A Rare Case of Ectopic Extramammary Paget’s Disease

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Abstract
Extramammary Paget’s disease is a rare cutaneous neoplasm sometimes associated with internal visceral malignancies. It is very rarely encountered in “ectopic” areas that are not associated with the presence of apocrine glands. Treatment with wide surgical excision can be curative, although recurrences are not uncommon. We present a case of ectopic extramammary Paget’s disease found on the forearm of a male.

Introduction
Extramammary Paget’s disease (EMPD) is a rare cutaneous adenocarcinoma first described in 1888.1,2 In a minority of patients, it has been found in conjunction with gastrointestinal or genitourinary malignancies. In the majority of cases, it represents a primary intraepithelial carcinoma, and its origins and pathogenesis are not well-understood.3 Clinically, it often appears as an unresolving, eczematous patch. Histologically, there are large cells with ample cytoplasm within the epidermis that stain positive for CK-7. Its association with apocrine-gland activity has been well-understood.4

Case Report
A 67-year-old male, well-known to the dermatology practice, presented with an asymptomatic lesion on his left dorsal forearm that had been present for about five months. His past medical history was significant for hypertension and deep vein thrombosis of the upper extremity. Surgical history was significant for orthopedic procedures related to athletic injuries and a normal colonoscopy four years prior to presentation. His only medication was daily aspirin. He was allergic to terfenadine. He had no history of smoking or other toxic habits.

On examination, the patient was found to have an erythematous, eczematous-appearing patch on his left dorsal forearm (Figure 1). Clinically, the patch measured about 3 cm x 1 cm. A shave biopsy was obtained, which showed intraepidermal proliferation of large, atypical epithelioid cells arranged both as small nests and single cells. The tumor cells were described as having ample cytoplasm, prominent nuclei, and conspicuous nucleoli while displaying pagetoid spread and involvement of adnexal epithelium (Figure 2). The intraepidermal proliferation was positive for CK-7. Melan-A immunostain highlighted a coincidental intradermal nevus. EMA was non-contributory. These findings were interpreted by the pathologist as being consistent with extramammary Paget’s disease.

The patient returned to the office for full excision of the lesion about one month after initial presentation. Pathology showed residual extramammary Paget’s disease with clear margins. The patient was then referred to oncology to rule out occult malignancy. Work-up, including blood tests, radiological scans and repeat colonoscopy, was negative. The patient remains disease-free five months after initial diagnosis.

Discussion
Paget’s disease presents as an eczematous or psoriasisform plaque of the nipple and surrounding skin due to epidermal extension of an underlying adenocarcinoma of the breast.1 Extra-mammary Paget’s disease (EMPD) is a rare, cutaneous, intraepithelial adenocarcinoma found outside the breast. It was first described by Crocker in 1888.2

Figure 1. 3 cm x 1 cm, oval-shaped, eczematous patch on the left dorsal forearm prior to excision, with bleeding due to injections of local anesthesia.

Figure 2. Intraepidermal proliferation of large cells with ample cytoplasm, arranged both as small nests and focally as single cells.

The milk-line is a band-like thickening of ectoderm running bilaterally along the ventral surface of the embryo. This milk-line contains apocrine glands and is the most common location of Paget’s disease outside the breast. EMPD is thought to be of apocrine origin because it commonly manifests in areas such as the vulva, scrotum, axillae, and anogenital regions. There are rare cases in which EMPD has been found in areas of the body that do not typically contain apocrine glands. These cases have been referred to as “ectopic EMPD.”3 Ectopic EMPD cannot be distinguished from EMPD other than by its location in a non-apocrine-bearing area. While it remains unclear how Paget’s disease arises in non-apocrine-bearing skin, it is hypothesized that an epidermal multipotent stem cell may eventually gain an apocrine phenotype.4

In about 75% of patients, EMPD represents a primary intraepithelial adenocarcinoma. In the remainder of patients, it may be related to underlying visceral adenocarcinoma, commonly in the gastrointestinal or genitourinary tracts.1 The intrapageotoid variant of Bowen’s disease.

EMPD and melanoma and the importance of distinguishing the two. Studies examining the dermoscopic features of pigmented EMPD have reported the presence of brown globules in a linear arrangement on a white background.5 Histopathologically, EMPD shows intraepidermal spread of large cells with pale-staining cytoplasm.6 Other histological features include pagetoid cells with atypical, hyperchromatic nuclei; positive staining for periodic acid-Schiff; and the presence of carcinoembryonic antigen (CEA) in immunohistochemical studies.7 EMPD may show similarities with melanocytic lesions such as superficial spreading melanoma. However, melanocytic lesions can be distinguished with markers such as Melan-A, S-100, and HMB-45. EMPD may also show histologic similarities with the pagetoid variant of Bowen’s disease.8

Because EMPD occurs more frequently in women, it was once thought that estrogen and/or progesterone receptors on pagetoid cells may play a role in the pathogenesis of the disease. In one pathological study, testing with antibodies revealed expression of androgen receptors and a general lack of estrogen and progesterone receptors on pagetoid cells. This finding may stimulate further investigation of these factors in the pathogenesis of EMPD.
investigations into the role of these androgen receptors and whether their blockade may be of benefit in the treatment of EMPD.

Another immunohistochemical study of EMPD found a molecule known as epithelial membrane antigen (EMA) to be nearly universally present in Paget cells. Notably, it was also present in some cells that did not have Paget-cell morphology. The authors suggest this finding may be representative of cells that have not yet transformed into Paget cells, which could explain the high rate of local recurrence after surgical excision. The authors proposed mapping the surgical margins of EMPD for EMA to improve accuracy and reduce recurrence.

Treatment of EMPD is mainly surgical, and there are high rates of local recurrence. Topical fluorouracil and radiation therapy have also been used, with varying degrees of success. Wide local surgical excision may not always be feasible, especially in elderly patients, who may be poor surgical candidates. In these circumstances, there have been reports of successful treatment with radiotherapy. One series of two patients studied both clinical and histopathological effects of radiotherapy on EMPD. Biopsies were performed at the same site before and after administration of radiotherapy. Histological examination after treatment revealed no residual tumor cells, which correlated with clinical clearance.

Another early study sought to understand the mechanism underlying the recurrence of disease after surgical excision. The authors suggested the high rate of local recurrence demonstrates that the clinical boundaries of the disease are not reliable indicators of its histological extent. In an EMPD patient in whom 5-fluorouracil (5-FU) had failed as a potential treatment, causing an inflammatory reaction, the authors used the inflammation to delineate the extent of disease prior to micrographic surgery. The study used a twice daily application of 5% 5-FU for 10 days, which resulted in thickening and inflammation both of clinically diseased skin as well as clinically normal-appearing skin, which reduced operative time and possible surgical complications. The study highlights the need to define the extent of disease prior to surgical excision. The authors also suggested the periodic use of 5-FU as a tool to check for recurrence after surgery.

**Conclusion**

Ectopic EMPD is a rarely encountered clinical entity, especially on the forearm of a male. Its underlying pathogenic mechanisms are not well understood. One histopathological study looking at sections from 55 patients concluded that EMPD is likely a spectrum of diseases. Most commonly, the disease begins in the epidermis and extends downward through hair follicles and eccrine sweat ducts. Less commonly, cells extending into the epidermis metastasize. Rarely, the cutaneous findings of EMPD result from direct extension of an adjacent adenocarcinoma in the gastrointestinal or genitourinary tracts. Additional studies and investigations are required both to further define the disease and to investigate its treatments.

**References**


