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Case Report

Clinicopathologic characteristics of extramammary Paget's disease of the scrotum associated with sweat gland adenocarcinoma—a clinical retrospective study

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Abstract

Extramammary Paget's disease of the scrotum with sweat gland adenocarcinoma is a rare malignant tumor. This study aims to summarize the clinicopathologic characteristics related to the prognosis of scrotal Paget's disease with underlying sweat gland adenocarcinoma. Clinical datum of four patients with scrotal Paget's disease with sweat gland carcinoma, treated in Beijing Chao-Yang Hospital from 2002 to 2009 was analyzed, and a literature review was conducted. The typical manifestation of scrotal Paget's disease with sweat gland carcinoma was eczematoid-like skin lesions. All patients underwent primary lesion resection plus inguinal lymphadenectomy. Three patients had inguinal lymph metastasis. One of them developed distant metastases in bone and bone marrow and died of metastatic carcinoma. The dead patient had higher serum carcinoma embryonic antigen (CEA) level, Her-2 overexpression and shorter disease course than the other patients. The other patients were observed for at least 3 years, and lived without tumor. Scrotal Paget's disease with sweat gland adenocarcinoma may be prone to inguinal lymph node and bone metastasis. Serum CEA level, Her-2 overexpression, dermis and lymphovascular invasion may be associated with the prognosis of scrotal Paget's disease with sweat gland adenocarcinoma. The primary lesion resection plus inguinal lymphadenectomy is the major treatment for scrotal Paget's disease with sweat gland adenocarcinoma. The effect of combination chemotherapy in the treatment of metastatic extramammary Paget's disease remains to be proven by prolonged follow-up and wide experience.

Keywords: Bone and bone marrow metastasis; Extramammary Paget's disease; Prognosis; Scrotum; Sweat gland adenocarcinoma

1. Introduction

Most often, Paget's disease occurs around the nipple as a consequence of the intraepidermal spread of an underlying mammary carcinoma. Paget's disease also occurs at extramammary sites, mostly in the genitoanal skin in women, whereas genitoanal extramammary Paget's disease (EMPD) in men is rare, and only small series of case reports have been reported (Table 1). The tumor cells in Paget's disease have abundant pale cytoplasm and large pleomorphic nuclei and contain mucopolysaccharides which are positive with PAS and alcian blue methods in about 60% of cases. The origin of these cells is unclear; most authors assume a relationship to apocrine glands because they occur in apocrine gland-bearing skin[1] and most but not all Paget cells stain positively for GCDFP-15, a marker of apocrine cells.[2]

About 25% of all cases have an underlying cutaneous adnexal carcinoma, mostly of apocrine type. A further 10% of patients have an internal carcinoma. EMPD of the scrotum with sweat gland adenocarcinoma is extremely rare.[3] We analyze the clinicopathologic features of four scrotal Paget's disease patients with sweat gland adenocarcinoma.

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Table 1
Summary of the literature review

Author	Publication date (year)	Article type	Topic	No of cases	Ref.
Zhang et al.	2006	Retrospective study	Pathology	23	10
Pascual et al.	2008	Case report	Scrotal EMPD	1	7
Aldewereld & Blanken	2009	Case report	Scrotal EMPD	1	1
Tu et al.	2009	Case reports and review	Scrotal EMPD with sweat gland adenocarcinoma	6	3
Plaza et al.	2009	Retrospective study	Skin neoplasms	47	8
Zhu et al.	2009	Retrospective study	Penoscrotal EMPD	43	9
Takahagi et al.	2009	Case report	Metastatic EMPD/targeted treatment	1	12
Zhang et al.	2010	Case reports and review	Scrotal EMPD	25	4

EMPD = extramammary Paget's disease.

2. Case report

Four male patients were initially treated for irritant and allergic contact dermatitis with topical creams in Beijing Chao-Yang Hospital. The median age was 61.0 years (range, 59.0–68.0 years). All the patients presented an oval-shaped, eczematoid, non-scaly, tender and erythematous lesion with surrounding clear uplift belts on the scrotum with a diameter of approx 3–5 cm. Results of physical examination were normal except for skin findings. There was no evidence of malignancy on abdominal and chest computed tomography examination. Serum CEA level was normal in three cases. Accompanying progression of the disease, three patients had palpable enlarged inguinal lymph nodes. All patients underwent a wide resection of the primary lesion plus inguinal lymphadenectomy. The three patients diagnosed with inguinal lymph node metastasis were treated with postoperative radiotherapy and administered under 5-fluorouracil-based adjuvant chemotherapy (Table 2). Histological examination of the resected specimen in the four cases led to the diagnosis of scrotal Paget's disease with sweat gland adenocarcinoma (Fig. 1). Additionally, immunohistologic staining revealed positive reactions to CEA, AE1/AE3, CAM5.2, Her-2 and strongly positive reaction to the apocrine marker GCDFP-15. Sections of inguinal lymph nodes showed metastatic adenocarcinoma in three cases. Among the three patients, one also had involvement in the dermis of the scrotum and groin. The patient was diagnosed with bone and bone marrow metastases by bone scan, bone marrow biopsy (Fig. 2) and morphocytology (Fig. 3) after operation, accompanied with elevated serum CEA, T-PSA, CA125, CA199 and CA72.4 level. Immunohistologic staining identified metastatic adenocarcinoma with CK8/18 (+), CEA (+), EMA (+), 34BE12 (+), CK5/6 (−), P63 (−) and PAS (+). The patient received one-cycle chemotherapy of NP regimen (vinorelbine 40 mg on Day 1 + cisplatin 40 mg on Days 2–4). The most serious toxicity reaction was bone marrow suppression of grade Ⅲ. The patient died with epistaxis and subcutaneous bleeding eventually. The overall survival time was 6 months. Other patients were observed for at least 3 years, and lived without tumor.

3. Discussion

Most of patients with scrotal Paget's disease are middle-aged or elderly people (>50 years old). The initial manifestation of the disease includes redness, roughness and itchiness of the skin lesion. Metastasis is reportedly less common.[4]

Table 2
Details of the four patients of scrotal Paget's disease with sweat gland adenocarcinoma

Clinical data	Case 1	Case 2	Case 3	Case 4
Gender	Male	Male	Male	Male
Age (yr)	59	60	62	68
Lesion diameter (cm)	5.00	3.50	3.50	3.00
Serum CEA level (normal ≤3.40 ng/mL)	263.70	1.92	2.41	2.04
Lymph node status (metastasis/dissection)	2/3	1/3	0/2	1/2
Primary treatment	Surgery	Surgery plus adjuvant chemotherapy and radiotherapy	Surgery plus chemotherapy	Surgery plus adjuvant chemotherapy and radiotherapy
Relapse/metastasis	Bone and bone marrow metastasis	No	No	No
Immunohistochemistry				
CEA	+	+	+	+
AE1/AE3	+	No	+	No
CAM5.2	+	+	No	+
GCDFP−15	+	+	+	+
Her-2	+++	+	+	±

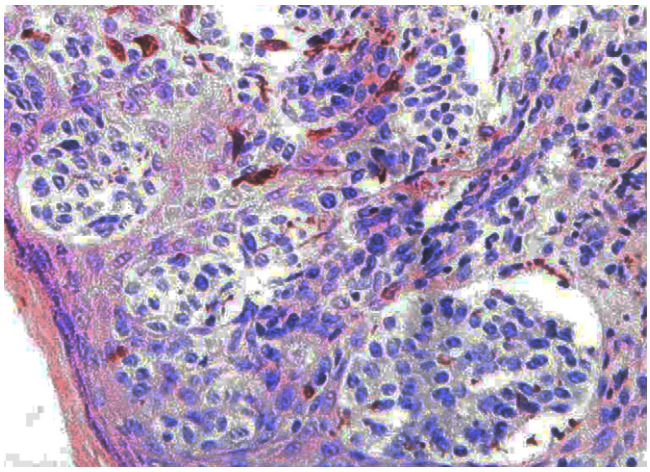

Fig. 1. Histopathology of scrotal lesions (tumor cells with bright cytoplasm, heteromorphic nuclear, thick nuclear membrane and marked nuclei were identified in epidermis 400×).

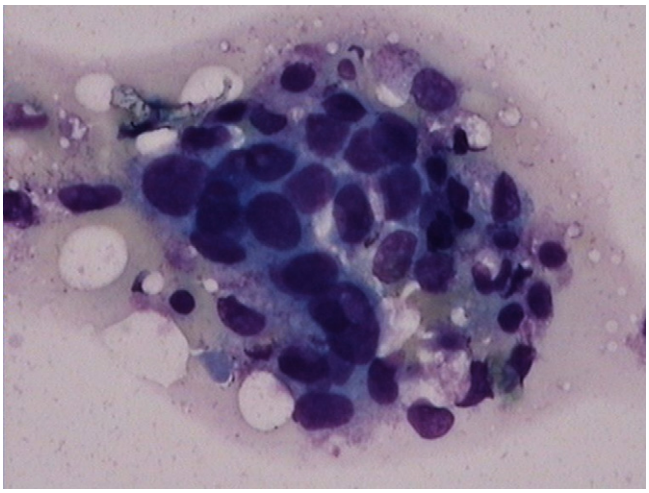

Fig. 3. Morphocytology of bone marrow (tumor cells were seen in bone marrow 1000×).

Sweat gland adenocarcinoma is rare and can be derived from apocrine and eccrine glands, sweat ducts, or secretory portion. The lesion grows slowly and is prone to recurrence after resection. The lymph node is commonly affected. The carcinoma expands regionally in early stage, and hematogenous spread or bone metastasis may occur subsequently.[5] The relationship between them has drawn much attention.

Whether the EMPD Paget cells are from adenocarcinoma cells or epidermal keratinocytes is still under debate. Immunohistochemistry revealed that Paget cells share similar structure with those of the apocrine gland. Accordingly, some scholars proposed that sweat gland adenocarcinoma and EMPD might originate from similar tissue, and the former was the development and metastatic form of EMPD, whereas EMPD was an early metastatic form of sweat gland adenocarcinoma. Other scholars considered that EMPD was a special type of skin *in situ* carcinoma and the cancer cells were derived from pluripotent dermocytes, whereby spreading to the underlying breast gland, hair follicle, sweat gland and apocrine ducts.[6] Recent studies of perianal and vulvar EMPD described distinct immunohistochemical subtypes, termed as cutaneous and endodermal. Cutaneous EMPD was characteristically positive for cytokeratin (CK)7, negative for CK20, and positive for gross cystic disease fluid protein (GCDFP) 15+, whereas endodermal EMPD showed a CK7+, CK20+, GCDFP-15 phenotype.[7] In the current study, the immunohistochemistry of four patients of scrotal Paget's disease with sweat gland adenocarcinoma showed CEA+, GCDFP-15+, Her-2 ±∼+++. We suggest sweat gland adenocarcinoma was the development and metastasis of scrotal Paget's disease.

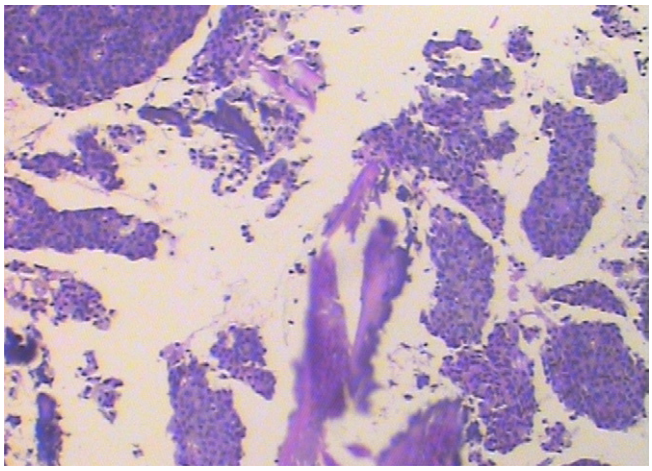

Fig. 2. Histopathology of bone marrow (adenoid cancer cells were seen in the bone marrow biopsy specimen 400×).

Her-2 overexpression implied a more aggressive behavior in breast cancer. Plaza[8] found the overall Her-2/neu expression was 31.9% in EMPD with and without underlying malignancy by immunohistochemistry. Zhu et al.[9] indicated serum CEA level can be a useful biomarker for monitoring disease course. Dermal or deeper invasion, lymphovascular embolization and negative expression of E-cadherin were important pathological predictors of metastasis. As has been found previously in metastatic EMPD, the dead patient had dermis and lymphovascular invasion, higher serum CEA level, Her-2 overexpression and shorter disease courses than the other patients.

The management of scrotal Paget's disease with sweat gland carcinoma is primarily surgical operation. Unfortunately, there is a high rate of recurrence, up to 50% depending on the method of surgery, because the disease often extends beyond the clinically visible margins.[10,11] However, the role of chemotherapy in metastatic EMPD with sweat gland carcinoma is uncertain. Zhu et al.[9] administered 5-fluorouracil- or docetaxel-based chemotherapy to metastatic EMPD patients, CR 20%, RR 50%, PD50%, and 2-year overall survival rate was 48%. Takahagi et al.[12] treated a 75-year-old patient of HER2-positive metastatic scrotal Paget's disease with paclitaxel and trastuzumab. Histopathological examination showed that most of HER2-positive tumor cells diminished during the regimen. In our study, all the present cohort patients had received surgical operation. The resection extension included

skin 2–3 cm off the primary lesion and the subcutaneous adipose tissues. Three patients without recurrence had received postoperative radiotherapy and chemotherapy, the dead patient underwent one course of palliative chemotherapy of NP regimen. The overall survival time was 6 months, and the major toxicities were grade III neutropenia and thrombocytopenia, respectively.

In conclusion, serum CEA level, Her-2 overexpression, dermis and lymphovascular invasion may be associated with the prognosis of scrotal Paget's disease with sweat gland adenocarcinoma. Combination chemotherapy may be considered in cases of inadequately excised microscopic lesion and its efficacy remains to be proven by prolonged follow-up and wide experience in metastatic scrotal Paget's disease with sweat gland adenocarcinoma.

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