CASE REPORT

Primary invasive triple extramammary Paget's disease with regional lymph node metastasis: A case report and review of the literature

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A R T I C L E  I N F O

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A B S T R A C T

Extramammary Paget's disease (EMPD) is a rare intraepidermal carcinoma and predominantly involves apocrine gland-bearing areas such as anogenital regions and axillae. EMPD usually involves a solitary area and, less often, two areas in the same patient (double EMPD). The simultaneous involvement of bilateral axillae and anogenital region, called triple extramammary Paget's disease (TEPD), is an extremely rare subgroup of diseases that has been reported mostly from studies conducted in Japan. Because of its rarity, the clinical course, pathology/immunohistochemical staining features, and prognosis of TEPD are still unclear. Herein, to our knowledge, we present the first case of primary invasive TEPD with regional lymph node metastasis in Taiwan, and review the literature.

Introduction

Extramammary Paget's disease (EMPD) is a rare intraepidermal carcinoma that primarily involves apocrine gland-bearing areas such as vulva, scrotum, and perianal regions as well as axillae. It is subdivided into primary and secondary EMPD based on whether there is an underlying malignancy, such as adenocarcinoma of skin appendage or noncutaneous carcinoma. The majority of primary cases are confined to the epidermis, but the incidence of dermal invasion has been reported to be as high as 18.8%. Dermal invasion is significantly associated with lymph node metastasis, distant metastasis, and poor prognosis.

Primary triple extramammary Paget's disease (TEPD) represents a very rare condition where the simultaneous occurrence of EMPD is noticed over bilateral axillae and the genital region. To our knowledge, case series of TEPD have been mostly reported in Japan, and TEPD in other races is extremely rare. The clinical course and prognosis of this rare disease are still unclear owing to the small number of reported cases and heterogeneous entities.

Herein, we present a case with primary invasive TEPD and review the literature. To our knowledge, this is the first Taiwanese TEPD case to be presented.

Case report

A 70-year-old man attended our dermatology clinic with a 6-year history of an erythematous plaque on the left armpit and a 5-year history of reddish plaques on bilateral groins and scrotum. He had previously received topical antifungal agents and topical corticosteroid for these skin lesions for 3 years in a local hospital with poor response. Moreover, cryotherapy over whole skin lesions every 1–3 weeks has also been given for about 1 year. Initially, the cryotherapy showed some clinical improvement over focal skin lesions, which healed with scaring and pigmentary change clinically, but skin lesions recurred and progressed under treatment later. During the entire treatment course, this patient did not undergo any investigation for the histopathologic examination. Owing to the progression of the disease under the aforementioned treatment, he was referred to our clinic. Dermatologic findings revealed an erythematous confluent erosive plaque over the base of the penis, the left side of the scrotum, and the left inguinal area. A residual shallow erosion was noticed over the left armpit, and an erythematous plaque was found on the right armpit. Hyperpigmented plaques with scarring change were noted over the left armpit and the right inguinal area (Figure 1). Incisional biopsies were performed from the clinically involved areas of bilateral armpits and left scrotum. The pathology of the right

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armpit and the left scrotum showed clustered intraepidermal Paget's cells with pleomorphic and hyperchromatic nucleus and pale cytoplasm. Paget's cells were immunoreactive to cytokeratin 7 (CK7) (Figure 2). The biopsy from the left armpit showed no epidermal involvement, while displaying clustered atypical cells with abundant pale cytoplasm within the fibrotic dermis (Figure 3). The atypical cells were immunoreactive to CK7, gross cystic disease fluid protein-15 (GCDFP-15), and GATA3. There was neither palpable inguinal nor axillary lymphadenopathy. Sonography over the breast and the left axilla did not show any abnormality. Results of laboratory investigations were unremarkable, and tumor markers, including carcinoembryonic antigen (CEA), were within normal limits except for the mildly elevated prostate-specific antigen (4.67 ng/mL; normal range, 0–3 ng/mL). Routine esophagogastroduodenoscopy, colonoscopy, and three sets of urine cytology did not show any evidence of malignancy. A whole-body positron emission tomography/computed tomography (PET/CT) revealed no fluorodeoxyglucose (FDG)-avid focus except for a small lymph node with mildly increased FDG uptake in Level II of the right neck, being considered with uncertain clinical significance.

After the full cancer workup, this patient underwent wide excision with a 3-cm margin over bilateral armpits and inguinal area, and skin defects were repaired by split thickness skin grafts harvested from inner thighs. Because hematoxylin and eosin pathologic examinations showed positive surgical margins over the lateral border of the right armpit and the lower border of the inguinal area accompanied with dermal invasion on the inguinal area, those two lesions were reexcised with frozen section examinations. All initial frozen section samples of margins from the right armpit were negative for tumor cells. Three frozen section samples

Figure 1 (A) The patient presented an asymptomatic, incidentally noticed erythematous plaque on right armpit; (B) a residual shallow erosion (arrowhead) with multiple hypopigmentation and hypopigmentation (arrow) that was caused by repeat cryotherapy; (C) an extensive erosive plaque over pubic area was also noticed; and (D) closer view of the plaque. Pigmentary change caused by cryotherapy was also visible over right inguinal region (arrow). Extramammary Paget's disease was histologically confirmed over the three aforementioned areas. Positive surgical margin sites in first wide excision were demonstrated (red arrowhead) over (A) right armpit and (C) inguinal area.

Figure 2 (A) Histopathologic examination showed typical clustered intraepidermal Paget's cells with pleomorphic and hyperchromatic nucleus and pale cytoplasm over all specimens except that from first incisional biopsy of left armpit (H&E; original magnification, × 100); and (B) Paget's cells were strongly immunoreactive to cytokeratin 7 (CK7; original magnification, × 400). H&E = hematoxylin and eosin.
demonstrated positive margins over the inguinal area, whereas the fourth sampling result was negative. Lymph nodes were palpable over the left inguinal area during the operation, and were excised for pathologic examination because of the established evidence of dermal invasion. Then, all wounds were covered with split thickness skin grafts harvested from bilateral thighs in the second operation, and the patient withstood the whole procedure well.

An histopathologic examination displayed typical EMPD epidermal involvement over three sites, and one of the three lymph nodes harvested intraoperatively, measuring 10×8×5 mm, showed metastasis. On immunohistochemical staining, Paget’s cells were strongly and diffusely positive for CK7 and focally positive for GCDFP-15. Additional stains for CEA and mucicarmine were also positive.

There was no evidence of local or distant recurrence 4 months after the last operation. Systemic chemotherapy was suggested by the hematologist as further adjuvant therapy.

Discussion

TEPD is a very rare subgroup among EMPDs, and only a few case reports or case series have been published. This is the first reported Taiwanese case of TEPD. Most cases were reported from Japan. There was a male predominance in the patient groups. Including our case, all but one of the 29 cases were male. In most TEPD cases, for unknown reasons, genital lesions preceded the axillary lesions except in one Japanese case and our own case. The presentation of TEPD, especially axillary lesion, was variable. Some reports in Japan showed subclinical diseases in axillae, which were confirmed by biopsies. Accordingly, some authors recommended to carefully check for almost invisible axillary lesions, even considering random biopsy, in patients with genital Paget’s disease. To our knowledge, our patient is the first case of TEPD to receive long-term cryotherapy even before the final diagnosis was made. The pigmented change and tissue scarring caused by cryotherapy distracted our attention initially, and fortunately we still noticed the asymptomatic small skin lesion over the right armpit during routine physical examination. The incidence of secondary EMPD in Asian populations is reported to be lower than that in Caucasian populations. Including two Caucasian cases, all cases of TEPD reported were primary diseases.

The incidence of invasive EMPD was reported as 18.8% in a retrospective study in China, including 48 patients (all were solitary EMPDs). To our knowledge, including this case, there were 12% TEPD patients (4/33 patients) with dermal invasion. There was a lack of solid evidence to clarify whether the severity of surface involvement can predict the risk of dermal invasion. However, dermal invasion had been confirmed as a predictor of distant metastasis, although it should be noted that the metastatic cases were not associated with larger skin lesions. Adachi et al reported one invasive TEPD case that presented an erythematous plaque over the left axilla for 20 years without treatment, and this lesion proceeded lately with an erosive tumor on the left axillary lesion, and erythematous plaques over the right axilla and genital area. Those three sites of lesions were pathologically confirmed as EMPD, and the erosive tumor corresponded to the invasive part. Similarly, our case also had long-lasting lesions over the left axilla and genital area, which were pathologically confirmed as invasive EMPD, even though no tumor lesion was noticed. In TEPD, further study is necessary to clarify the relationship between the chronicity of disease, the measurement of epidermal involvement, and the development of invasive disease.

Whether immunohistochemistry can be a reliable tool to differentiate primary from secondary EMPD is still debatable, and many studies have led to inconsistent results. Paget’s cells of both origins are usually immunosensitive to CK7, CEA, and

Figure 3 Histopathologic examination of the first incisional biopsy from left armpit. (A) Clustered atypical cells with abundant pinkish cytoplasm (arrowhead) within fibrotic dermis. There was no epidermal involvement (H&E; original magnification ×40); (B) closer view of atypical cells within middle dermis (H&E, original magnification ×400); (C) atypical cells were labeled by cytokeratin 7 (CK7; original magnification ×400); and (D) atypical cells were also immunosensitive to GATA3 (GATA3; original magnification ×400). H&E = hematoxylin and eosin.
epithelial membrane antigen, but the expression of CK20 and GCDFP-15 is variable. A review article noticed that CK20 was found more frequently in cases of secondary EMPD, whereas GCDFP-15 was more associated with the primary disease. However, only 58% of primary EMPD cases had the immunophenotype CK20(−)/GCDFP-15(+) reported in a Taiwanese study. The study of immunophenotype in TEPD has been scanty. Among the 32 reported cases of primary type, only two presented immunophenotype: one was positive to CK7, CEA, and estrogen and progesterone receptors, but negative to CK20 and GCDFP-15; the other was immunosensitive to CK7 but not CD20. As a primary TEPD, our case was observed to be immunosensitive to CK7, GCDFP-15, CEA, and estrogen receptor, which was consistent with previous studies.

TEPD, regarded as a multicentric EMPD, seems to display similar immunophenotype to solitary EMPD. The first specimen from the left axilla was observed to be immunoreactive to GATA3, which is well known as a useful stain to label breast cancer cells, especially in axillae. However, a recent study in China presented GATA3 expression in all cases of vulgar Paget’s disease. Therefore, further study is necessary to confirm the role of GATA3 expression in vulvar/nonvulvar EMPD. It was reasonable to survey for underlying adenocarcinoma, especially breast cancer, in the clinical setting where GATA3-positive cells in axillae were encountered.

PET/CT, which is proven to detect nodal involvement and distant metastasis in many malignant tumors, seems to be a useful tool to evaluate EMPD based on previous studies. PET/CT can reveal occult nodal and distant metastasis, guide treatment plan, and enable more accurate prognosis in cases of EMPD. However, PET/CT was reported to have a low sensitivity for detecting metastatic nodes smaller than 10 mm. Moreover, dermal invasion is proven to be significantly associated with regional nodal involvement and distant metastasis, and lead to a worse prognosis. Thus, several studies suggested that elective lymph node dissection/sentinel lymph node biopsy should be taken as well as local wide excision in every case of EMPD with reticular dermis or deeper invasion, and even negative results in the PET/CT scan. Our patient, whose PET/CT report was negative, also received lymph node dissection over the invasive part of TEPD, and the pathology report revealed nodal involvement, which is a marker of poor prognosis. The false-negative result of PET/CT in our patient could be, at least partially, ascribed to the small size of the positive lymph node (only 10 × 8 × 5 mm in size). We recommended elective lymph node dissection accompanied with local wide excision for cases of EMPD with deep invasion, even though the preoperative PET/CT showed negative findings. When regional lymph nodes are involved, this disease seems to be a systemic problem, and distant metastasis, maybe an occult one, could be noticed soon. In a Chinese study including six cases of penosacral EMPD and inguinal lymph node metastasis, three cases showed occult distant lymph node involvement in the following PET/CT scan, and the other three patients, who only received wide excision and inguinal lymphadenectomy, developed distant metastasis within 1 year. Our patient was planning to receive systemic chemotherapy as an adjuvant therapy.

The level of dermal invasion and status of nodal/distant metastasis were significantly associated with decreased survival in EMPD. However, tumor size and longest diameter of skin lesion were not associated with poor prognosis. These results implied that the area of the involved skin regions alone may not lead to a different prognosis in TEPD. Primary noninvasive TEPD was reported to have a favorable outcome, but to our knowledge, aside from our case, only three cases of invasive TEPD have been published in the literature. Prognosis was mentioned in two cases: one had lung metastasis in 2 years and the other one died from stroke during admission. Whether TEPD has similar a clinical course and prognostic factors with solitary EMPD requires further evaluation.

TEPD is a rare subgroup of EMPDs, and this disease entity has highly variable clinical presentation, especially over the axillary area. This is the first case of TEPD reported in Taiwan, and physicians may easily be unaware of its presence during the initial consultation. Therefore, we strongly recommend that a thorough physical examination of every patient with EMPD be conducted, regardless of whether it is in the pubic or axillary area, and skin biopsy should be considered for suspicious lesions. Although the clinical course, prognostic factors, and survival rate of TEPD still require further studies to clarify, multifocal EMPD, level of dermal invasion, and status of metastasis seem to be reasonable predictors of the outcome. PET/CT is a good tool to evaluate the disease burden, but we should be aware of its limitations. We suggest that regional lymph node dissection be considered in every case of invasive EMPD/TEPD, even if PET/CT shows a negative result. If metastasis is noticed, we suggest treating this disease in a systemic method, such as chemotherapy, when the patient can tolerate its adverse effects.

References