

Synchronous primary extramammary Paget's disease and rectal cancer: A case report

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ABSTRACT:

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Extramammary Paget's disease is one of a rare malignant dermatologic condition that may arise from epidermal apocrine gland or visceral malignancies. Although it normally presents with non-specific clinical manifestations, early recognition could decrease associated morbidity and mortality as well as disease progression. We report a case of 79 year-old man, presenting with a pruritic erythematous plaque on perianal area for two years. New lesion subsequently occurred on his right groin for six months. The histopathology showed characteristic Paget's cells. Primary invasive extramammary Paget's disease was diagnosed based on the immunohistochemical studies. He also had concurrent rectal cancer and liver metastasis.

Key word: Extramammary Paget's disease, rectal cancer

บทคัดย่อ:

ศิริยาภา ดีรัศมี, ประภาวรรณ เขาวะวนิช รายงานผู้ป่วยโรค PRIMARY EXTRAMAMMARY PAGET'S DISEASE ร่วมกับมะเร็งลำไส้ตรง วารสารโรคผิวหนัง 2556; 29: 242-248.

สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

Extramammary Paget's disease เป็นโรคมะเร็งผิวหนังที่พบไม่บ่อย อาจมีกำเนิดมาจากต่อม apocrine ที่ผิวหนังหรือมะเร็งของอวัยวะภายใน มีอาการแสดงไม่จำเพาะ ถ้าวินิจฉัยได้ตั้งแต่ต้นและรับรักษาจะช่วยลดอัตราการเจ็บป่วยและตายได้ รายงานฉบับนี้นำเสนอผู้ป่วยชายอายุ 79 ปี มีผื่นคันบริเวณก้นรอบทวารหนักมาเป็นเวลา 2 ปีและต่อมามีผื่นใหม่เกิดขึ้นที่บริเวณขาหนีบเป็นเวลา 6 เดือน ลักษณะทางพยาธิวิทยาของชิ้นเนื้อพบ Paget's cells และผลตรวจทาง immunohistochemistry เข้าได้กับโรค primary invasive extramammary Paget's disease นอกจากนี้ยังตรวจพบมะเร็งบริเวณลำไส้ตรงและมีการแพร่กระจายไปที่ตับในผู้ป่วยรายนี้ด้วย

คำสำคัญ: โรคพาเจทนอกเต้านม, มะเร็งลำไส้ตรง

Case report

A 79 year-old Thai man from Ratchaburi province, presented with pruritic erythematous plaque on the buttock for 2 years. The lesion gradually enlarged and sometimes bled. He was treated with various topical treatments at the local hospital but the skin lesion did not improved. Subsequently, a new lesion occurred on his right groin, and rapidly expanded in 6 months. He had a history of changes in bowel habit, but had no family history of colorectal carcinoma. The underlying disease was hypertension. The skin biopsy from right groin was obtained at Ratchaburi hospital, and he was then referred to the Institute of Dermatology.

Physical examinations revealed a well-circumscribed moist erythematous polycyclic plaque on the perianal area, extending to the buttocks. Multiple confluent erythematous to brownish papules, nodules with crusts on ill-defined erythematous plaque at the right groin were also noted (figure 1). Left inguinal lymph nodes, average of 2 cm in size, were palpated. Neither liver nor spleen was palpable. The clinical

differential diagnosis was extramammary Paget's disease with cutaneous metastatic carcinoma.



Figure 1 Physical examination revealed (A) a well-circumscribed moist erythematous polycyclic plaque on the perianal area, extending to the buttocks and (B) multiple confluent erythematous to brownish papules, nodules with crusts on ill-defined erythematous plaque at the right groin.

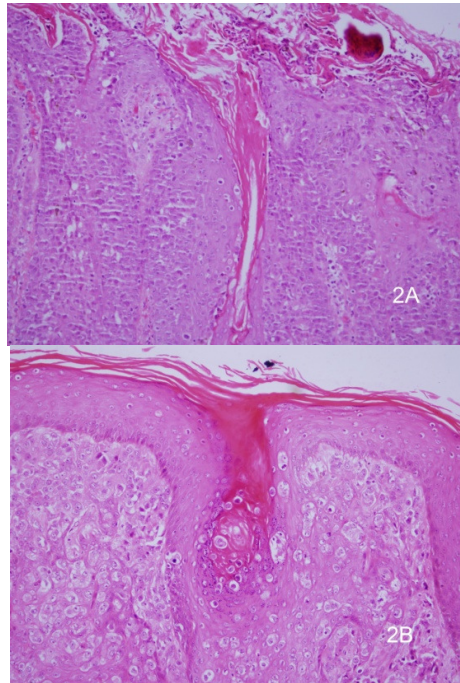


Figure 2 Incisional biopsy of the lesion on the buttock (A) showed a proliferation of atypical Paget's cells in the epidermis (H&E x10); the lesion on right groin (B) revealed Paget's cells within the epidermis and a proliferation of multiple nests and cords of atypical large round cells in the whole dermis (H&E x20)

multiple nests and cords of atypical large round cells in the whole dermis. Microscopic diagnosis was Paget's disease with dermal invasion and the differential diagnosis was cutaneous epidermotropic metastasis. The immunohistochemical staining of Paget's cells from the lesion on both the buttock and the right groin were positive for CK7 and gross cystic disease fluid protein-15 (GCDP-15) but negative staining for CK20, CDX2 (figure 3). The results favored the diagnosis of Paget's cells spreading from

cutaneous origin. Chest and the whole abdominal computed tomography scan reported rectal cancer 3.7x2.8 cm² with multiple liver and aortocaval lymph nodes metastases. The patient was referred to the National Cancer Institute of Thailand, but he denied treatment with chemotherapy and radiotherapy. He was then treated with herbal medicine and has passed away in 6 months after the diagnosis.

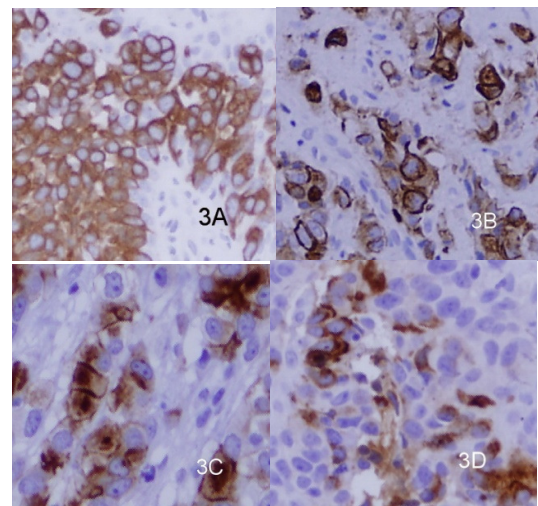


Figure 3: (A, B) CK7 staining, (C, D) GCDP-15 staining. Immunohistochemical staining of the lesions on the buttock (A) and the right groin (B) were positive for CK7. The lesions on the buttock (C) and the right groin (D) stain positively for GCDP-15.

The histopathological result of the lesion on the buttock (figure 2A) revealed proliferation of atypical Paget's cells. They were large rounded cells with clear pale vacuolated cytoplasm, mostly were in confluent nests within the epidermis with some extension along the hair follicle. Inflammatory cells infiltrations were

found in the superficial dermis. Microscopic diagnosis was Paget's disease. The histopathological examination of skin biopsy from the right groin (figure 2B) showed Paget's cells within the epidermis and proliferation of

Discussion

Extramammary Paget's disease (EMPD) is a rare malignant dermatologic neoplasm. Annual incidence rate of EMPD is 0.6 per 100,000 person¹. It is commonly found in elderly people and is more common in women. The median age of onset is 74 years (range 36-96 years)¹.

There is still a controversy in the pathogenesis of EMPD. It can originate from dermal apocrine/eccrine glands and epidermal stem cells (primary EMPD), or spread downward from colorectal, genitourinary, tubo-ovarian cancers (secondary EMPD), or combination of the two pathway²⁻⁴. Besides there is another theory that a common carcinogenic environment stimulates a multicentric reaction in adjacent structures (apocrine, epidermis and glandular structures of the rectum and the urethra) causing simultaneous cancer. Paget's cells represent an adenocarcinoma in situ and can metastasize if untreated⁵. EMPD mostly arises as the primary neoplasm, less commonly (15-30%) from the underlying malignancy⁶. Other synchronous or metachronous primary malignancies (second primary tumors) occurred in 8.6% of patients with invasive EMPD¹.

The clinical manifestation of EMPD is a solitary well-demarcated erythematous, scaly plaque,

occasionally crusted, ulcerated, fissured with regional lymphadenopathy⁶. It is slowly progressive and unresponsive to topical antifungal or corticosteroid therapy⁷. The most common symptom is pruritus, followed by burning, irritation, pain, tenderness, swelling and bleeding. But it maybe asymptomatic⁸. The median time to the diagnoses was delayed to 2 years⁸.

The most common site of secondary EMPD is the vulva in female and the perianal region, scrotum as well as penis in male⁶. Infrequently, the axillae, buttocks, thighs, eyelids and external auditory meatus may be involved⁸. Associated malignancy of secondary EMPD of perianal area is adenocarcinoma of the gastrointestinal tract; while groin, penile, or scrotal lesions may be associated with genitourinary malignancy⁷. Liver, bone, lung, and suprarenal glands are sites of metastases⁴.

Perianal Paget's disease is an uncommon intraepithelial adenocarcinoma beneath the dentate line and within 6 cm around anal area⁹. Recent study revealed that up to 42% of perianal Paget's disease was related with underlying malignancies such as vulva, bladder, renal, liver and colorectal cancer¹⁰. Any perianal dermatitis that is unresponsive to conventional medication within 1 month may require biopsy for histopathological examination⁵. EMPD should be evaluated for underlying malignancy by complete physical examinations and proper investigations such as

pelvic ultrasound, sigmoidoscopy, colonoscopy, cystoscopy, mammogram and chest X-ray⁸.

Histopathologic features show Paget's cells within the epidermis. They are large cells with large nuclei, obvious nucleoli and ample pale cytoplasm⁸. Paget's cells could be found as a single cell or in clusters¹¹. They are mostly located in the lower part of epidermis, but could also be found in the upper part of epidermis, pilosebaceous units, as well as in the sweat glands and ducts. This lead to the confusion about the origin of the malignancy, whether from the epidermis or apocrine glands¹¹. The epidermis shows acanthosis, papillomatosis, parakeratosis and enlargement of the interpapillary ridges¹². A dense inflammatory cells infiltration is related to malignancy¹¹. In more than 90% of EMPD, Paget's cells were composed of mucin which stains positively for Alcian blue at pH 2.5, mucicarmine and periodic acid-Schiff with diastase resistance¹¹. Poor prognoses of primary EMPD are dermal invasion, which presents in 20% of case, and lymphovascular invasion¹¹.

Immunohistochemical staining is needed to differentiate EMPD from other diseases that have pagetoid spreading and to classify the origin of the tumor¹¹. Extramammary and mammary Paget's disease have similar immunophenotypes: CEA(+)/CAM5.2(+)/CK7(+)/EMA(+)¹¹. Superficial spreading melanoma/lentigo maligna stains positive for HMB-45, while Paget's cells stain negative. Pagetoid Bowen's disease has absent staining for CEA and CK7.

Mycosis fungoides stains positive with CD3 and UCHL-1, which are markers for T cell¹¹. Primary EMPD mostly has positive staining for GCDFP-15, but the expression of GCDFP-15 does not exclude dermal apocrine tumor¹¹. EMPDs that originated from colorectal or urothelial carcinomas frequently have positive staining for CK20 but negative staining for GCDFP-15¹¹.

CK7 is expressed in sebaceous glands, apocrine glands, eccrine glands, epithelium of breast, lung, and genitourinary tract¹³. CK20 is a marker for Merkel cells and also expressed in colorectal adenocarcinomas¹³. BRST-2 is a monoclonal antibody that detects GCDFP-15, which is expressed in apocrine and minor salivary glands¹³. CDX2 is a transcription factor that modulates small and large intestinal epithelial development¹³.

Perrotto J, et al. demonstrated that CK7, CK20 and BRST-2 could not discriminate primary from secondary EMPD because CK7 was positive in all 61 cases while CK20 and BRST-2 were positive in large subsets of both groups¹³. They also found that CDX2 and HER-2/neu may be useful markers in distinguishing primary EMPD from EMPD secondary to anorectal adenocarcinoma [CDX2 were positive in 5 of 6 cases (83%) and HER-2/neu were negative in all 6 cases (100%) of EMPD secondary to anorectal adenocarcinoma]¹³. But these two markers failed to distinguish primary EMPD from EMPD secondary to other types of cancer¹³.

In our case, the histopathology and immunohistochemical staining results of the cutaneous lesions [CK7(+), GCDFP-15(+), CK20(-), CDX2(-)] supported the diagnoses of invasive primary EMPDs. But the patient also had concurrent rectal cancer with liver metastasis. The rectal cancer might be a synchronous primary malignancy or the metastasis of his invasive primary EMPD. Unfortunately, he refused the treatment so we did not have the immunohistochemical staining result from his rectal cancer that might help in determining the nature of the tumor.

Shutze WP and Gleysteen JJ proposed a staging system and recommended therapies for perianal Paget's disease as shown in Table 1¹⁴. Treatment is based on disease staging, and the prognosis is worse in accordance with advance stages³. EMPD relapsed frequently, thus long term follow-up, physical examination, proctosigmoidoscopy, and random biopsy specimens once a year are needed³. Colonoscopic examination should be done every 2 to 3 years³.

Table 1 Staging system and recommended therapies for perianal Paget's disease adapted from Shutze WP and Gleysteen JJ^{10, 14}

Stage	Clinical/histological description	Recommended therapies
I	Pagetoid cells in the perianal epidermal epidermis with no adnexal involvement	Wide local excision with a margin of 1-3 cm, Moh's micrographic surgery
IIA	Cutaneous Paget's disease with associated adnexal carcinoma	Same as stage I
IIB	Cutaneous Paget's disease with associated anorectal carcinoma	Abdominoperineal resection
III	Paget's disease with regional lymph nodes metastases of associated carcinoma	Inguinal lymph node dissection and abdominoperineal resection/ wide local excision
IV	Paget's disease with distant metastases of associated carcinoma	Chemotherapy, Radiotherapy, Local palliative management

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