• Clinical Research •

Extramammary Paget’s disease of the scrotum with underlying sweat gland adenocarcinoma: a report of six cases with literature review

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[Abstract] Background and Objective: Extramammary Paget’s disease (EMPD) of the scrotum with sweat gland adenocarcinoma is a rare malignant tumor. This study was to summarize the clinicopathologic characteristics of scrotum Paget’s disease with underlying sweat gland adenocarcinoma, and analyze the treatment outcome. Methods: Clinical data of six scrotum Paget’s disease patients with sweat gland adenocarcinoma, treated in Sun Yat-sen University Cancer Center from 1964 to 2004, were analyzed with literature review. Results: The typical manifestation of scrotum Paget’s disease with sweat gland adenocarcinoma was eczematoid-like skin changes. All patients underwent primary lesion resection plus uni-inguinal lymphadenectomy, one patient underwent rectus abdominis pedicle flap transplantation. Three patients died of tumor at 15, 26, 38 months after operation, respectively. Other three patients were followed up for 48, 50, 55 months, respectively, and were alive without tumor. Conclusion: The primary lesion resection plus uni-inguinal lymphadenectomy is the major treatment for scrotum Paget’s disease with underlying sweat gland adenocarcinoma.

Key words: Paget’s disease, scrotum, sweat gland neoplasm, surgical operation, efficacy

In 1847, Paget firstly reported breast Pagets disease. It is mostly occurred in the mammary and is characterized histologically by the presence of Pagets cells, with large, transparent cytoplasm, in epidermis. Extramammary Pagets disease (EMPD) is rare. EMPD of the scrotum with sweat gland adenocarcinoma is extremely rare. Up to now, only 3 cases of this disease have been reported in literature. The development sequence of scrotum Pagets disease and sweat gland adenocarcinoma, or whether they originate from the same blastodermic disc remains unclear. We analyzed the clinicopathologic features of six scrotum Pagets disease patients with sweat gland adenocarcinoma.

Materials and Methods

Clinical data. From 1964 to April 2004, six patients were initially treated for scrotum Pagets disease with sweat gland adenocarcinoma at Cancer Center of Sun Yat-sen University.
diagnoses were confirmed by pathology. The median age at presentation was 62.5 years (range, 58 to 72 years). The mean duration of disease was 18 months (range, 8 to 30 months). Most patients initially presented rash or erythematous lesions with surrounding clear uplift belts, and had pruritus or thermalgia on the scrotum. Many patients were first treated with topical creams before a biopsy was performed. The lesions developed with epidermis thickening. Small papules or vesicles appeared, with exudate, erosion or infection after scratching. New lesions appeared around old ones and merged, sometimes, accompanied with skin ulcer and invaded adjacent organs. In this study, three patients had involvement of the epidermis of the penis and groin; two had involvement of the corpus cavernosum, perineum, loin, groin and femoral medial skin when the lesions progressively penetrate through the basal membrane; all had palpable inguinal lymphadenopathy; One had retroperitoneal lymph node metastases.

Treatment methods. All patients underwent primary lesion resection plus ipsilateral inguinal lymphadenectomy. Five patients with lesions of less than 5 cm × 5 cm underwent local excision. One patient with a lesion of 15 cm × 13 cm × 18 cm underwent resection of 19 cm × 17 cm × 21 cm. This patient also had an intumescent lymph node of 5 cm × 3 cm × 3 cm in the right groin and a hard mass of 5 cm × 3 cm × 1.5 cm in the penile base, therefore, he underwent excision of the penis, scrotum and involved testis, as well as urinary meatus reconstruction with a rectus abdominis pedicle flap transplantation. Two patients were treated with postoperative radiotherapy and topical application of 5-fluorouracil (5-FU) cream.

Results

Pathologic findings. All cases were diagnosed as scrotum Paget’s disease with sweat gland adenocarcinoma by pathology. Microscopically, large cells with bright cytoplasm, heteromorphic nuclear, thick nuclear membrane and marked nuclei were identified in epidermis, and there were inflammatory cell infiltration in superficial dermis, which is consistent with Paget’s disease. Streak-like and adenoid cancer tissues were seen in the subcutaneous adipose layer (four cases) and corpus cavernosum (two cases), and there are transitions from cancer tissue to epidermis and sweat duct. The diagnosis was scrotum Paget’s disease with sweat gland adenocarcinoma that infiltrated to the subcutaneous adipose layer and root of corpus cavernosum. Sections of inguinal lymph nodes showed metastatic adenocarcinoma. Patients with skin flap metastasis were pathologically proven to have grey-white mass sections at the root of penis, and there were Streak-like and adenoid cancer tissues in the fibrous tissues at the root of penis. There are transitions from cancer tissue to epidermis and sweat duct, involving urethra and corpus cavernosum. The testis tissue sent for pathological examination showed no cancerous tissues. Immunohistochemistry was performed in two cases, showing CK (+), CEA (+), S100 (-).

Follow-up results. The median follow-up was 35.5 months (range, 15-55 months). Three patients died of tumor at 15, 26 and 38 months after operation, respectively. No patient developed tumors in other organs. One had stenosis at the reconstruction site at 5 months after operation. Other three patients were followed up for 48, 50 and 55 months, respectively, and were alive without tumor.

Discussion

In 1889, Crocker reported the first Pagets disease involving penis and scrotum. And subsequent literatures reported that other sites of the body could also be involved, especially those with abundant apocrine glands, including perineum, perianal region, axillary and popliteal fossa. This entity is called extramammary Paget’s disease (EMPD). Scrotum Paget’s disease, also termed scrotal inflammatory cancer or eczematoide carcinoma, is a rare type of EMPD. There are only 100 cases reported in English literatures, and most of them were middle aged or aged people (>50 years old). The disease progresses slowly. It is commonly misdiagnosed as scrotal eczema or
other dermatosis for a long period of time and treated repeatedly. The initial presentations of the disease include redness, roughness and itching of the skin lesion. There exhibited exudates and vesicular rashes when the lesion is scratched, followed by incrustation and desquamation. The symptom relapsed repeatedly and the skin thickened, presenting orange-peel like lesion, inflammatory nodule, proliferative erosion and ulcerations. The metastasis is reportedly less common, and lesions are primarily limited in the epidermis, rarely infiltrate deeply to the organs in the scrotum, and distant metastasis is rare. Differentials of scrotal Pagets disease include penis Bowens disease, Queyrat’s erythroplasia and melanoma. The final confirmation needs pathological examination. The treatment is extensive resection of the lesion, including skins 2 cm off the margins of macroscopic lesion, and subcutaneous tissues deep to the perididymis. Inguinal lymph node is the major metastatic site, while preventive lymph node resection is controversial. The radiotherapy and chemotherapy are ineffective with considerable side effects, and therefore are not recommended.

EMPD is accompanied by malignant tumor of surrounding tissues or visceral organs, including rectum, lung, prostate, kidney and urethra. The incidences of malignant tumor in other organs were reportedly ranged between 4.5% and 86% in different follow up periods. Other literature reported that about 35% EMPD Pagets disease affected accessory organs, and 27% affected visceral organs, including rectum and prostate. Moreover, there are reports showing positive prostate specific antigen in scrotal Pagets disease, which supports the proposal that it is the visceral or epidermis carcinoma that spread to dermis, resulting in Pagets disease. Whether these presentations represent different subtypes of EMPD remains to be elucidated.1

There are case reports of the EMPD with sweat gland adenocarcinoma, whereas the scrotal Pagets disease with sweat gland adenocarcinoma is much less. The relationships between them have drawn many attentions. 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 at early stage, and hematogenous spread or bone metastasis may occur subsequently.2 Castelli summarized seven cases of axillary Pagets disease with sweat gland adenocarcinoma.3 In Chinese literature, Chen-Xiaoduan has reported one case of vulvar Pagets disease with sweat gland adenocarcinoma.4 Up to date, there are only three cases of scrotal Paget’s disease with sweat gland adenocarcinoma, 56 aged between 70 and 77. One case had concomitant systemic metastasis involving inguinal lymph nodes, retroperitoneal lymph nodes and lung, and another case was confirmed pathologically to have penis involved. Liu-Yujiang et al reported one case of scrotal Paget’s disease with sweat gland adenocarcinoma and renal clear cell carcinoma.7 These cases are characterized by ages of more than 60, long disease courses, seeking medical care and misdiagnosed repeatedly, and final diagnosis was made by pathology. The present cohort patients had long disease courses, with inguinal lymph node enlargement. The pathological section revealed sweat gland metastasis. We proposed that sweat gland carcinoma is the development and metastasis of scrotal Paget’s disease.

The relationship between EMPD and sweat gland carcinoma is worthy of further investigations. Generally, breast Paget cells are derived from breast duct cells instead of keratinocytes on the epidermis of papilla. However, whether the EMPD Paget cells are from adenocarcinoma cells or epidermal keratinocytes is still under debate. Xu-Liangzhong et al.8 detected c-erbB-2 gene in EMPD Paget cells and found that Paget cells of EMPD were from adenocarcinoma. EMPD primarily affects the sites that are abundant of apocrine glands, such as axillary, perineum, perianal region and eyelid. The immunohistochemistry revealed that Paget cells share similar structures with apocrine gland. Accordingly, some scholars proposed that sweat gland carcinoma and EMPD might originate from similar tissue, and the former is
the development and metastatic form of EMPD, while EMPD is an early metastatic form of sweat gland carcinoma. Other scholars consider that EMPD is a special type of skin in situ carcinoma and the cancer cells are derived from pluripotent dermocytes, whereby spreading to the underlying breast gland, hair follicle, sweat gland and apocrine ducts. Also there are some scholars consider that EMPD, sweat gland carcinoma and other visceral tumors (rectal cancer, prostate cancer and renal carcinoma) were originated from the same embryonic cells.\(^7\)

The management of scrotal Paget’s disease with sweat gland carcinoma is primarily the surgical operation. The resection extension includes skins 2-3 cm off the primary lesion and the subcutaneous adipose tissues. The lesion is usually extensive, involving medial side of the thigh, inguinal region, penis, pubic and perineum region. Thus, skin resection of large areas is needed. The skin defect can be sutured with loosening. When intraoperative frozen pathological examination revealed lymph node metastasis, lymph node radical resection of the inguinal region should be performed to prevent recurrence. The lymphatic fistula and rupture of the wound resulting from massive skin defect after primary resection and radical lymph node resection are major issues that obsessed surgeons most. Currently, the problem can be solved by modified lymphatic resection and rectus abdominis pedicle flap transplantation. In the present study, one case with large skin defect (measuring 19×17×21 cm) underwent rectus abdominis pedicle flap transplantation to cover the wound. The wound reached stage I healing and no scar contracture was observed. The patient moved freely. The chemotherapy and radiotherapy are limited to the adjuvant therapy for part of patients. Recently, some investigators found that the external application of imiquimod was effective. And radiotherapy is regarded as ineffective. Some researchers have used the photodynamic therapy, but the study is not conclusive due to small sample size, and further investigations are mandatory.\(^9\)

References