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Case presentation

Multifocal extramammary Paget's disease-associated adenocarcinoma: a rare condition of flexoral skin of multiple sites

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Abstract

Extramammary Paget disease (EMPD) is a rare malignant neoplasm of apocrine sweat glands that is morphologically and histologically identical to Paget disease of the breast. The primary lesion is usually a solitary, well-demarcated, erythematous, scaly plaque that may contain crust, erosions, or ulcerations. The vulva is the most common site, but any area containing apocrine sweat glands may be involved. We present a case of triple extramammary Paget disease of the groin and bilateral axillae in a diabetic patient whose axillary lesions appeared consistent with acanthosis nigricans. This case demonstrates the need to consider EMPD in the evaluation of acanthosis of the axilla given its ability to mimic more common conditions.

Keywords: extramammary Paget's disease, acanthosis nigricans

Abbreviations: CEA: carcinoembryonic antigen, CK7: cytokeratin 7, CK20: cytokeratin 20, EMPD: extramammary Paget's disease, PAS-D: Periodic acid-Schiff-diastase

Case synopsis

A 63-year-old man presented with an approximate five-year history of asymptomatic rash in his groin and bilateral axillae. The onset of the rash occurred shortly after he received the diagnosis of diabetes mellitus type two. He had been evaluated by several physicians and prescribed various topical medications, including anti-fungal agents and corticosteroids, none of which were effective. He then underwent abdominoplasty and resection of the plaques in the bilateral axillae and groin by plastic surgery. All of the surgical specimens were placed into a single container and sent for pathology. The pathology was read as Paget disease, present at the tissue edge, with areas of focal adenocarcinoma and associated seborrheic keratosis. Shortly thereafter he presented to our clinic with residual lesions.

His past medical history included hypertension, hypercholesterolemia, gastroesophageal reflux disease, gout, benign prostatic hypertrophy, and history of pulmonary embolism. Medications included Metformin and rivaroxaban.

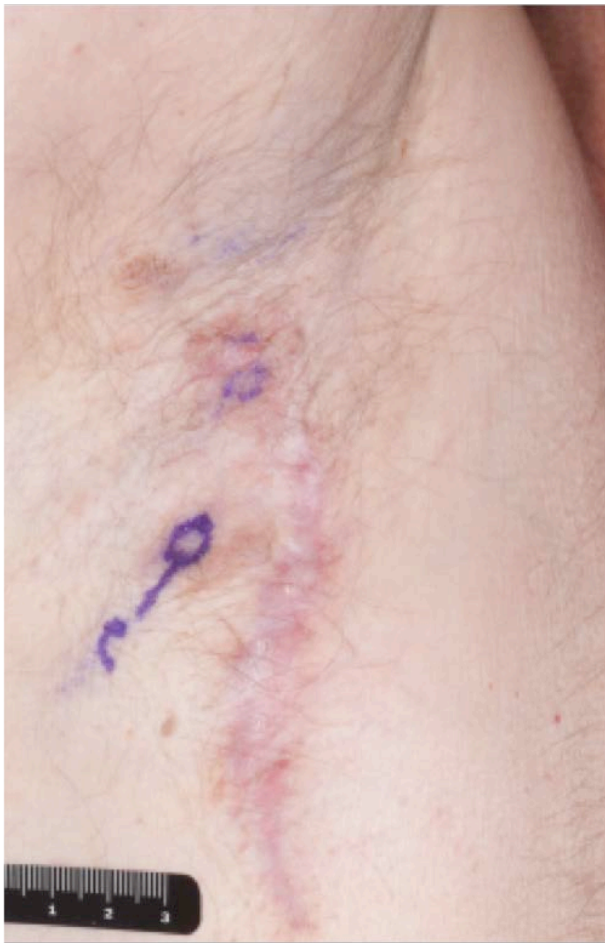


Figure 1. Cobblestoned and pebbly acanthotic skin colored and light pink to brown plaques of the right axilla. **Figure 2.** Well demarcated, pink and brown plaques of the suprapubic area and right groin.

Physical exam revealed cobblestoned and pebbly acanthotic skin colored and light pink to brown plaques of the bilateral axillae (Figure 1). In the suprapubic and bilateral inguinal areas, there were several pink and brown, well demarcated plaques, some of which were sclerotic and others acanthotic (Figure 2). There were also well-healed scars from the recent cosmetic surgery in the bilateral axillae and suprapubic area.

The groin plaques appeared to be highly suspicious for extramammary Paget disease. However, given the patient's history of diabetes, the axillary lesions were suspected to be acanthosis nigricans. Punch biopsies were taken from the bilateral axillae and groin.

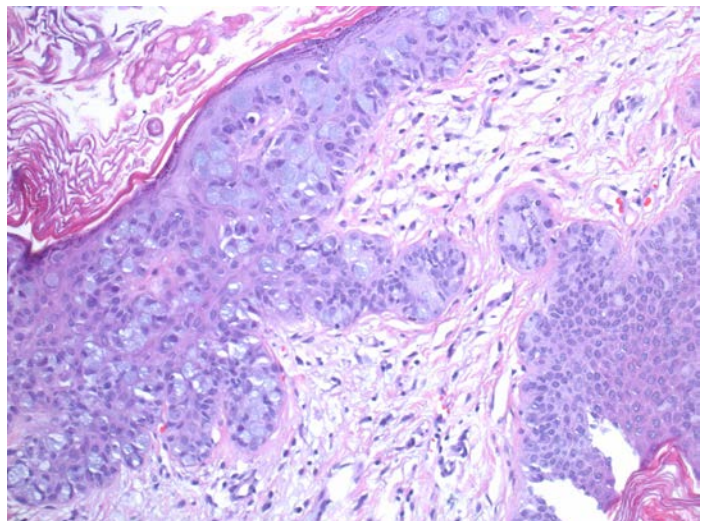
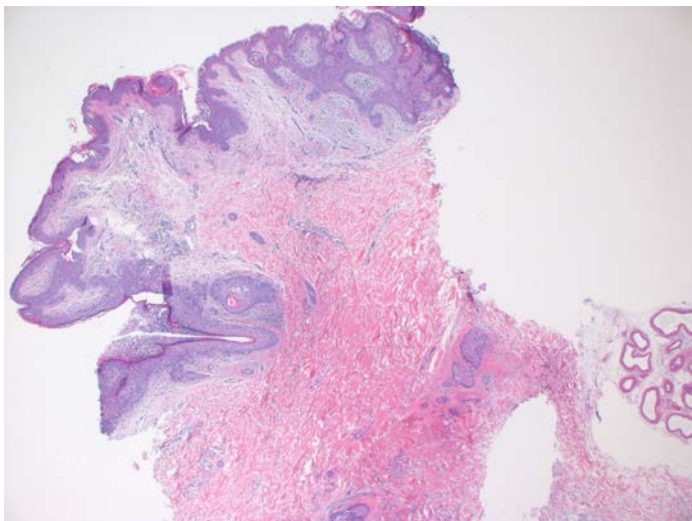


Figure 3. H&E stain of punch biopsy showing large, round, pale staining cells (Paget cells) scattered throughout the epidermis. **Figure 4.** H&E stain of punch biopsy showing Paget cells with abundant, pale, basophilic cytoplasm and enlarged, central nuclei with nuclear atypia.

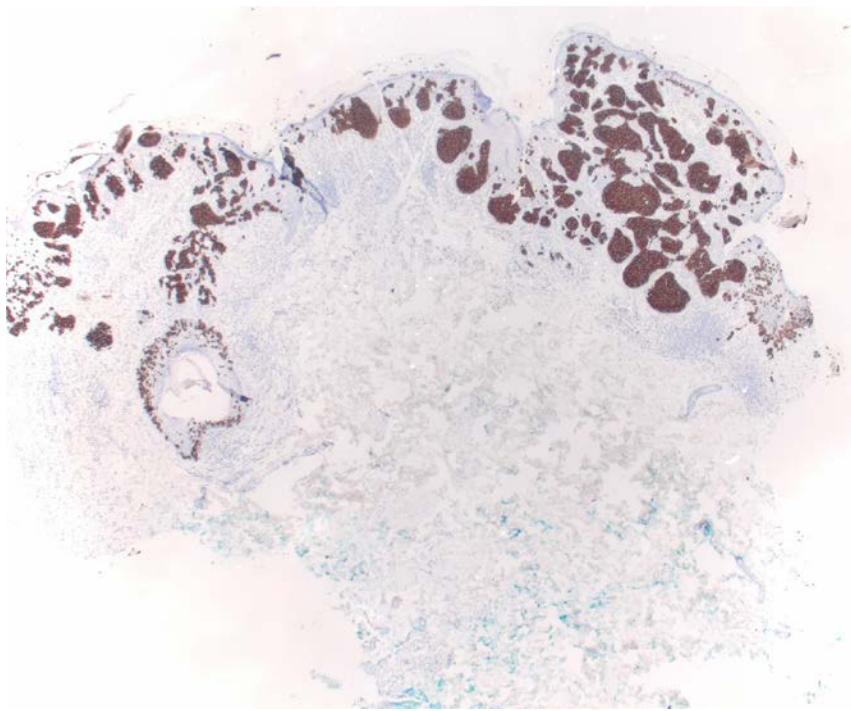
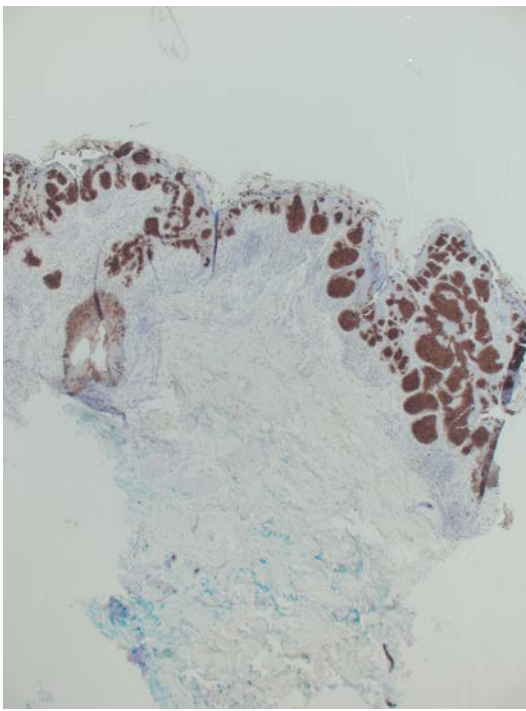


Figure 5. Positive immunohistochemistry stain for CEA. **Figure 6.** Positive immunohistochemistry stain for CK7.

The biopsies revealed areas of pale staining Paget cells scattered throughout the epidermis (Figures 3, 4). Focal invasion (adenocarcinoma) was seen in one specimen. Immunohistochemistry stains of the groin biopsy were positive for cytokeratin 7 (CK7) and carcinoembryonic antigen (CEA) (Figures 5, 6), whereas the axillary biopsies were positive for CK7 alone. Cytokeratin 20 (CK20) stain was negative.

The patient received further workup for underlying malignancy including a mammogram, ultrasound, and computed tomography of the abdomen and pelvis, all of which were essentially negative for malignancy. Surgical resection was decided as the treatment of choice. The patient is currently doing well without evidence of disease for one year.

Discussion

Extramammary Paget Disease (EMPD) is a rare intra-epithelial adenocarcinoma that is morphologically and histologically identical to Paget disease of the breast. Like Paget disease of the breast, it is also associated with an increased risk of internal malignancy. EMPD comprises 6.5% of all cutaneous Paget disease and generally affects individuals 50 to 80 years of age, with a peak incidence around age 65 [1]. The vulva is the most common site, comprising 65% of EMPD, but it can be found in any area containing apocrine sweat glands [1]. EMPD of the axilla has previously been reported, but multifocal EMPD is quite rare [2,3]. In a review of 76 patients with EMPD, two patients had exclusive axillary involvement and three patients had both genital and axillary involvement, while the remainder had solely anogenital disease [4].

There are a wide variety of clinical presentations of EMPD. The primary lesion is usually a well-demarcated, scaly plaque that may contain overlying crust, erosions, or ulcerations. The color can range from pink to red to reddish brown. Infiltrated nodules, vegetative lesions, and lymphadenopathy may be present. Lesions are usually solitary, and either hypo- or hyperpigmentation may be seen. Pruritis is reported in 90% of patients [5]. The clinical differential diagnosis includes superficial fungal infection, psoriasis, and various forms of eczematous dermatitis. The lesions are often initially misdiagnosed and treated with topical steroids or antifungal agents [1]. Because of EMPD's broad spectrum of clinical presentations, any inflammatory skin condition involving an area containing apocrine sweat glands should be biopsied if it does not respond to standard topical treatments [6].

Histopathological examination reveals an intraepithelial proliferation of large round cells ("Paget cells") with abundant, pale, basophilic cytoplasm and enlarged, central nuclei with nuclear atypia. Paget cells are predominantly found in the lower epidermis and can be grouped in nests or occur as single cells [1]. The pathological differential diagnosis includes superficial spreading malignant melanoma, Bowen disease, mycosis fungoides, Langerhans cell histiocytosis, and Spitz nevus [7].

Immunohistochemistry is often helpful in diagnosis. Most cases of EMPD stain positive for CK7, CK20, and CEA. Unlike its mammary counterpart, EMPD has mucin-containing tumor cells that stain positive for Periodic acid-Schiff-diastase (PAS-D) [8].

Another difference is that 50% of Paget's disease of the breast cases are positive for estrogen and progesterone receptors, whereas EMPD cases generally are not [9].

The mainstay of treatment for EMPD is surgical excision with 1 cm margins. Alternative treatment modalities include electrodesiccation and curettage, laser surgery, aminolevulinic acid photodynamic therapy, radiotherapy, and topical chemotherapy. It has been suggested that topical imiquimod 5% cream be considered as an initial treatment for EMPD, with surgical excision or alternative modalities reserved for recurrent or persistent disease [10]. Along with resection of the primary lesion(s), patients should undergo lymph node assessment and investigation for underlying malignancy. Rates of underlying malignancy vary widely in the literature, ranging from 8 to 86%, but are believed to be lower than in Paget disease of the breast [11]. A workup for malignancy may include urine cytology, colonoscopy, and pelvic ultrasound [1].

EMPD generally carries a favorable prognosis, with a five year survival rate of 72% [12]. The average rate of recurrence is 35-44%; therefore patients should be closely followed for at least two years [13,14]. The use of Mohs micrographic surgery is associated with a lower rate of recurrence (8-26%) [15,16]. Important prognostic indicators include invasion level and the presence of lymph node metastases [4].

Our case is unique in that the disease was multifocal and involving the axillae. The axillary plaques appeared clinically consistent with acanthosis nigricans, a much more common diagnosis, especially in the context of diabetes. The patient presented with extensive involvement of the groin and axillae after having failed several topical medications. This case illustrates the necessity for increased awareness of the diverse presentations of EMPD to allow earlier detection of an associated malignancy.

Conclusion

EMPD can present in a variety of different clinical manifestations and it is often initially misdiagnosed. This case demonstrates the need to consider EMPD when evaluating patients presenting with acanthosis of the axilla, given its ability to mimic more common conditions. Increased awareness about atypical presentations of EMPD can help improve early recognition of the disease and lead to earlier diagnosis of any underlying malignancy.

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