

CASE REPORT

Extramammary Paget's Disease of the Scrotum Associated with Hepatocellular Carcinoma

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Extramammary Paget's disease (EMPD) is a rare cutaneous carcinoma of epidermal origin. The diagnosis is frequently delayed, and the disease tends to be associated with an underlying adnexal or internal malignancy. There have been several reports of EMPD associated with carcinoma of the bladder, prostate, kidney, and colon. The association of hepatocellular carcinoma (HCC) with EMPD appears to be exceedingly rare; to our knowledge, it has been reported only once in the English literature. Herein, we report an unusual case of EMPD of the scrotum associated with HCC. EMPD was diagnosed 1 year after the appearance of an erythematous plaque, and HCC was noted 19 months after the diagnosis of EMPD. From our experience and literature review, in patients with nonspecific skin lesions that are unresponsive to conventional treatment, EMPD should be considered and skin biopsy performed. Long-term follow-up is needed to watch for the appearance of adnexal carcinoma or internal malignancy. [*J Chin Med Assoc* 2009;72(10):542–546]

Key Words: extramammary Paget's disease, hepatocellular carcinoma, scrotum

Introduction

Extramammary Paget's disease (EMPD) accounts for 6.5% of all cases of Paget's disease¹ and is a rare cutaneous carcinoma of epidermal origin and glandular differentiation. It usually occurs in sites containing apocrine glands and can be associated with an underlying adnexal carcinoma or internal malignancy.

There have been several reports of EMPD associated with carcinoma of the bladder,² prostate,^{2,3} kidney,^{2,4} and colon.³ The association of hepatocellular carcinoma (HCC) with EMPD appears to be exceedingly rare; to our knowledge, it has been reported only once in the English-language literature.⁵

Herein, we report an unusual case of EMPD associated with HCC and review the literature on this rare disease entity.

Case Report

A 60-year-old man with scrotal Paget's disease was admitted because of neck and bilateral shoulder pain for 1 month.

Thirty-one months before admission, the patient had found an erythematous plaque on his right scrotum. Despite conventional treatment, the lesion extended to the whole scrotum, penile phallus, right thigh, and perineal and suprapubic regions over the course of the following year (Figure 1). Nineteen months before admission, the patient underwent a wide excision of the lesion and rotational flap repair. Histological examination of the resected specimen led to the diagnosis of EMPD (Figure 2). Laboratory examination revealed normal levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT); the patient did not



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Figure 1. Erythematous plaques over the scrotum, penile phallus, right thigh, and perineum and suprapubic regions. A tumor mass over the right scrotum was also noted.

know whether he had had previous hepatitis infection. He also received gastroscopy, colonofibroscopy and intravenous pyelography plus post-voiding examinations; the results were normal. He was then regularly followed-up at the outpatient department.

On this current admission, physical examination revealed no local tumor recurrence. Laboratory examinations revealed serum AST level of 79.83 U/L, serum ALT level of 62.72 U/L, and positive HBsAg. Serum carcinoembryonic antigen level was normal, but the α -fetoprotein level was 271.26 ng/mL. C-spine radiography showed osteolytic change, especially at C5–7 (Figure 3). Magnetic resonance imaging of the spine disclosed multiple signal abnormality mass lesions over the C-spine and T-spine vertebrae, and narrowing of the spinal canal (Figure 4). Bony metastases were established.

Abdominal computed tomography revealed an ill-defined tumor mass about 5.0 × 5.7 cm in size in S6 of the liver (Figure 5). Sonoguided needle biopsy was

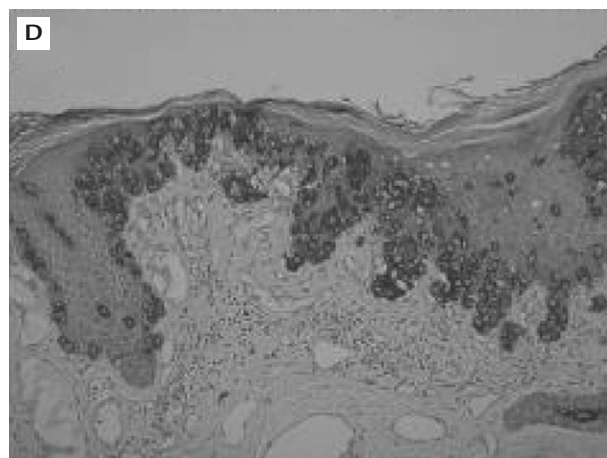
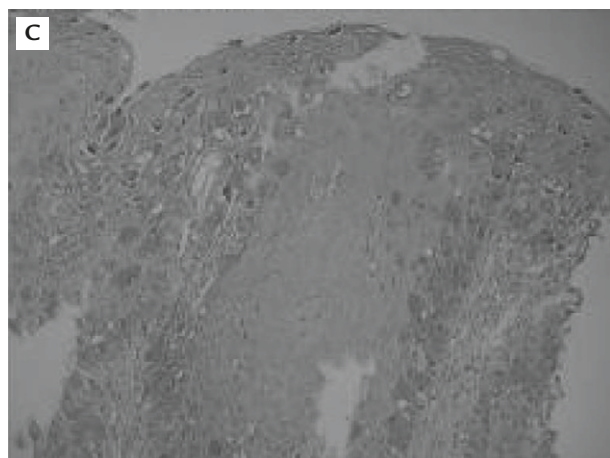
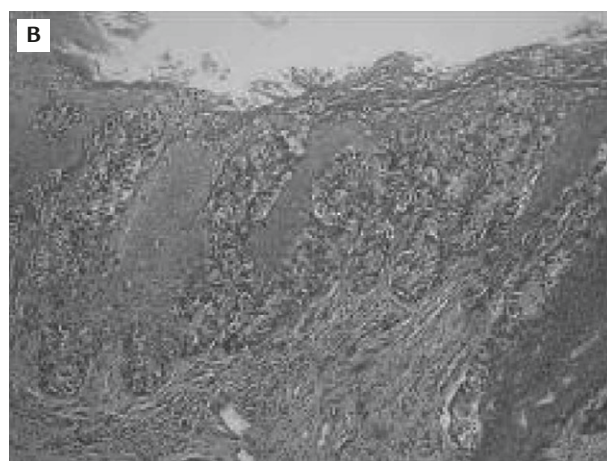
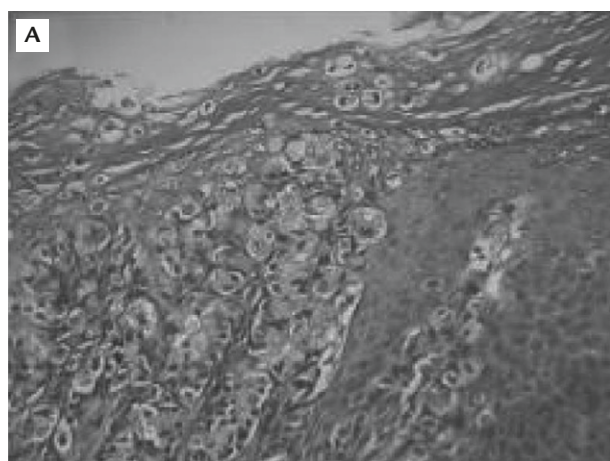


Figure 2. Histological findings of extramammary Paget's disease. (A) The epidermis was diffusely infiltrated by Paget cells, singly or in clusters (hematoxylin & eosin, 400 \times). (B) The cells were large, with abundant pink-staining cytoplasm and vesicular nuclei with prominent eosinophilic nucleoli (hematoxylin & eosin, 200 \times). (C) The cells stained positive for mucicarmine (100 \times). (D) The cells revealed strongly positive reactions to epithelial membrane antigen (200 \times).



Figure 3. Radiography shows osteolytic change in the C-spine (arrows), in favor of metastatic lesions.

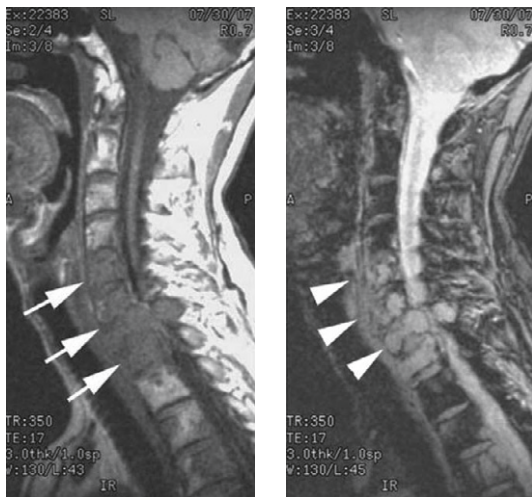


Figure 4. Magnetic resonance imaging shows multiple signal abnormality mass lesions over the C-spine and T-spine, with low signal intensity on T1-weighted imaging (arrows) and high signal intensity on gradient echo imaging (arrowheads), causing narrowing of the spinal canal and cord compression, especially at the C7 and T1 vertebral level. Metastatic malignancy was indicated.

performed and HCC was diagnosed (Figure 6). The clinical condition of the patient deteriorated rapidly, and he died 1 month later.

Discussion

Paget's disease, usually occurring in sites containing apocrine glands, is an intraepidermal adenocarcinoma of the nipple and/or areola of the breast (mammary Paget's disease; MPD) or in extramammary body zones such as the anogenital and perineal skin and the axilla (EMPD).



Figure 5. Abdominal computed tomography reveals an ill-defined tumor mass (arrow) with peripheral irregular contrast enhancement (arrowhead) in S6 of the liver. The differential diagnoses included primary hepatic malignancy and metastasis.

EMPD primarily affects elderly people² between 65 and 70 years of age; 90% of cases occur in people older than 50 years.^{6,7} It is seen more frequently in females than males, and occurs predominantly in the vulva, followed by the perianal region.² The scrotum is an uncommon site for the presentation of EMPD, and only small series or a few case reports have been reported. The typical appearance of EMPD is a single or multifocal erythematous and eczematoid plaque. Pruritus is the most common symptom. It is often mistaken for an inflammatory or infective condition, and the diagnosis is often delayed by an average of 2–3 years after disease onset.³

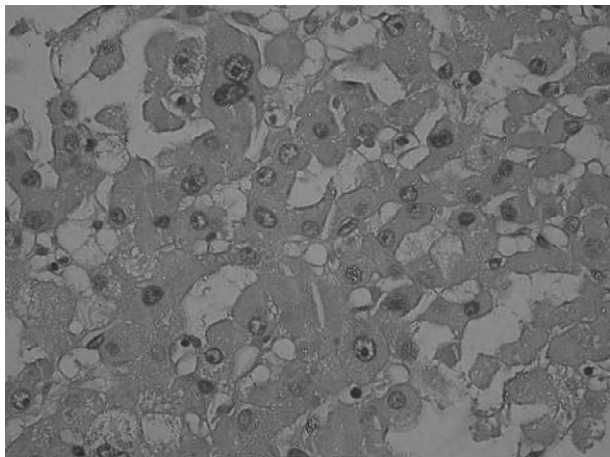


Figure 6. The tumor cells of the hepatocellular carcinoma have eosinophilic cytoplasm, distinct cell borders, and prominent nuclei and nucleoli. A trabecular pattern of growth was also noted (hematoxylin & eosin, 400 \times).

MPD, first described by James Paget in 1874,⁸ is, as a rule, associated with underlying breast cancer. EMPD, first described by Crocker in 1889,⁹ shares many common clinicopathological features with MPD, whereas association of EMPD with underlying malignancies occurs much less frequently.

Because of the rarity of EMPD, most reports consist of individual case studies or small series. In a retrospective analysis of 197 cases of EMPD reported in the English literature from 1962 to 1982, Chanda² found that 46 (24%) cases had an underlying adnexal carcinoma. The incidence of underlying adnexal carcinoma has been reported to vary, and it depends on the anatomic sites affected. Reported frequencies are from 14% to 20% in patients with vulvar EMPD,^{10,11} and from 50% to 86% in perianal EMPD.¹² The incidence of underlying adnexal carcinoma in penoscrotal EMPD is exceedingly rare, and only a few studies have been reported. Lai et al³ reported that 7 (21.2%) of 33 patients had underlying adnexal carcinoma. No patient had underlying adnexal carcinoma in Wada and Urabe's study,¹³ but some did in Yang et al's report.⁴

The question of the relationship of EMPD to internal malignancy is difficult. There seems to be an impression in the literature that EMPD is associated with underlying internal malignancy and occurs concurrently with or before the internal malignancy. Therefore, there is a suggestion that EMPD may be a cutaneous marker for internal malignancy.^{2,14,15} In Chanda's study,² the location of the underlying internal malignancy appeared to be closely related to the location of the EMPD, that is, a vulvar location was associated with malignancy of the female genitourinary system. A perianal location was associated with

adenocarcinoma of the digestive system, and a penoscrotal location with genitourinary malignancy.

In Chanda's analysis,² 4 (22.2%) of 18 patients with penoscrotal EMPD had internal malignancies (1 bladder carcinoma, 1 renal cell carcinoma, 2 prostate carcinomas). Lai et al³ reported that 3 (9.1%) of 33 patients with penoscrotal EMPD had associated internal malignancy (1 rectosigmoid carcinoma, 2 prostate carcinomas). Yang et al⁴ reported that 1 (2.8%) of 36 patients with penoscrotal EMPD had internal malignancy (renal cell carcinoma). None of the 22 patients with penoscrotal EMPD had an associated internal malignancy in Chang et al's study.¹⁶

However, in our case, the location of the underlying malignancy was not closely related to the genitourinary location of the penoscrotal EMPD. The same findings were reported by Lai et al,³ in that 1 patient with penoscrotal EMPD had an associated rectosigmoid carcinoma, and Saitou et al⁵ reported that 1 patient with scrotal EMPD had an associated underlying HCC. Therefore, it is suggested that in patients with penoscrotal EMPD, not only the genitourinary system but also the digestive system should be examined for the possibility of associated internal malignancy.

Based on recent reports of penoscrotal EMPD,^{3,16-18} the prevalence of internal malignancy is 8.9% in Oriental males.¹⁹ It is tempting to speculate that the incidence of penoscrotal EMPD is high in Asians, but the incidence of associated internal malignancy in Asians seems to be lower than in Caucasians.^{3,16} The precise pathogenesis of EMPD remains unknown, and the mechanism of EMPD associated with underlying malignancies is also unclear; however, any molecular factors could be related. Our patient had HBV infection, and the patient reported by Saitou et al⁵ had HCV infection. It is possible that HBV or HCV influences the DNA and leads to carcinogenesis of mucosa cells as well as hepatocytes, resulting in the development of EMPD and HCC; however, more studies are needed to elucidate the mechanisms involved.^{5,20,21}

Although we did not know the hepatitis status of our patient before the diagnosis of HCC, based on the fast tumor growth rate of HCC (with a doubling time that ranges from 29 to 398 days, and an arithmetic mean of 136 days),²² the time sequence of HCC after EMPD is reasonable. This further confirms the literature findings that EMPD could occur before internal malignancy and may be a cutaneous marker for internal malignancy.^{2,14,15}

The usual treatment of EMPD is surgical. However, due to the multicentricity and ill-defined disease margins, even extensive resections are complicated by a high local recurrence rate.²³⁻²⁵ The level of invasion

and whether or not there are multiple lymph node metastases are important prognostic factors in EMPD.²⁶ Owing to invasive EMPD being frequently associated with regional lymph node metastasis and having a poor prognosis, intraoperative frozen section to reduce the risk of incomplete resection and thus to reduce the rate of recurrence is recommended.^{4,19}

In conclusion, EMPD is an uncommon neoplasm of apocrine gland-bearing skin. The diagnosis is frequently delayed. EMPD has a tendency to be associated with underlying adnexal or internal malignancy. In patients with nonspecific skin lesions that are unresponsive to conventional treatment, EMPD should be considered and skin biopsy performed. Long-term follow-up is needed to watch for the appearance of adnexal carcinoma or internal malignancy.

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