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Case Report

Extramammary Paget's disease of the scrotum

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Abstract

Extramammary Paget's disease is an uncommon intra-epidermal malignant neoplasm that arises in area rich in apocrine glands. Common sites of occurrence include the vulva, perianal region, perineum, and scrotum. The lesion may be accompanied by an invasive adenocarcinoma or adenocarcinoma *in situ* of the apocrine glands. Generally, the prognosis is poor. Herein, we report two cases of extramammary Paget's disease, one involving the penoscrotal area with bilateral inguinal and pelvic lymph node metastases, the other involving the scrotal area without metastases.

Keywords: Extramammary; Paget's disease; Scrotum

1. Introduction

Paget first described Paget's disease of the nipple with underlying ductal carcinoma of the breast in 1874.[1] In 1889, Crocker described the first extramammary Paget's disease (EMPD) involving the scrotum and penis.[2] EMPD of scrotum and penis is rare. Most cases of EMPD are located on the vulva and anus. The lesion is located deep within the dermal to epidermal layer, and underlying carcinoma of the sweat glands has been suggested as a possible etiology. This lesion may be associated with either subjacent or distant malignancies or may potentially be an invasive adenocarcinoma. EMPD must be differentiated from benign papulosquamous diseases, squamous cell carcinoma, and melanoma. Commonly, it is mistaken as eczema or contact dermatitis. The diagnosis is confirmed by the presence of Paget's cells on histopathological examination of a tissue specimen. Surgical resection is the standard method for treatment for scrotal EMPD, as well as EMPD in other areas. We herein report two cases of this uncommon disease, and discuss treatment options and outcomes.

2. Case report

2.1. Case 1

A 68-year-old male patient presented to a dermatologic clinics with an erythematous and eczematoid skin rash on his scrotum for 6 months (Fig. 1). The skin lesion had failed treatment with a topical antifungal medication. The patient's medical history was unremarkable except for benign prostatic hypertrophy, and he denied any history of malignancy. Physical examination revealed a healthy elderly man without systemic symptoms. Histopathological examination of a biopsy specimen of the skin lesion revealed infiltration of the epidermal-dermal junction by atypical polygonal cells, singly and in clusters, which were characterized by round nuclei and finely granular to clear cytoplasm (Figs. 2 and 3). Findings were consistent with EMPD of the scrotum. Staging workup that included chest radiography, serum prostatic specific antigen (PSA), and computed tomography did not reveal signs of metastasis. The patient underwent wide

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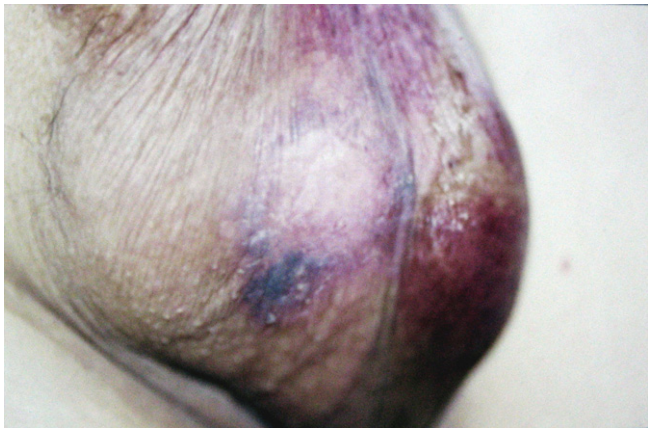

Fig. 1. An erythematous plaque on the right side of the scrotum.

excision of the skin lesion with a 2-cm margin to the macroscopic normal tissue, and primary closure. Surgical margins were histopathologically negative, and the wound healed without complications. Follow-up at 2 years revealed no signs of recurrent disease.

2.2. Case 2

A 65-year-old male presented with a 10-month history of recurrent, itchy, eczematous erosion, and indurated patchy lesion on left side of penoscrotal area (Fig. 4). The patient had been initially treated for an erythematous, pruritic lesion on the scrotum with topical corticosteroids. He had been treated with the steroids for 8 months, however, the lesion had progressed to an erosive mass with extension to the penis base. His medical history was only remarkable for transurethral resection of the prostate for benign prostatic hypertrophy without evidence of malignancy. Physical examination revealed a fixed lymph node palpable in the left inguinal areas. Biopsy of the skin lesion demonstrated poorly differentiated extracutaneous adenocarcinoma. Computed tomography scan of the abdomen showed enlarged lymph nodes in the inguinal areas bilaterally, and involvement of the external and internal iliac arteries. Possible underlying urothelial and prostatic malignancy were ruled out by normal serum PSA and urinalysis. The patient received wide excision of the skin lesion with a margin of 3 cm, and bilateral pelvic and inguinal lymph node dissection. The skin defect was repaired with a scrotal flap. Histopathological examination showed infiltrating poorly differentiated invasive carcinoma of the dermis, epidermis and sweat glands, which was classified as EMPD.

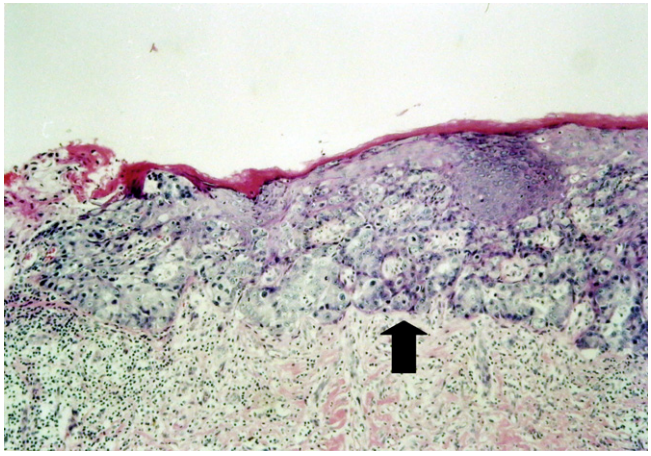

Fig. 2. Nests of pale-staining Paget's cells are seen within the epidermis(arrowhead). (hematoxylin & eosin, ×40).

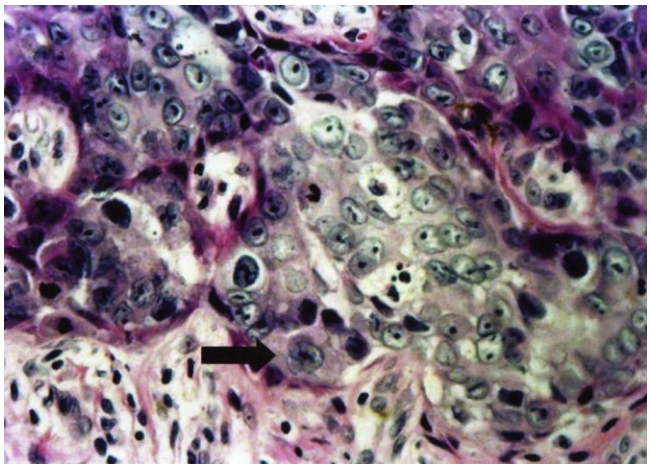

Fig. 3. Paget's cells with typical foamy cytoplasm and reticulated nuclei (arrowhead). (hematoxylin & eosin, ×400).

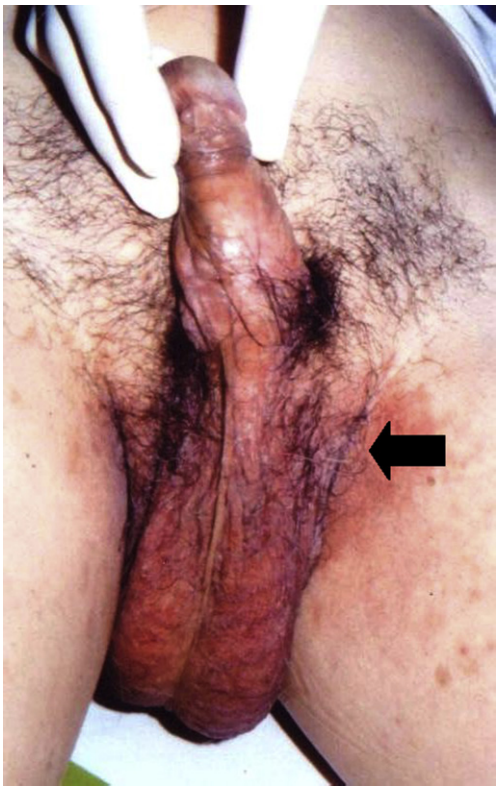

Fig. 4. An eczematous, erosion, and indurated patchy area on left side of the penoscrotal area.

Although the surgical margins were negative for malignancy, all the lymph nodes removed from the inguinal, external iliac, internal iliac and obturator regions were positive for malignancy. Postoperative radiotherapy and chemotherapy were advised, but the patient declined. Local recurrence and metastasis of the liver and lung were found at 6 months postoperatively. The patient died of the disease at 8 months postoperatively.

3. Discussion

EMPD is an epithelial disorder, and a rare form of adenocarcinoma that is usually observed in cutaneous apocrine gland-bearing regions. The most common site of EMPD is the vulva, and more than 200 cases have been reported.[3] The second most common site is the perianal region, with more than 86 cases documented.[3] Other locations include the perineum, scrotum, axilla, and eyelids. EMPD generally occurs between the ages of 50 and 80, most frequently in Caucasians. Overall, it is more common in women than men, with a reported female-to-male ratio of 1.4:1.[3–5]

Since the first description of EMPD, the pathogenesis has remained controversial, and several theories have been proposed. One theory postulates that Paget's disease is the result of metastasis of underlying malignant cells to the overlying epidermis.[6,7] Another theory suggests that Paget's disease is the result of multiple foci of malignant transformation of a population of cells with a common embryological origin. This theory would account for the reportedly high incidence of "skip areas" between the subjacent invasive adenocarcinoma and the epidermal lesions.[5,7] Other investigators suggest that Paget's cells either derive from or differentiate toward exocrine and apocrine gland cells. This pathogenesis could explain why EMPD usually occurs in areas of the body containing exocrine sweat gland, and suggested that isolated EMPD may represent intraepithelial metastasis of an underlying exocrine gland adenocarcinoma.[5–7]

It has been suggested that patients with EMPD should be segregated into two subgroups; those with disease confined to only the epidermis and dermis (primary), and those with involvement of visceral organs as well, especially genitourinary and gastrointestinal tract (secondary).[7] The clinician should therefore search for an underlying malignancy in EMPD.

The clinical manifestation of EMPD is variable. Lesions of EMPD typically present as sharply demarcated, infiltrated, erythematous to gray-white plaques, which are occasionally eczematoid, crusting, papillomatous, scaling, or, rarely, ulcerated. The lesions may be asymptomatic, or pruritus, a burning sensation, and pain may be noted.[3–5,7] The nonspecific clinical findings and slow-growing characteristic often lead to misdiagnosis and extended periods of topical or systemic medical management.[3–6] The clinical differential diagnosis for EMPD includes contact dermatitis, fungal infection, psoriasis, eczema, Bowen's disease, and melanoma.[3,4,6,8] When lesions in apocrine gland-bearing regions do not heal within 1 month, the diagnosis of EMPD should be considered.[3,5] Histopathological examination of a biopsy specimen is necessary for diagnosis.

EMPD is confirmed by the presence of Paget's cells on routine hematoxylin-eosin histological section. Paget's cells are large, vacuolated cells with pale-staining cytoplasm and reticulated nucleus, and may be observed in the epidermis and/or adnexal epithelium (Figs. 2 and 3). Paget's cells also stain positive for low-molecular-weight cytokeratin and carcinobryonic antigen.[3,5,9] Although these findings are not applicable to all cases, these patterns of immunoperoxidase staining may allow the presence or absence of association of internal malignancy to be predicted. Occasionally, tumor cells will stain positive for PSA, especially when an associated adenocarcinoma of the prostate is present.[5] It should be understood that patients with EMPD also have a high risk of noncontiguous malignancy; most EMPD cases reflect a primary intraepithelial adenocarcinoma, which is probably derived from a pluripotent cell in the basal layer of the epidermis. Usually, secondary EMPD and the internal malignancy are anatomically associated. Most internal malignancies reported in association with EMPD of the penis or scrotum or groin occur in the genitourinary tract, including prostate, bladder, and rectal carcinoma, in up to 24% of the patients.[8] Approximately 15% of patients with vulvar EMPD have had other concomitant urogenital malignancies.[3] In cases of perianal EMPD, colorectal adenocarcinoma is present approximately about 33% of the time.[3] Therefore, we recommend routine immunoperoxidase study for carcinobryonic antigen and low-molecular-weight cytokeratin when secondary EMPD and internal adenocarcinoma are suspected.

The prognosis of localized EMPD is much better than that of invasive form of disease; therefore, the treatment is different. Treatments of noninvasive EMPD include surgical resection, radiation, topical chemotherapy, photodynamic therapy, and CO_2 laser vaporization.[4] The best treatment of noninvasive EMPD is local wide excision with a large margin.[3,4,6–8,10] Most authors recommend a 1- to 3-cm margin of grossly uninvolved tissue.[5,8,10] Intraoperative frozen section has been used to define surgical margins for complete resection. Because EMPD always extends beyond the clinically visible margin, Mohs micrographic surgery has been recommended. Frederic E. Mohs originated the technique as a cancer research assistant in the early 1930s. After the tumor is excised, microscopic processing is used to check the margins of the specimen for residual tumor. Representative vertical sections may be obtained at 2- to 4-mm intervals throughout the specimen by using the bread-loaf method and in each of 4 quadrants by using the quadrant method. This is a surgical technique for the removal of certain cutaneous carcinomas that allows precise microscopic marginal control by using horizontal frozen sections. In fact, compared with wide excision, Mohs micrographic surgery offered lower recurrence rates for EMPD (33% *vs.* 23%, respectively).[3,4,6] Lymph node dissections are necessary if there is clinical evidence of involvement. Prophylactic lymph node dissection is not recommended. In patients with invasive EMPD, surgical excision is not curative. Adjuvant therapy such as radiotherapy or systemic chemotherapy may be necessary. Chemoradiotherapy using 5-fluorouracil and mitomycin-C has been proven effective in inadequately excised and advanced EMPD.[3] Surgical approaches for EMPD

associated with underlying genitourinary or gastrointestinal malignancies depend on the different diseases. The treatment methods are the same to the primary EMPD.

Most sources agree that EMPD may be a multifocal process.[3,6,7] This is why EMPD is difficult to treat and has a high recurrence rate of 31−61% despite adequate resection.[7,10] The prognosis for patients with scrotal Paget's disease depends on the presence or absence of an underlying malignancy, and the extent of metastatic disease. The prognosis is more optimistic with noninvasive disease than advanced disease, but there are insufficient data available to directly address the issue.[5] In our two patients, the outcome of noninvasive EMPD (Case 1) was better than in Case 2 with advanced EMPD, although the follow-up period for Case 1 has not been long. Long-term follow-up is required to exclude recurrence of the disease and other concomitant malignancies.

In conclusion, EMPD is a rare entity often associated with adnexal and visceral malignancies, and a poor prognosis. Early biopsy is very important to establish a correct diagnosis in patients who fail to respond to conventional topical therapy. Furthermore, diagnostic evaluation is necessary to rule out associated malignancy or metastasis. Because of limited experience, larger studies are needed to provide guideline for treatment as well as post-treatment surveillance modalities and duration.

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