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Extramammary Paget's Disease with Aggressive Behavior : A Report of Two Cases

Extramammary Paget's disease (EMPD) is an intraepithelial neoplastic disorder which is included as a rare malignant condition. However, it sometimes shows aggressive behavior of local recurrence and coexisting malignancy. We had experienced nine cases of EMPD involving the scrotum for seven years. Two cases of them presented metastasis. The first case presented extensive inguinal lymph node metastasis with underlying adnexal adenocarcinoma one year after wide local excision. The second case initially presented multiple metastasis to the liver and in the lymph node. The latter, showing fulminant progression with liver metastasis, may be only the second case reported in English literature. EMPD is considered as a malignant neoplasm with aggressive behavior from initial presentation. Because wide local excision of the lesion alone may be occasionally insufficient, a careful follow-up must be done to detect recurrence or internal malignancy.

Key Words : *Paget's disease, extramammary; Scrotum; Neoplasm metastasis*

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INTRODUCTION

Extramammary Paget's disease (EMPD) can arise from any intraepidermal region bearing apocrine sweat glands (1, 2). EMPD of the scrotum and perineal region may be associated with malignancy of the regional area or internal viscera such as the rectum, anus and urogenital organs (3). This may not only cause diverse outcome, but create confusion in therapeutic principle. EMPD with other malignancy or metastasis generally seems to produce a limited prognosis despite aggressive treatment.

Nine cases of EMPD involving the scrotum had been treated from the year 1990 to 1997 at Asan Medical Center, Seoul Korea. All cases were male Koreans. Two cases among 9 presented metastatic growth; one case of inguinal lymph node metastasis, and the other case of liver and inguinal lymph node metastases.

CASE REPORTS

Case 1

A 66-year-old man presented multiple erythematous scaly patches on the left scrotal area for 2 years. It was treated by wide local excision and diagnosed to be EMPD without accompanying adnexal tumor. After one year, the patient visited our hospital again with brownish plaque and several subcutaneous movable masses on the left inguinal area. The incisional biopsy at the left inguinal mass revealed Paget's cells with adnexal adenocarcinoma. Tumor cells were positive for periodic acid-Schiff (PAS) stain. The immune staining for lower-molecular-weight cytokeratin and carcinoembryonic antigen (CEA) were positive, but it was negative for S-100 protein. There was no evidence of malignancy on upper gastrointestinal X-ray and barium enema. Serum CEA level was normal. CT at lower extremities showed several enlarged inguinal lymph nodes on the left side. Wide local excision and radical groin dissection were performed. The affected left groin dissection included iliac lymph nodes. The lesion was diagnosed as apocrine adenocarcinoma of scrotum with extensive left ilioinguinal lymph nodes metastasis (Fig. 1). The patient remains free of disease 26 months after surgery for recurrence.

Case 2

A 67-year-old man visited our hospital due to scrotal and

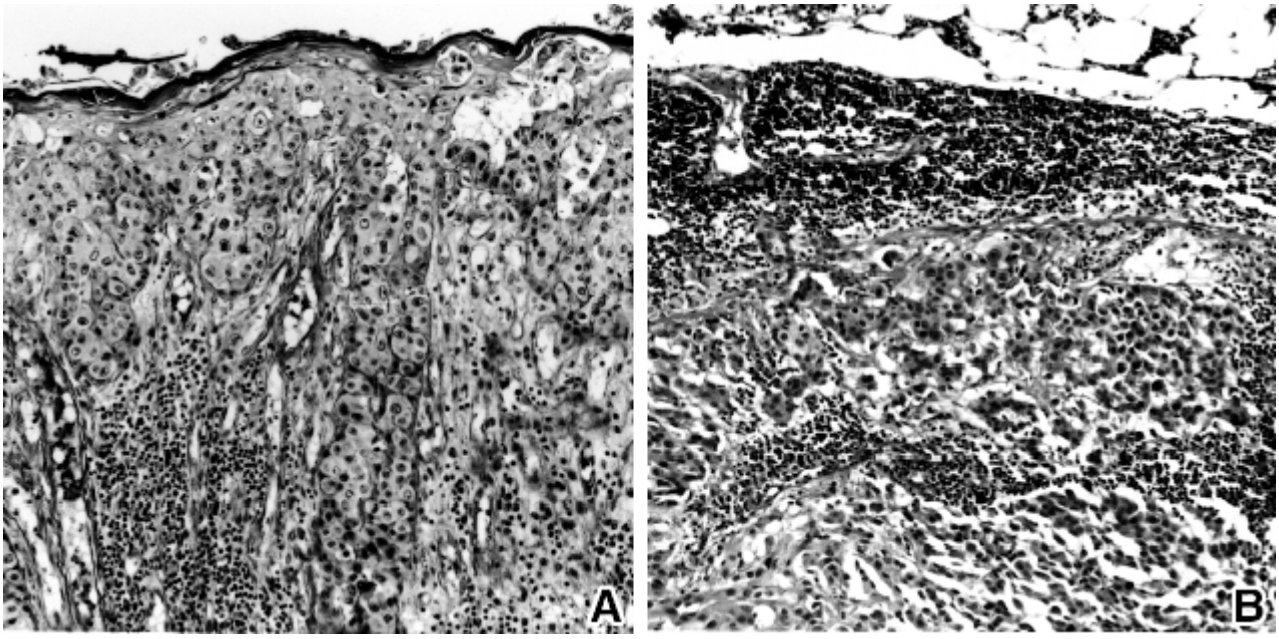

Fig. 1. Extramammary Paget's disease involving the scrotum (Patient 1). A; Small nests of atypical cells with abundant cytoplasm and round nuclei (H & E, original magnification ×100). B; Scrotal skin showing extensive infiltration of Paget' s cells into epidermis, dermis and skin appendages (×40).

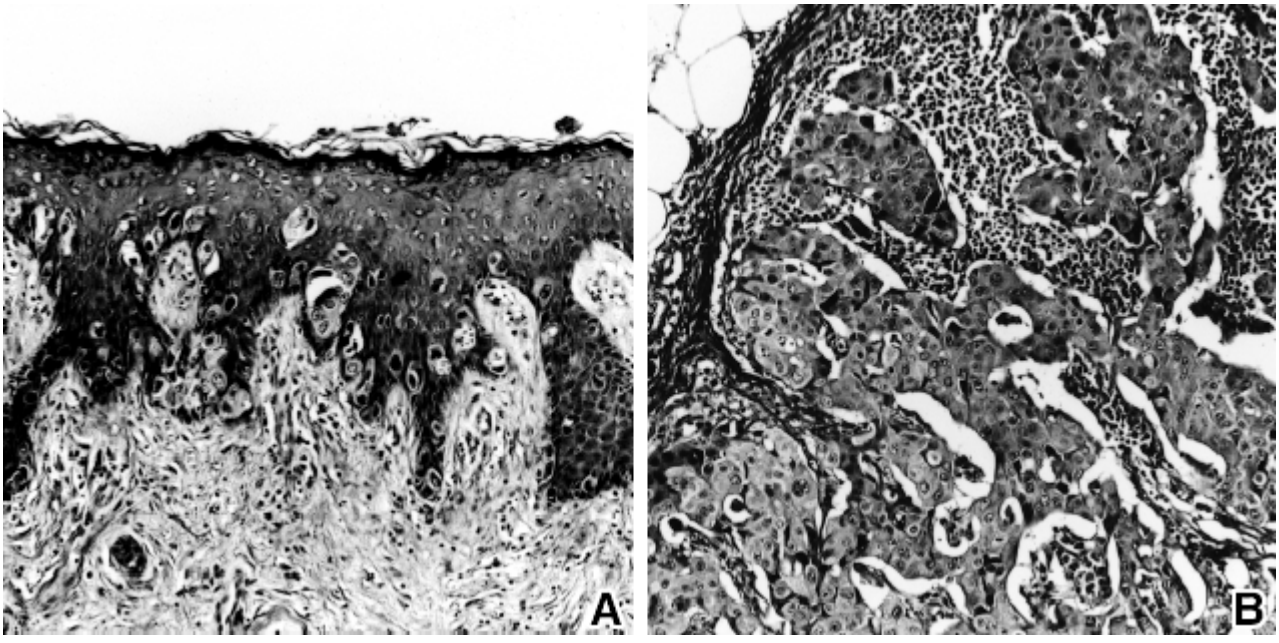

Fig. 2. Extramammary Paget's disease involving the scrotum with systemic metastasis (Patient 2) (H & E, original magnification ×100). A; Pagetoid spread of tumor cells in the epidermis. B; Infiltration of tumor cells forming nests in lymph node.

right inguinal reddish plaque and ulceration with exudative discharge for three years. He also complained of swelling in both legs and scrotum for one month. The skin lesion was confirmed as infiltrative EMPD which invaded enlarged inguinal lymph nodes (Fig. 2). It also included malignant tumor cells, probably from the apocrine gland, infiltrating epidermis and dermis along the hair follicles. Abdominopelvic MRI showed multiple metastatic nodules in the liver (Fig. 3) and enlarged paraaortic lymph nodes. Endoscopic evaluation for gastrointestinal or urinary tract revealed no evidence of

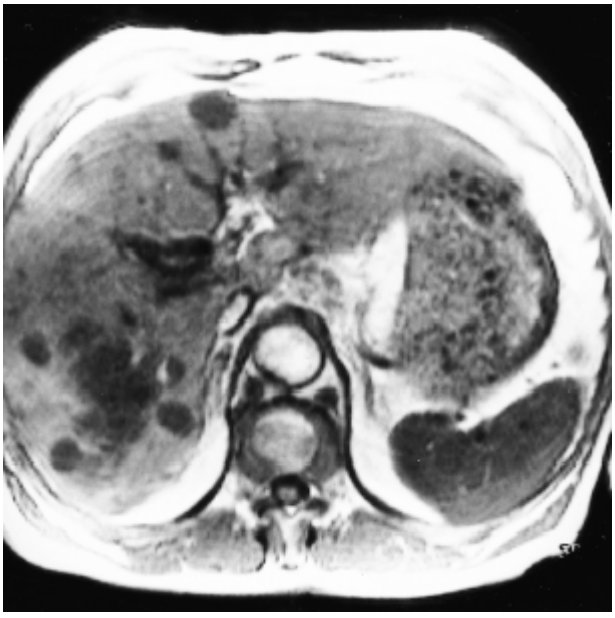

Fig. 3. Multiple hepatic metastases of EMPD in patient 2. Gradient-echo T1-weighted MRI showing multiple lesion of low intensity in both lobes of the liver.

malignancy. Aspiration cytology from the hepatic nodule also revealed similar malignant tumor cells found in the scrotal lesion. Serum CEA level was elevated to 60.2 ng/mL (normal value, up to 6 ng/mL). Palliative excision at the scrotal lesion with split-thickness skin graft was made due to painful ulceration. The cells were positive for PAS stain and negative for alcian blue stain. The immune staining for lower-molecular-weight cytokeratin and CEA were positive, but it was negative for S-100 protein. The patient suffered from sustained fever probably caused by systemic metastases and died 2 months later.

DISCUSSION

EMPD usually occurs in sites with profuse apocrine glands, such as anogenital region, axilla, eyelids, scalp, and buttocks of both sexes (1, 4). It is known to be more common in patients over 50 years of age. Although it is more frequently seen in female than in male Caucasians (2), it seems to show absolute male-predominance in Asians (5) as all cases in this report are male Koreans. EMPD at scrotum was first described by Croker in the year 1888 (6) and it has been reported as a common site in male patients (5, 7, 8). Lesions can not easily differentiate EMPD from other eczematous lesions and it also presents diverse clinical feature from asymptomatic to symptomatic, such as pruritic, burning, or painful (1) as shown in this report. Several months or years of local treatment was used unsuccessfully until the lesion was confirmed by a biopsy (2).

In most cases, EMPD can be confirmed by the presence of Paget's cells on routine hematoxylin-eosin staining (H-E) or further clarification by additional techniques using alcian blue or PAS stain (2). All cases in this report were confirmed by H-E and positive staining for PAS stain. Other sophisticated immunohistochemical staining, such as lower-molecular-weight cytokeratin, gross cystic disease fluid protein (GCDFP-15), S-100 protein, and CEA may sometimes be needed in differentiating from its imitators, such as Bowen's disease, superficial spreading malignant melanoma, etc (1, 9, 10).

The origin of the Paget's cells and EMPD are not exactly known. They may arise multifocally from the epidermis (9) or adnexal epithelium (2). Paget's cells in the epidermis are assumed to be carcinomatous transformations of pluripotential cells (1) or intraepidermal metastasis of a sweat gland adenocarcinoma (11, 12). Although there has not been any conclusive evidence showing the exact pathogenesis of EMPD, two theories may be likely based on the clinical observation of infiltrative growth and recurrence. A genetic basis using oncogenes or oncoproteins such as C-erbB-2 may give further insight into the pathogenesis of EMPD (13).

Although excised specimens did not reveal infiltration of Paget's cells on multiple marginal sections, local recurrence was experienced in three cases of curative excision. Local recurrence has been reported in around 40-50% of cases with equivalent rate of positive margin after surgical excision (8, 14). However, it has also been reported in many cases with tumor-negative margin, suggesting the possibility of the skipped tumor foci from either multifocal origin or intraepidermal metastasis. There are several trials evaluating enhanced lesional demarcation by preoperative use of topical 5-fluorouracil or visualization by fluorescence with limited results (15, 17). Until a tool to visualize the whole Paget's lesion becomes available, pre-excisional mapping of the lesion with multiple punch biopsies (18, 19) can only be warranted to cope with the multifocal presentation of EMPD.

Malignant behavior of EMPD seems to be inherent regardless of extent of primary lesion. Jones et al. (20) suggested a variant of epidermal adenocarcinoma as the most common form of EMPD that extended into adnexae, dermis and lymph nodes in their review of 55 cases. Among more than 20 cases of EMPD reported in the Korean literature, only a few cases presented aggressive behavior of the lymph node or distant metastasis (21, 22). Two cases in our report also presented fulminant progression unrelated with extent of primary EMPD. The incidence of concurrent and metachronous adnexal tumor is as high as 27-38% (3, 8, 13). Metastatic spreading beyond regional lymph nodes is rare and a few case reports showed metastasis in the liver, lung, and bone (23-25). EMPD may be even regarded as a cutaneous marker of internal malignancy because it tends to combine a vari-

ety of internal malignancies (2, 3, 5, 8, 24). The incidence or site of internal malignancy seems to be more or less associated with the primary site of EMPD and anorectal malignancy being the most common (1, 5, 8, 13, 19).

Wide local excision including sufficient free margin is accepted as a preferred surgical treatment in most institutions (4, 5, 18, 19, 24). Mohs micrographic surgery or carbon dioxide laser treatment can be efficient alternatives to radical excision with the advantage of maximal tissue sparing of the critical anatomical site (17). Lymph nodes dissection may be performed if they are clinically involved and prophylactic dissection is not recommended. Although radiotherapy produces a successful outcome in several small cases of EMPD (8), it may be reasonable to reserve such treatment for the surgically unfit or adjuvant purposes after curative surgery. Combination of chemotherapy utilizing 5-fluorouracil and mitomycin C may be considered in cases of inadequately excised or remnant microscopic lesion (14) and their efficacy remains to be proven by prolonged follow-up and wide experience. Although there has been a limited number of reports about the prognosis of EMPD with adenocarcinoma, they generally showed a high mortality rates up to 50% irrespective of the site (3, 19). Moreover, the cases with pulmonary or liver metastasis died within 1 year after diagnosis (23, 24).

Two cases of EMPD involving the scrotum accompanied metastasis to lymph nodes and liver. As there is no efficient tool to predict whether one EMPD presents aggressive behavior or not, definitive surgical treatment and continued surveillance are mandatory to decrease intractable cases.

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