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ORIGINAL RESEARCH

Clinicopathological Analysis of 40 Cases of Extramammary Paget Disease: A Retrospective Study

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Background: Extramammary Paget Disease (EMPD) is a rare intra-epithelial malignancy often misdiagnosed due to diverse clinical manifestations. This study retrospectively analyzed the clinicopathological features of 40 EMPD patients to provide references for clinical practice.

Methods: Clinical data of 40 patients with pathologically confirmed EMPD were collected, including demographics, clinical features, histopathological and immunohistochemical findings, treatments, and follow-up outcomes.

Results: Of the 40 patients (27 males, 13 females; mean age 68.8 years), the most common onset location was the external genitalia (n = 33). Lesions primarily presented as erythema or red plaques (n = 38), with itching being the most common symptom (n = 26). Immunohistochemically, tumor cells were positive for CK7, CEA, and EMA, with positive rates of 70% for GCDFP-15 and 25% for CK20. Thirty-nine patients underwent surgical excision, and one received photodynamic therapy combined with radiotherapy. During follow-up after surgery, one patient with invasive features (tumor mass in the dermis) recurred but achieved remission after reoperation; the other 38 patients remained disease-free. Invasive EMPD was associated with a higher risk of recurrence.

Conclusion: EMPD's varied presentations pose diagnostic challenges. Key diagnostic differentials include eczema, psoriasis, and melanoma, particularly for rare pigmented or depigmented variants. For clinicians, a high index of suspicion and prompt biopsy are crucial for early diagnosis. For pathologists, a comprehensive immunohistochemical panel is essential, while CK20's utility in distinguishing primary from secondary disease is limited and warrants further malignancy screening. Surgical excision remains the primary treatment, with alternative therapies effective for inoperable cases. Early diagnosis, appropriate treatment, and long-term follow-up are crucial for optimal prognosis.

Keywords: extramammary, Paget disease, clinical characteristics, pathological manifestations, pigmented

Introduction

Extramammary Paget Disease (EMPD) is a rare intra-epithelial malignancy, occurring in areas rich in apocrine glands, such as external genitalia, axillary and perianal.[1] Similar with the classical Paget disease of the nipple, EMPD presents with abnormal proliferation of intraepidermal tumor cells, but its anatomical location and clinical manifestations have some uniqueness. EMPD can be classified as primary, originating within the epidermis, or secondary, representing epidermotropic spread from an underlying visceral malignancy, such as rectal, urogenital, or gynecologic carcinomas. Distinguishing between primary and secondary EMPD is of paramount importance, as the latter necessitates a thorough work-up for an associated internal tumor, which significantly impacts patient management and prognosis. EMPD is more common in the elderly, and its pathogenesis has not been fully clarified, involving a variety of molecular genetic abnormalities, such as hotspot mutations in FOXA1 and ERBB2 genes. These mutations are distributed in different populations, suggesting potential targeted therapy value.[2]

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Diagnosis of EMPD always takes a long time because of its diverse clinical manifestations, which are easily confused with diseases such as eczema, psoriasis and candidiasis, leading to misdiagnosis and delayed treatments.[3,4] Combined clinical manifestations with histopathology and immunohistochemical auxiliary diagnosis are important to improve the diagnostic accuracy of EMPD. Established prognostic factors in EMPD are critical for risk stratification. Among these, the presence of dermal invasion, defined by tumor cells breaching the basement membrane and extending into the dermis, is widely recognized as a key indicator of aggressive behavior and an increased risk of recurrence and metastasis. In terms of treatments, surgical excision is the first choice, while photodynamic therapy (PDT), radiation therapy and topical medication are other solutions,[5–8] and emerging immunotherapies are being explored. By retrospectively analyzing 40 EMPD patients, this study summarized the clinical and histopathological findings of EMPD, in order to provide a reference for clinical diagnosis and treatment.

Materials and Methods

Study Design and Patients Selection

This retrospective study was conducted at the Department of Dermatology, Beijing Hospital. We searched the departmental pathology database from January 2009 to December 2024 to identify all patients with a histopathologically confirmed diagnosis of EMPD. Inclusion criteria were: (1) availability of complete clinical and pathological records; (2) a definitive diagnosis of EMPD confirmed by at least two experienced dermatopathologists. Exclusion criteria were: (1) insufficient clinical data or follow-up information; (2) prior history of treatment for EMPD at another institution. A total of 40 patients met the inclusion criteria and were enrolled in this study. Related clinical information was collected, including gender, age, onset location, time from onset to diagnosis, characteristics of skin lesions, symptoms, histopathology, etc. All patients underwent comprehensive screening to exclude secondary EMPD. The diagnostic workup included: (1) Detailed medical history and physical examination focusing on urological, gynecological and colorectal symptoms. (2) Imaging studies: CT scan of abdomen and pelvis was performed in all patients. For perianal cases (n = 3), additional colonoscopy was conducted. For genital cases (n = 33), cystoscopy was performed when indicated. (3) Immunohistochemical panel included CK7, GCDFP-15, CK20, CEA, EMA, and p63. For the patient with bladder cancer, additional markers including GATA3 and uroplakin III were performed.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinicopathological characteristics of the patients. Continuous variables were expressed as mean ± standard deviation (SD) or median (range), while categorical variables were presented as counts and percentages. Due to the small sample size and low number of events (recurrence), formal inferential statistical analysis for prognostic factors was not performed.

Results

Demographics

Among the 40 patients, 27 (67.5%) were males and 13 (32.5%) were females, with an average age of 68.83 ± 10.79 years (ranging from 50 to 87 years).

Clinical Characteristics

Time from skin lesions to confirmed diagnosis ranged from 3 to 120 months, with a mean time of 45.23 ± 35.96 months. The most common onset location was external genitalia (n = 33), including scrotum, penis and pubic region among male patients, and vulva at labia majora among female patients. Besides, 4 cases and 3 cases had onset location at axillary and perianal, separately.

With regard to skin lesions, 38 patients presented with erythema or red plaques, with erosions, scaling, hyperplastic masses, hypopigmentation or hyperpigmentation on the surface (Figure 1). In addition, 1 patient each manifested as brown patch (Figure 2a) and depigmented patch (Figure 2b). In terms of subjective symptoms 26 patients reported varying degrees of itching, 3 patients had pain, while 11 patients were without obvious symptoms.

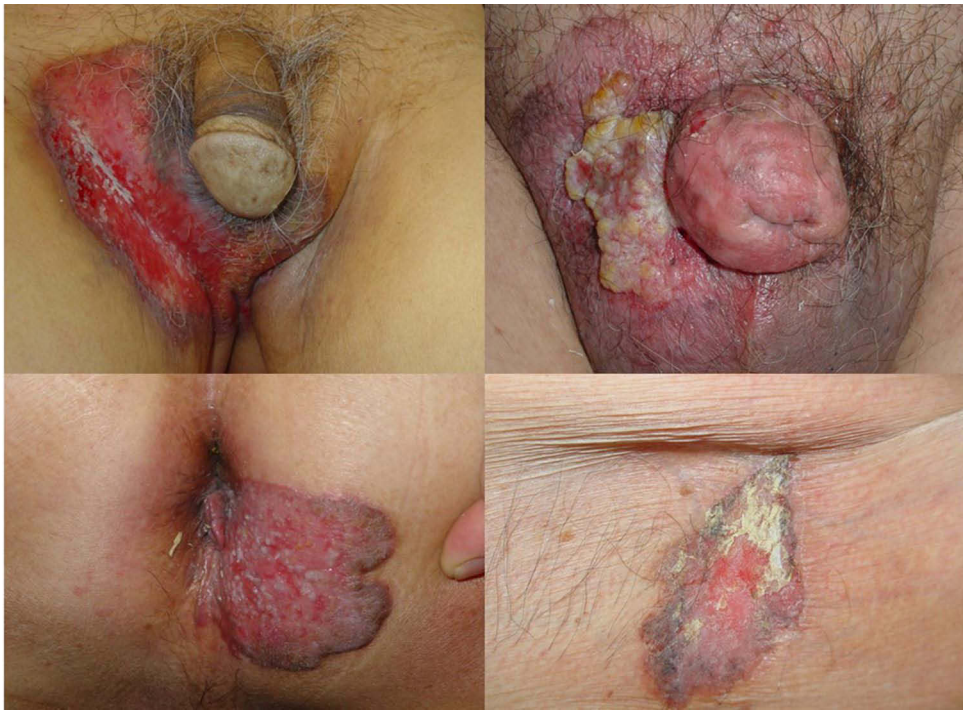

Figure 1 EMPD is common in skin areas rich in apocrine sweat gland, such as the external genitalia, perianal area, and axilla. It often presents as erythema or red plaque, accompanied by infiltrates, scales, and exogenous masses.

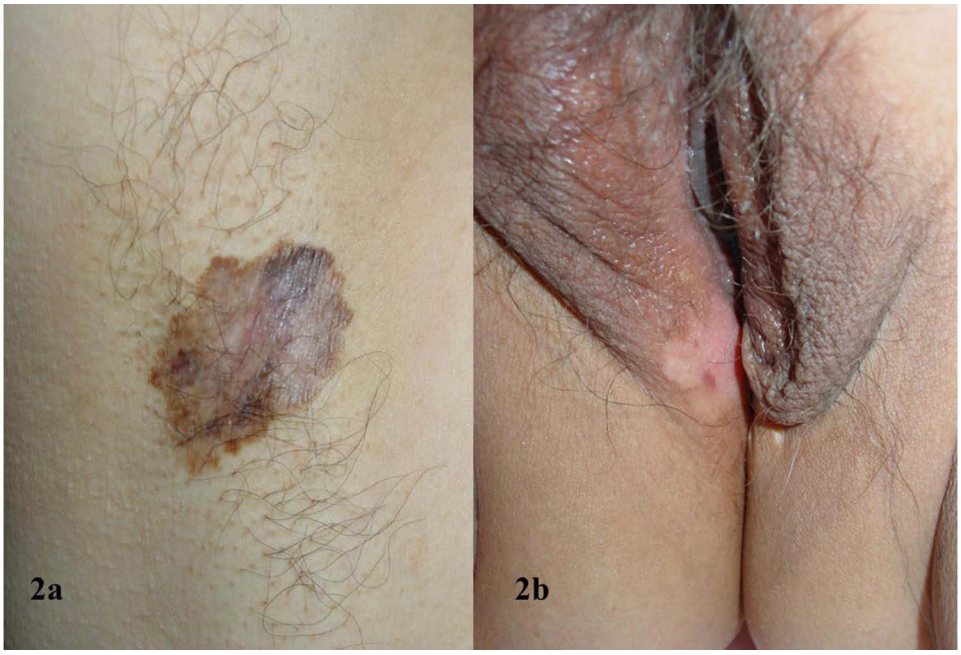

Figure 2 Special types of EMPD: pigmented EMPD (**a**) and depigmented EMPD (**b**). They are manifested as pigmented patch and depigmented patch, which are easily confused with other pigmentary diseases in clinical practice.

No internal or adjacent urogenital, colonic, or rectal tumor was found in 39 patients after comprehensive screening. One patient was diagnosed with concurrent bladder cancer, which was confirmed to be unrelated to the cutaneous lesion based on clinical presentation, imaging studies, and immunohistochemical profile.

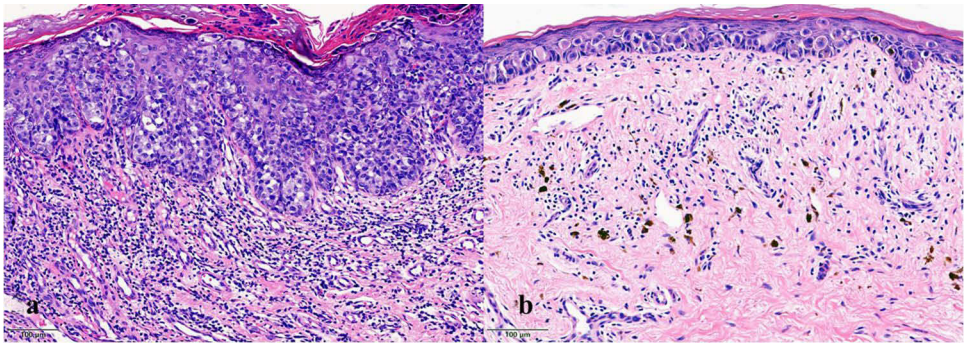

Figure 3 The basic histopathological manifestation of EMPD is the scattered or nest like distribution of Paget cells within the epidermis, with large, round or oval cell bodies, rich cytoplasm with light staining, and large nuclei with deep staining ((**a**), H&E, ×400); Pigmented EMPD shows pigmented granules within the dermis ((**b**), H&E, ×400).

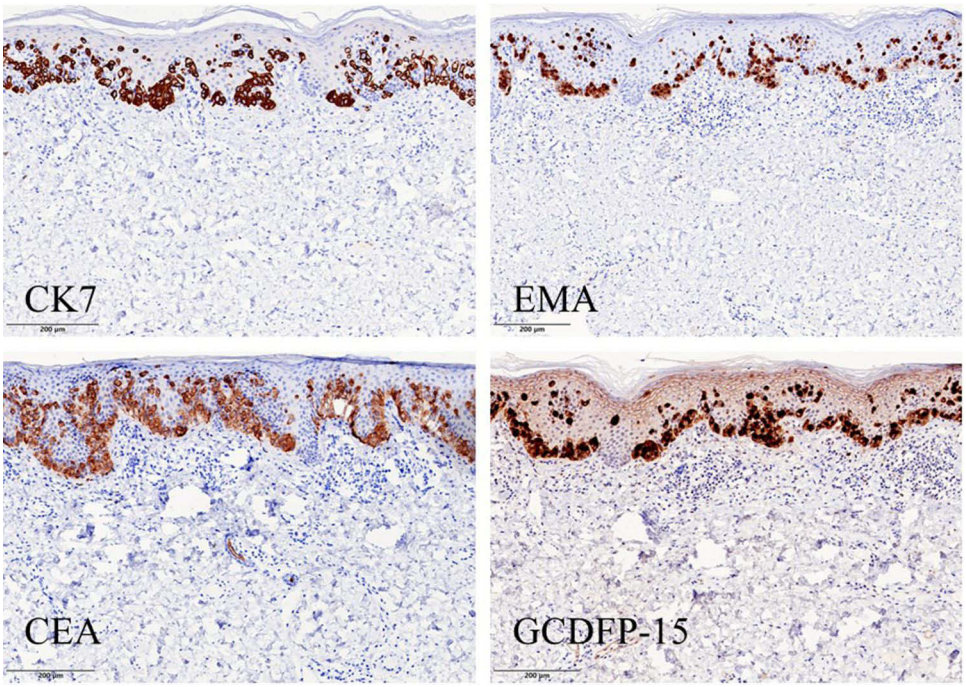

Figure 4 Immunohistochemical staining of EMPD tumor cells shows CK7, CEA, and EMA positivity, while GCDFP-15 is often positive in primary EMPD (×400).

Histopathological Features

All patients showed scattered or nested Paget cells in the epidermis, with large, round or oval cell bodies, abundant pale cytoplasm, and large hyperchromatic nuclei (Figure 3a). Some appeared epidermal hyperkeratosis or parakeratosis, accompanied by inflammatory cell infiltration in the superficial dermis. One patient presented with a tumor mass in the dermis, who had recurrence after 4 months of surgery. Tumor cells involved hair follicles in 4 patients and acantholysis was observed in 2 patients. The only 1 patient with pigmented patch also showed pigment granules within the histopathologic dermis (Figure 3b).

Immunohistochemical results indicated that staining of tumor cells was positive for CK7, CEA and EMA (Figure 4), while 70% (28/40) and 25% (10/40) positive rate of GCDFP-15 and CK20, separately. Results for the only 1 patient with pigmented patch were Sox-10 (-), Melan-A (-) and S-100 (-).

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Treatments and Follow-Up Visit

One patient refused surgery due to large lesion area at perianal, thus received 8 times of PDT to decrease lesion area, followed by radiotherapy until complete resolution of skin lesions, and no recurrence was found during the 6-year follow-up period. Wide local excision (WLE) was conducted in 39 patients, with all negative surgical margins. Postoperative follow-up time ranged from 8 to 194 months, with a mean time of 85.98 ± 55.43 months. Only 1 patient had recurrence after 4 months, which did not recur for 78 months after reoperation of WLE. The remaining 38 patients had no recurrence.

Discussion

Typical clinical manifestations of EMPD are slowly expanding erythema or plaques in the affected area, often with desquamation, exudation or erosion, and the lesion borders are usually irregular and chronically progressive. Discomfort symptoms occur mainly including itching and burning, while some cases may have subclinical lesions that are difficult to detect by visual inspection, resulting in clinical borders inconsistent with pathological borders.[1,9] EMPD is easily confused with diseases such as eczema, psoriasis, and fungal infections, leading to misdiagnosis, delayed treatments, as well as the increased risk of disease spread and invasion.[1,3] Consistent with previous studies, there were more male patients in our study, the overall average age was 68.83 ± 10.79 years, disease duration was over months or even years, external genitalia was the most common onset location, and a majority of skin lesions were erythema or plaques. The two special types of EMPD, pigmented EMPD[10,11] and depigmented EMPD,[12] present with hyperpigmentation and depigmented macules, respectively, can be easily misdiagnosed with melanoma and vitiligo. There was 1 each with pigmented EMPD and depigmented EMPD in our study, increased awareness of these rare clinical types is needed in clinical settings. Pigmented lesions in apocrine gland-rich areas require vigilance for EMPD, and differential diagnosis requires the help of immunohistochemical staining, including staining of a range of epithelial and melanocytic components. Pigmentation in EMPD may be associated with reactive proliferation and colonization of melanocytes,[11] and depigmentation may be caused by symbiotic disturbances between melanocytes and keratinocytes, including melanocyte destruction and disturbances in melanosome transmission to keratinocytes.[12]

EMPD can be divided into primary and secondary, of which the latter is anal canal adenocarcinoma, colorectal cancer, bladder cancer, and gynecological cancer extending at the intraepidermal level of anal and vulvar skin, with clinical manifestations mostly symmetrical masses.[13,14] Kosano et al has reported that secondary EMPD appears to have more symmetrical, well-defined and raised skin lesions, which has great significance in differentiating primary and secondary EMPD.[14]

Skin biopsy is the gold standard for diagnosis of EMPD, which requires sampling of sufficient depth and extent to confirm the presence of Paget cells. The histopathological features of EMPD are mainly characterized by substantial Paget cells of different sizes in the epidermis, which have abundant cytoplasm, often lightly stained or foamy, and the cells are scattered or clustered in the epidermis and basal layer.[3] The epidermis often presents with parakeratosis and acantholysis. Tumor cells can sometimes involve the hair follicle openings and sweat gland ducts, manifesting as show adnexal structural invasion that is also a common feature of EMPD. Histopathology suggests that invasive EMPD frequently has tumor cells mostly solid nests or glandular structures, marked cellular atypia, and signet-ring Paget cells. Besides, some cases may present with pathological features such as lymphangiectasia and vascular invasion, pointing out that the risk of metastasis needs to be highly concerned.[3] In this study, scattered or nested Paget cells were observed in all patients, and the only patient who relapsed after follow-up was found to have histopathological features of tumor cell masses in the dermis, which showed invasive EMPD. The above results are consistent with previous studies reporting that tumor invasion (eg, depth of invasion) is generally considered to be a prognostic factor. Therefore, histopathological examination should focus on depth of intradermal invasion, vascular and lymphatic invasion, which is essential for prognostic evaluation and treatment decisions.[15]

Detection of immunohistochemical markers is of great value in the diagnosis of EMPD and differential diagnosis. Typical EMPD tumor cells have positive expression in CK7, GCDFP-15, CEA, EMA and HER2, assisting in distinguishing Paget cell from other tumors of cutaneous origin.[1,3,16,17] While CK20 positivity is more frequently observed in secondary EMPD, it is not a reliable marker for distinguishing primary from secondary disease, particularly in perianal

lesions where both primary and secondary EMPD can express CK20. Therefore, definitive differentiation relies on clinical correlation, endoscopic examination, and imaging studies rather than CK20 immunohistochemistry alone. Although TRPS1 immunohistochemistry was not performed in our cohort, recent studies have demonstrated its utility in distinguishing primary from secondary EMPD, particularly in non-perianal locations.[17] However, its utility may be limited in perianal cases. Additionally, TRPS1 positivity can be observed in pagetoid squamous cell carcinoma in situ (SCCIS), necessitating the inclusion of p63 in the immunohistochemical panel for accurate differentiation. In addition, pigmented EMPD shows positive Paget cell (eg, CK7, etc.), while some concomitant melanocytic hyperplasia is often misdiagnosed as melanoma, melanin markers such as S100, MelanA and HMB45 are used to differentiate the two.[11] In the histopathological differential diagnosis of EMPD, particularly pagetoid variants, SCCIS and melanoma in situ must be considered. While SOX10, Melan-A, and S-100 help exclude melanoma, p63 or p40 immunostaining is essential to distinguish EMPD (typically p63-/p40-) from SCCIS (p63+/p40+). This distinction is crucial as management approaches differ significantly.

Surgical excision remains the first treatment option for EMPD. The extent of resection is usually recommended to be at least 2 cm beyond the gross lesion to ensure complete removal of the tumor, but still faces challenges of positive margins and high postoperative recurrence rate.[18,19] Because of its edge control advantages, Mohs microsurgery can effectively reduce the local recurrence rate and is the recommended surgical approach.[1,20] Radiation therapy is considered as the adjuvant or alternative therapy among inoperable patients or positive margins. The side effects of radiotherapy are controllable, and the safety and tolerance of subsequent PDT have been proved under certain conditions.[8,21,22] Conversely, some studies have supported that radiotherapy is not significantly associated with overall survival, even may lead to worse prognosis.[23,24] PDT and topical agents such as imiquimod and 5-fluorouracil also have some efficacy, particularly in patients with recurrent or inoperable disease.[5–7] In our study, 1 patient refused surgery due to large area of skin lesion, thus received combination of PDT and radiotherapy. The remarkable effect demonstrated such combined therapy could be possible superior alternatives.

The overall prognosis of EMPD is relatively good, with 5-year survival rate of 75%–95%, but patients with invasive EMPD or lymph node and distant metastasis appear to have poor prognosis.[1,3,19,23]

In conclusion, our study corroborates much of the existing knowledge on EMPD and provides incremental data on its clinical spectrum. Our findings add to the growing body of retrospective analyses that collectively refine our understanding of this disease. The low event rate for recurrence limits our ability to draw definitive prognostic conclusions, highlighting the need for larger, multi-center studies.

Conclusion

As a rare intra-epithelial malignancy, EMPD is easily misdiagnosed due to its diverse clinical manifestations, especially pigmented EMPD and depigmented EMPD are misdiagnosed with other pigmented disorders, leading to delayed treatment. Histology shows invasion of typical Paget‘s cells and adnexa, and immunohistochemical staining can be helpful for diagnosis and differential diagnosis. Recent studies[25,26] have further validated the role of TRPS1 in EMPD diagnosis, though awareness of potential pitfalls, such as TRPS1 positivity in pagetoid SCCIS, is essential. Combining TRPS1 with p63 in an immunohistochemical panel can enhance diagnostic accuracy. Surgical excision remains the first choice, while PDT and radiation therapy are supplemental solutions. Patients with localized EMPD appear to have good prognosis, while those with invasive EMPD have poor prognosis. Future research should focus on molecular mechanism analysis and targeted therapy development to improve treatment outcomes and quality of life. In summary, early diagnosis, multidisciplinary treatment and long-term follow-up are the key to optimize patient management and prognosis as well.

Ethics Approval and Informed Consent Statement

The study was approved by the Ethics Committee of Beijing Hospital (2022BJYYEC-208-02). Informed consent was obtained from each patient. The patient signed a consent form for the publication of case details and images. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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Disclosure

No potential conflict of interest was reported by the authors.

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