, several of the anogenital cases have been associated with the Paget phenomenon (14–26) however, such changes have never been described in extraperineal mucinous carcinoma.

In this paper, we shall detail in two patients the intersection of these three morphological tumor patterns, i.e. mucinous carcinoma, the Paget phenomenon, and fibroepithelioma. In addition, we also discuss these findings in relation to two similar, but not identical, cases previously described in the literature. Finally, we offer a theory to explain the morphological changes and propose histological and clinicopathological concepts that will serve to unite the findings in the anticipation of the discovery of new cases.

Clinical histories

Patient 1 was a 67-year-old Hispanic man who presented at the Audie L. Murphy Memorial Veterans Administration Hospital with a 6-month history of an exudative, erythematous, moist, perianal lesion that extended onto the perineum and had recently developed erosions and nodules. The lesion was surgically excised, after several separate procedures, with negative margins, confirmed by frozen section. A systemic work-up, in order to pursue a possible visceral carcinoma, was negative. The patient remains well 2 1/2 years after his tumor was removed.

Patient 2 was a 73-year-old white woman who presented in Tufts University – New England Medical Center with a history of a crusted, variegated, perineal plaque that had been present for several months. It was surgically removed, and a systemic work-up was negative. She has remained disease free for 1 1/2 years.
Material and methods

In both cases, routine hematoxylin & eosin (H&E) stains were obtained on 10% neutral-buffered, formalin-fixed tissues. Special histochemical stains on case 1 included periodic acid-Schiff (PAS) – alcian blue (pH 2.5 and 1.0), and PAS with and without hyaluronidase. Immunoperoxidase stains on both cases included carcinoembryonic antigen (CEA, 1:50 monoclonal, ZYMED).

Specimens from Case 1 were taken from formalin-fixed tissue and processed for electron microscopy in 0.1 M phosphate buffer, 1% osmium tetroxide, embedded in epon, then sectioned and photographed with a JEOL 100 CX electron microscope.

Pathology

Gross – The excision from Case 1 measured 14 × 7.5 × 1 cm within which was a 10 × 5 × 0.5 cm irregular, variegated plaque. In multiple adjacent sections, there was a broad zone of epidermal hyperplasia (Fig. 1, arrows) that gradually tapered to epidermis of normal thickness. In one section (Fig. 1, arrowhead), there was a mucin lake. The excision from Case 2 had similar features, but the lesion was more extensive, measuring 7 × 7 × 1 cm, with a prominent nodular surface and obvious mucin lakes on cut section.

Light microscopy – Low-power views of the sections from Case 1 revealed that the hyperplastic areas corresponded to fibroepitheliomatous changes, whereas the mucin lake was a small mucinous carcinoma (Fig. 2). Individual and aggregates of adenocarcinoma cells were found within the mucin pool. A few aggregates had an acinar configuration. Cytologically, the typical tumor cell contained abundant cytoplasm with large mucin vacuoles, although some were cuboidal and devoid of obvious mucin. A section adjacent to the mucinous lake was characterized almost exclusively by fibroepitheliomatous changes (Fig. 3). In these areas, the lesion was reticular, extending into the superficial reticular
dermis. Cytologically, it contained basaloid cells with minimal cytoplasm and homogenous nuclei. The mucinous carcinoma of Case 2 was similar histologically, but was approximately twice as large as that of Case 1 (Fig. 4). Like Case 1, the fibroepitheliomatous changes of Case 2 were separated from the mucinous carcinoma by 1 to 2 cm (Fig. 5). In the epidermis above the mucinous carcinoma, few Paget cells were present in either case; however, several millimeters to several centimeters distal to the tumors, the intraepidermal cells of the Paget phenomenon were observed. In several areas in each case, the Paget cells coexisted with fibroepitheliomatous areas and were best visualized with the PAS-alcian blue stain at pH 2.5 (Fig. 6). The typical Paget cell contained abundant amphophilic cytoplasm with a large mucin vacuole and was 3 to 4 times the size of an adjacent keratinocyte. Free mucin pools were present in the dermis under some areas of the fibroepitheliomatous lesion. Some of the fibroepitheliomatous foci had mesenchymal components similar to hair germs or papillary mesenchymal bodies (Fig. 7).

Special stains — In Case 1, the mucin in the mucinous carcinoma, as well as in areas of the Paget phenomenon, was positive for PAS-alcian blue at pH 2.5 (purple), but negative at pH 1.0 (red) as PAS positivity was present at both pH levels. In certain tumor cells, either PAS (red) or alcian blue (blue) positive mucin was present (pH 2.5). Additionally, the mucin in this lesion was resistant to hyaluronidase digestion. In both cases, CEA was present in the mucinous carcinoma, as well as the Paget phenomenon (Fig. 8), either alone or coexistent with the fibroepitheliomatous lesion.

Ultrastructure — By ultrastructural observation of formalin-fixed tissue from case 1, one could differentiate epidermal keratinocytes as well as several large epithelial cells containing cytoplasmic mucin vacuoles. In some areas, the mucin was diffusely, whereas
in other areas, small mucin aggregates were present (Fig. 9). The remainder of the cytoplasm contained few organelles, notably dilated rough endoplasmic reticulum.

Fig. 8. Case 1. Carcinoembryonic antigen is extensive in the Paget cells within the fibroepitheliomatous component. Both cases were similar.
Fig. 9. Case 1. In the low-power ultrastructural view of a single Paget cell, there are numerous, circular, mucin spheres within a large, intracytoplasmic, mucin lake. The cell is surrounded by keratinocytes.

Discussion

Historically, Pinkus and Gould, in 1939 (10), described the association of a basaloid fibroepithelial lesion with extramammary Paget's disease of the perianal region. Their patient (their Case 3), a 57-year-old black man, had a perineal lesion associated with inguinal lymphadenopathy of 1 year known duration. This man died soon after the diagnosis was established, and a rectal carcinoma was found. In the low-power photograph supplied in the article, there was coexistence of the Paget phenomenon and a reticular basaloid lesion described by the authors as "a marked atypical proliferation of the epidermal ridges, which formed a complicated network" similar to the cases Pinkus later described as "premalignant fibroepithelial tumors of skin" (1).

Warner et al, in 1982, were the first authors to recognize the fibroepithelioma-extramammary Paget's disease association as such (27). Their patient was a 39-year-old man who developed a red, cracked, flaking perineal lesion. After a negative systemic evaluation, he was successfully treated by a Mohs' surgical technique and was clinically disease free for 4 years. Additional follow-up revealed that the patient died of metastatic anal carcinoma in 1982 (Dr. Thomas F. C.S. Warner, personal communication, November 7, 1990).

Our cases are morphologically similar to the literature cases, except that both of our patients had an underlying mucinous carcinoma unassociated with a visceral malignancy, based on the context of our knowledge at the time of this report. Additionally, the special stains for mucins in our Case 1 are similar to sweat gland mucins. Based on these data, we conclude that the origin of the Paget phenomenon in our cases was most likely from the respective anogenital mucinous carcinomas.
The common histologic features of our cases and those from the literature are the fibroepithelioma-cutaneous or visceral adenocarcinomas. Thus, as a diagnostic or clinicopathological concept, all the known information, both histological and clinical, must be considered, especially in application of the concept to an individual case. It is for this reason that we, like Pinkus and Gould (10), differentiate between the histological concept of adenocarcinoma cells existing individually and in clusters within the epidermis (the Paget phenomenon) and the diagnostic concept of Paget's disease of either type, which includes the Paget phenomenon plus any other cutaneous or visceral adenocarcinoma that may give rise to, or result from it. Because it is well established that the Paget phenomenon can be an attribute of extramammary Paget's disease or can occur without other disease, a systemic search should be undertaken to rule out any other cutaneous or visceral malignant tumor if such knowledge is not already known at the time of diagnosis.

Regarding the association of the fibroepithelioma-like changes with the Paget phenomenon, there are two possible mechanisms. First, it could represent a collision tumor. Although this is possible, both of these tumor types are uncommon and their chance association would seem unlikely, especially when the clinical and pathological extent of the lesions in our cases is considered.

The second possibility is that one lesion could somehow influence or induce the formation of the other. The most likely possibility would be that the Paget phenomenon would be the inducer of the fibroepithelioma, similar to follicular proliferaions that have been associated with lesions such as superficial angiomyxomas (trichogenic) (28, 29) or dermatofibromas (30, 31). In some of the reported lesions, the basa1oid proliferations displayed a complex reticular architecture and even produced papillary mesenchymal bodies, similar to both of our cases. A proposed mechanism in our cases is that the basaloid proliferations formed from the mechanical barrier of dermal mucin, in contrast with dermatofibromas or the mucin of the trichogenic myxomas in the cases from the literature.

From a different viewpoint, it would seem unlikely that a follicular tumor or even a basal cell carcinoma could somehow cause an adenocarcinoma to form, especially if one considers the rarity of extramammary Paget's disease (or, for that matter, any sweat gland carcinoma) compared to the abundance of basal cell carcinomas or basa1oid hamartomas. The only reasonable mechanism in such a context would be that of mucinous syringome-traplasia in the fibroepithelioma-like areas. Such observations have been reported as isolated lesions (32), but, to our knowledge, have never been observed in fibroepitheliomas.

In conclusion, we propose that the term fibroepitheliomatous Paget phenomenon be used as a concept to denote future cases in which there are histological features in common with our cases and those previously reported. These features are: individual, clustered, or both patterns of intraepidermal cells of phenotypic adenocarcinoma associated with basaloid fibroepithelioma-like changes. Based on current evidence regarding the nature of (muco) cutaneous Paget's disease of any type, it would seem reasonable that these lesions would most likely occur in the perineum, but we suspect that it could be possible for a similar relationship to occur elsewhere, such as the axilla or breast. Additionally, we speculate that it will ultimately be shown that this association will have a natural history spectrum similar to typical cases of (muco) cutaneous Paget's disease of any type.

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References


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