

Perianal Paget's Disease: A Case Report and Literature Review

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Abstract. *Perianal Paget's disease is a rare condition characterized by an intraepidermal growth of neoplastic cells with apocrine glandular differentiation (Paget's cells), often associated with an underlying malignancy. Fewer than 200 cases have been reported in the literature over the past 20 years. Here we discuss the clinical case of a young woman who was referred to our institution for this rare disorder and briefly review the literature.*

Cutaneous Paget's disease (PD) is a rare disorder of the skin, predominantly involving the breasts, characterized by an intraepidermal growth of neoplastic cells with apocrine glandular differentiation (Paget's cells). It was first described by Sir James Paget in 1874 as a malignant change of the areola skin in association with underlying breast carcinoma (1). He believed the neoplastic cells derived from large lactiferous ducts and that changes in the skin both preceded and induced malignant change in the underlying breast tissue. Paget suggested that similar changes might be seen at other epithelial sites and some years later, extramammary Paget's disease (EMPD) of the scrotum and penis were described (2). The vulva, scrotum, penis, perineal and perianal regions have been reported as the most common sites of EMPD (3). Unusual sites of involvement are represented by the axilla, eyelids, and external auditory canal (4-6). Ectopic EMPD has rarely been described arising from areas devoid of apocrine glands (7). The precise incidence of EMPD is unknown. It affects individuals between the ages of 50 and 80 years and is more common in women and Caucasians (8-10). Familial occurrence is rare. Given the low incidence of the disease, literature data on EMPD come

mainly from small studies or case reports. Perianal PD (pPD) is a very rare condition and was first described in 1893 (11). We present a rare case of pPD and discuss diagnostic-, clinical- and treatment-related issues of this disease.

Case Report

A 45-year-old Caucasian woman was referred to our institution in October 2011, with a one-year history of a whitish and itchy lesion in the perianal region, resistant to local corticosteroid therapy, and not associated with other symptoms. The patient had a history of breast cancer diagnosed at the age of 39, for which she underwent an upper-outer left quadrantectomy and axillary dissection. Histologically, the breast tumor was a 1.1-cm ductal invasive carcinoma, with a medium-low grade of differentiation (G2-G3), and with no lymph node involvement pT1c, pN0 (0/11), M0. Immunohistochemical staining of the tumor was negative for estrogen and progesterone receptors, ERBB2-negative (score 1), and the Ki-67 expression was 60%. Following surgery, adjuvant chemotherapy with four cycles of doxorubicin plus cyclophosphamide and radiotherapy (5000 cGy in 25 fractions to the whole breast with an additional tumor bed boost of 1000 cGy), were administered. Subsequently, the patient was constantly monitored for the risk of breast cancer recurrence at an oncological center. Physical examination of the perianal area revealed a scaly, crusting, and partially eroded eczema-like lesion, measuring about 2x2 cm (Figure 1a). A biopsy of the lesion was carried out and demonstrated diagnosis of pPD [carcinoembryonic antigen (CEA)-positive, S100-negative] by immunohistochemistry. Thus, a complete abdominal ultrasound, whole-body computed-tomography (CT) scan, and a bone scan were carried out; all were negative for macroscopic neoplastic lesions. A proctoscopy only showed the presence of grade IV hemorrhoids. A wide surgical excision under general anesthesia was subsequently performed by high frequency radio-scalpel. The surgical margins were evaluated in order to maintain them sufficiently distant from the periphery of the lesion (Figure 1b). The wound healed by secondary intention without any complication. Macroscopic examination of the

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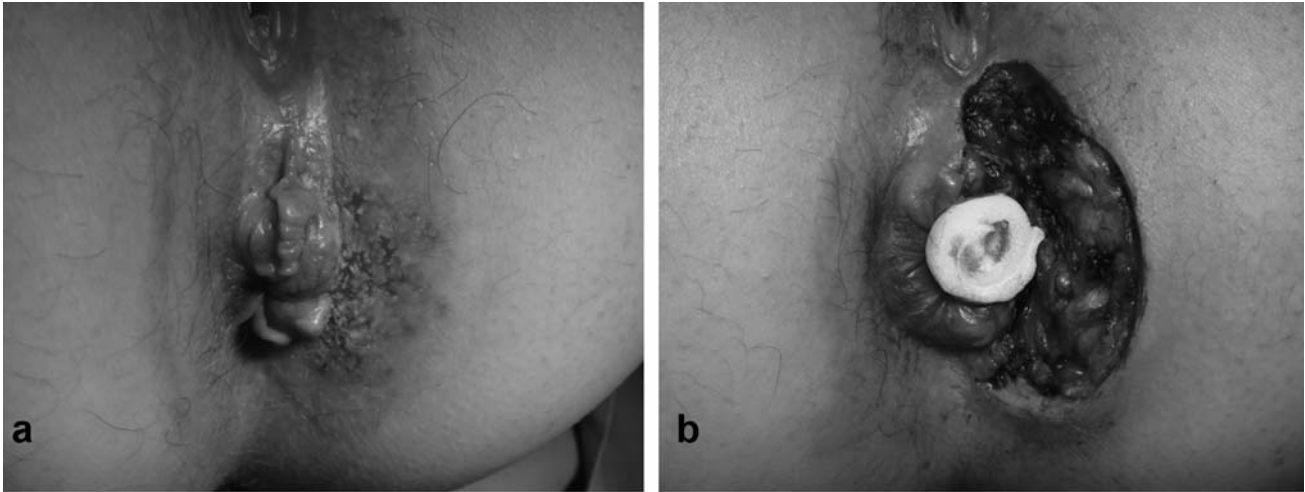


Figure 1. a: Perianal Paget's disease presenting as an erythematous scaly plaque; b: wide surgical excision of Paget's disease performed by high-frequency radio-scalpel.

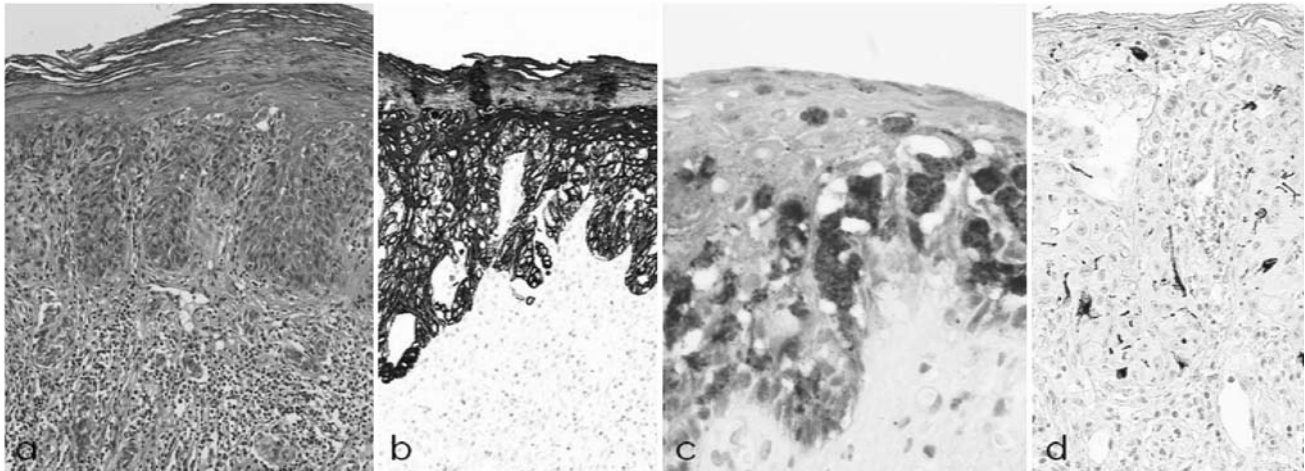


Figure 2. a: Paget's cells confined to epidermis (hematoxylin and eosin, $\times 300$); b: pan-cytokeratin-positive ($\times 400$); c: carcinoembryonic antigen-positive ($\times 400$); d: S100 and human melanoma black 45-negative ($\times 300$).

resected specimen revealed cutaneous and subcutaneous tissue of $2.7 \times 2.5 \times 1$ cm, within a flat brown-red tumoral mass of 1.5 cm with irregular and undefined margins. At the center of the lesion, an ulcerated and bleeding area of 0.3 cm was observed, probably caused by the previous biopsy. After resection, the lesion appeared to be a yellowish 0.2 cm-thick mass confined to dermis. Definitive histological examination revealed Paget's cells confined to the basal epidermis, which were pan-cytokeratin- and cytokeratin 7 (CK7)-positive, CEA-positive, human melanoma black 45 (HMB45)-negative, and S100-negative, and were surrounded by a chronic inflammatory infiltrate (Figure 2). There was no evidence of dermal infiltration on multiple sections examined. Surgical

margins were all negative for tumor cells (deep margin at 0.7 cm). A 7-month follow-up with a physical examination, a biopsy of the margins of the primary lesion, and a proctoscopy showed no evidence of recurrence or underlying malignancy. As discussed below, a long-term follow-up is warranted to exclude relapse of pPD.

Discussion

pPD is an uncommon form of neoplasm arising from the apocrine glands of the perianal skin. To date, fewer than 200 cases have been described in the literature. The growth of neoplastic cells is usually limited to the epidermis, even

Table I. Stage and management of perianal Paget's disease.

Stage	Description	Management
I	Paget's cells found in perianal epidermis and adnexae without primary carcinoma	WLE
II A	Cutaneous Paget's disease with associated adnexal carcinoma	WLE
II B	Cutaneous Paget's disease with associated anorectal carcinoma	APR
III	Paget's disease in which associated carcinoma has spread to regional nodes	ILND + WLE/APR
IV	Paget's disease with distant metastases of associated carcinoma	CT + RT + LPM

WLE: Wide local excision; ILND: inguinal lymph node dissection; CT: chemotherapy; RT: radiotherapy; LPM: local palliative management.

though a potential dermal invasion has been previously described (12). Moreover, about one-third of patients affected by pPD have an underlying malignancy, often represented by an anorectal carcinoma (13, 14). The pathogenesis of EMPD is still unknown. Some authors have considered Paget cells as primary, derived from epidermal stem cells of the basal layer as a consequence of a defective apocrine differentiation of these cells (15). On the contrary, due to their frequent association with an underlying malignancy with similar immunohistochemistry characteristics, some authors have hypothesized that Paget cells represent a particular form of metastatic spread into the epidermis or secondary epidermotropic infiltration (16-18). In summary, there is evidence of the presence of at least two different types of pPD. The first type can be considered as a primary cutaneous intraepithelial neoplasm in which Paget's cells are usually CK7⁺, CK20⁻, and gross cystic disease fluid protein 15 (GCDFP15)⁺. The second type is often characterized by the presence of numerous signet ring cells, with gastrointestinal-type glands and intraluminal dirty necrosis, and CK7⁺, CK20⁺, and GCDFP15⁻ Paget's cells. The latter form is likely to be associated with synchronous or metachronous rectal adenocarcinoma (18). Although staining with hematoxylin and eosin and periodic acid Schiff reaction are generally sufficient for the diagnosis of PD, other immunohistochemical markers can be helpful in the differential diagnosis from other malignancies. CK7, epithelial membrane antigen (EMA, MUC1), Cam 5.2 (a monoclonal antibody that stains 40-kDa, 45-kDa, and 52.5-kDa low molecular weight keratins), and CEA are considered sensitive but non-specific markers for Paget's cells (19-21). GCDFP15 is a marker of apocrine epithelium and its negativity or positivity has been proposed as a marker to distinguish EMPD from that without underlying malignancy, respectively. S100 and HMB45 may be useful in differentiating EMPD from pagetoid malignant melanoma *in situ*, since melanocytes stain positively with these proteins (22, 23). Serum receptor-binding cancer antigen expressed on SiSo cells (RCAS1) has been proposed as a useful tumour marker for monitoring patients with invasive EMPD, with a higher sensitivity than CEA (24). Due to the lack of data in

literature, the prognosis of pPD is difficult to assess. To date, the most representative experiences at the Cleveland Clinic Foundation, the Memorial Sloan-Kettering Cancer Center, and the Mayo Clinic suggest that both overall and disease-free survival are approximately 60% at 5 years (25-27). Moreover, characteristics such as the evidence of invasive or noninvasive EMPD, the presence or absence of clear margins, and the association with underlying malignancies seem to represent the most important prognostic factors, affecting the therapeutic management decision (Table I) (28, 29). It has been reported that about 42% of the cases of pPD are associated with a synchronous or metachronous malignancy (*e.g.*, anorectal adenocarcinoma, adenosquamous carcinoma, adenocarcinoma of the adnexa, carcinoid tumor, *etc.*) (30). Clinically, pPD is early characterized by a chronic eczema-like rash of the skin around the anogenital region, associated with pain, itching and sometimes bleeding. The diagnosis is generally delayed by the clinical characteristics of the disease, which mimics benign inflammatory dermatological conditions, and is usually made after extensive and unnecessary use of various cortisone-based creams and antibiotics. For these reasons, any rash in the anogenital area that is not responsive to 6 to 8 weeks of topical therapy should be biopsied. Although limited by a high incidence of relapse, wide local excision, with or without reconstructive surgery, is considered the treatment of choice of pPD. Excision of rectum or abdominoperineal excision for invasive disease or lesions associated with underlying malignancies are recommended. The rate of recurrence is reported to be about 33-66% (10) as a consequence of the multifocal nature of the tumor and its tendency to extend beyond the clinically visible margins. For this reason, the margins of the lesion should be carefully evaluated in order to maintain a safe distance that must still be confirmed by histological examination. Moreover, a long-term follow-up is needed for pPD, considering that relapses may occur even several years after surgery. Periodic physical examination, biopsy of the margins of the primary lesion, and colonoscopy should be considered (31). To implement the surgical procedure, we used a high frequency (HF) radio-scalpel, a new tool that is able to simultaneously cut and

coagulate tissues by an electrode, using the heat generated by the passage of high-frequency radio waves (32, 33). The main difference from a traditional electric scalpel lies in the higher frequency of the HF radio-scalpel (4 MHz vs. 500 KHz), which allows use of a lower power (60 W vs. more than 300 W) and development of a lower temperature (45-70°C vs. 300-600°C), reducing burn injury (34, 35). Currently, several different departments such as general surgery, plastic surgery, vascular surgery, dermatology, orthopedics, neurosurgery, and ophthalmology, take advantage of the use of the HF radio-scalpel. Recently, the finding that the use of a HF radio-scalpel may improve the early and long-term results of all major proctological procedures has encouraged the spread of this novel tool in practice (33). Other non-surgical and alternative approaches to pPD have been reported, with the aim of reducing the recurrence rate of the disease. Mohs micrographic surgery provides an accurate intraoperative microscopic evaluation of the tissue margins (36). Radiation therapy has been proposed as a primary, adjuvant, or salvage treatment of pPD (37, 38). Chemoradiotherapy and/or systemic chemotherapy are usually used for the treatment of invasive disease, or in the presence of an underlying carcinoma (39-42). Topical application of the immune response modifier imiquimod or chemotherapeutic agents such 5-fluorouracil and bleomycin have been investigated for the treatment of noninvasive or recurrent EMPD (43-47). Photodynamic therapy is a promising modality for treating EMPD, which allows a selective destruction of cells that have accumulated a photosensitizing substance (5-aminolevulinic acid, methyl aminolevulinate), using an appropriate wavelength of light (48). Due to the rarity of EMPD, all these alternative modalities have been poorly investigated in randomized trials. Their role in the treatment of EMPD remains uncertain and mainly dependent on the location and the extent of the disease.

Conflicts of Interest

The Authors declare no conflicts of interest.

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