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ORIGINAL RESEARCH

Independent Risk Factors for Postoperative Recurrence of Patients with Primary Extramammary Paget's Disease: A Retrospective Analysis

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Background: Extramammary Paget's disease (EMPD) is a rare skin cancer with unclear pathogenesis, insidious progression, and high recurrence rate. The purpose of this study was to investigate the clinical features and postoperative recurrence factors of primary EMPD.

Methods: We retrospectively analyzed the medical records of 40 patients with primary EMPD who underwent wide local excision surgery at a single medical center between 2009 and 2019. Risk factors for recurrence of primary EMPD were analyzed using multivariate binary logistic regression.

Results: The study included 40 patients with primary EMPD, comprising 31 males (77.5%) and 9 females (22.5%), with a median age of 75.52 years (range 52–99 years). The most common lesion location was the scrotum (22 cases, 55.0%), followed by the vulva, penis, scrotum, underarm and anus. Multivariable regression analysis revealed significant differences in the presence of ill-defined tumour borders, exudation and nodules in the primary lesion affecting the relapse of primary EMPD ($p<0.05$).

Conclusion: Our findings indicate that ill-defined tumour borders, exudation and nodules in the primary site should be considered as independent risk factors for disease recurrence, which may provide useful suggestions for the diagnosis, treatment and follow-up of primary EMPD.

Keywords: extramammary paget's disease, factors, recurrence, postoperative, retrospective

Background

Primary extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma with the same cytomorphology and histology as Paget's disease (PD),[1] a subtype of Paget, mainly because of the different anatomical site.[2] Primary EMPD often occurs in sites rich in apocrine glands, such as the vulva, perianal, scrotum, and penile regions, and less frequently in the axilla, buttocks and abdomen. Common clinical signs are pruritus, rash, erythema, vesicles, pain and oozing.[3] PD is found almost exclusively in women, whereas primary EMPD is found in both men and women, with a significantly higher proportion of men and Asian men and white women being the high-risk groups.[4] EMPD occur at 0.6 per million person-years in Europe and 0.4 per million person-years in China.[1,5] Although morbidity is low, mortality is high. The high rate of postoperative recurrence is a cause for concern. Due to its slow growth and non-specific symptoms, as well as the low susceptibility of the elderly, primary EMPD can easily be neglected, leading to delays in diagnosis. Treatment of Paget's disease includes alternative therapies and surgery, the former including photodynamic therapy, radiotherapy, laser therapy, local therapy, chemotherapy, and cell-specific therapy, but surgical resection is one of the main approaches to treat primary EMPD, mainly using wide local excision (WLE) and Mohs micrographic surgery.[6]

However, owing to its poorly understood pathogenesis and insidious progression,[7] studies have shown that the postoperative recurrence rate of this disease is 30–60%, which has a great impact on the life of patients.[8] More scholars have studied its pathologic factors, as well as factors affecting prognosis. Considering the high recurrence rate of this

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disease, the aim of this study was to retrospectively analyze the clinical features affecting the postoperative recurrence of primary EMPD. This may provide additional information for clinicians to diagnose, treat and follow-up primary EMPD in clinical practice.

Materials and Methods

Materials

The study was approved by The First Affiliated Hospital of Chongqing Medical University with the ethical principles of Helsinki medical research. A retrospective review of patients seen at the Department of Dermatology in the First Affiliated Hospital of Chongqing Medical University, Chongqing, China, between January 2009 and January 2019 was conducted. The clinical data were collected from inpatient, out-patient medical records and telephone follow-up. Relevant patient demographics, previous treatment, clinical symptoms, and disease characteristics were collected. Every case had complete and detailed medical records and had provided written informed consent to present their clinical data.

Methods

All patients who received biopsy with final diagnosis of EMPD were identified through an Electronic Patient Records search using the term "EMPD" in the pathology results from the database of the First Affiliated Hospital of Chongqing Medical University (n = 48) who met the criteria with complete clinical information. All patients must meet the following inclusion and exclusion criteria. Inclusion criteria: (1) patients aged 18 years and above. (2) Biopsy resulted confirm EMPD. Exclusion criteria: (1) Secondary extramammary Paget's diseases. (2) Combination of other malignant tumors. (3) Combination of other serious underlying diseases. The patients were divided into a group with recurrence and a group without recurrence. The study excluded 6 patients with secondary tumors and 2 patients lost to follow-up who refused telephone follow-up and had no record of outpatient follow-up. We retrospectively analyzed the sex, age, clinical symptoms, residence, social support and history of immunosuppression of the 40 patients with primary EMPD. The 5-year recurrence status was confirmed through electronic patient records. If the recurrence status cannot be confirmed, phone interview was performed.

Primary Endpoints

The primary endpoint was the 5-year recurrence rate of primary EMPD, defined as recurrence within 5 years after patients received surgical treatment. The poor prognostic factors of 5-year recurrence were identified. The related risk factors of recurrence were also analyzed.

Follow-Up

All patients underwent surgery, and postoperative biopsy showed negative margins. The median postoperative follow-up time was 28 months (range: 12–48 months). Telephone follow-up and access to the outpatient medical record system were conducted on January 4, 2024, to record the condition to relapse.

Statistical Analysis

All data were analyzed by SPSS 24.0 software. Discrete variables are expressed as percentages, and continuous variables are expressed as the mean and standard deviation.[9] All the included factors were analyzed by single-factor analysis. To avoid the omission of influencing factors, the variables with *t*-tests of value ≤0.1 in single-factor analysis were included in logistic regression analysis.[10] The significance of all tests was set to $P \leq 0.05$.

Results

Clinicopathological Data of the Study

For the period from January 2009 to January 2019, 42 patients were diagnosed with primary EMPD in our hospital. To assess recurrence within 5 years after surgery, telephone interviews were conducted with all patients in addition to electronic medical records, and 40 patients were finally enrolled. Table 1 lists the demographic characteristics of 40 eligible patients. And all patients were Chinese, including 31 males (77.5%) and 9 females (22.5%), aged with a median

Table 1 Demographic and Clinical Characteristics of Patients

Variable	Patients	Recurrence rate	χ^2	*P*
Age				
<60 years old	4	25.000%	0.004	0.950
60~79 years old	21	42.857%		
≥80 years old	15	33.333%		
Gender				
Male	31	35.484%	0.228	0.635
Female	9	44.444%		
Social support				
Family members	36	36.111%	0.284	0.597
Living alone	4	50.000%		
Course of disease				
<10 years old	24	33.333%	2.091	0.156
10~19 years old	11	27.273%		
≥20 years old	5	80.000%		
Region				
Scrotum	22	40.909%	0.001	0.979
Penis	6	16.667%		
Vulva	7	42.857%		
Mons veneris	2	50.000%		
Perianal	1	0.000%		
Axillary	2	50.000%		
Clinical symptoms				
Yes	15	46.667%	0.835	0.366
No	25	32.000%		
Misdiagnosis				
Yes	31	38.710%	0.082	0.776
No	9	33.333%		
History of immunosuppression				
Yes	30	36.667%	0.034	0.855
No	10	40.000%		
Single/Multiple				
Single	16	31.250%	0.427	0.517
Multiple	24	41.667%		
Boundary				
Clear	32	25.000%	13.818	0.001
Unclear	8	87.500%		
Size				
<10 cm^2	13	23.077%	0.938	0.339
10~19 cm^2	15	46.667%		
≥20 cm^2	12	41.667%		
Erosion				
Yes	18	50.000%	2.192	0.147
No	22	27.273%		
Exudation				
Yes	11	72.727%	9.550	0.004
No	29	24.138%		
Scales				
Yes	10	20.000%	1.730	0.196
No	30	43.333%		

(*Continued*)

Table 1 (Continued).

Variable	Patients	Recurrence rate	χ^2	*P*
Nodules				
Yes	7	85.714%	10.125	0.003
No	33	27.272%		

of 75.52 years (ranging from 52 to 99 years). Their disease course ranged from one month to 20 years, with a median of 48 months. Fifteen patients presented with local recurrence (37.5%). Primary EMPD tended to be multiple (60.0%) and was most commonly found in the scrotum (55.0%), followed by the vulva (17.5%), the penis (15.0%), the mons veneris and axillary (5.0%), and the perianal (2.5%). And the size lesions ranged from 1 to 28 square centimeters, with a median of 16 square centimeters. Among the clinical manifestations of all the people, 12 people had blurred lesion boundaries of the skin lesions, localized as erythema as in Figure 1, and 7 people had obvious protrusions in the location of the skin lesions, and the hand could touch a nodule protruding out of the skin as in Figure 2, also 11 patients had localized epidermal breaks, blisters, and small number of exudates can be seen on the basis of erythema as in Figure 3.

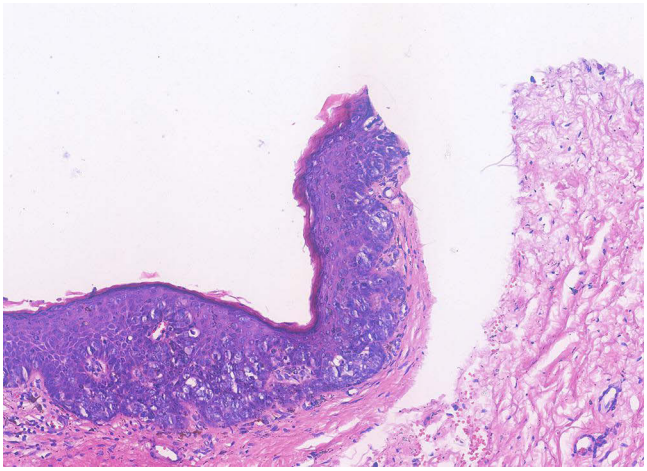

Figure 1 Ambiguous pathological boundary can be observed (original magnification x 200, H-E).

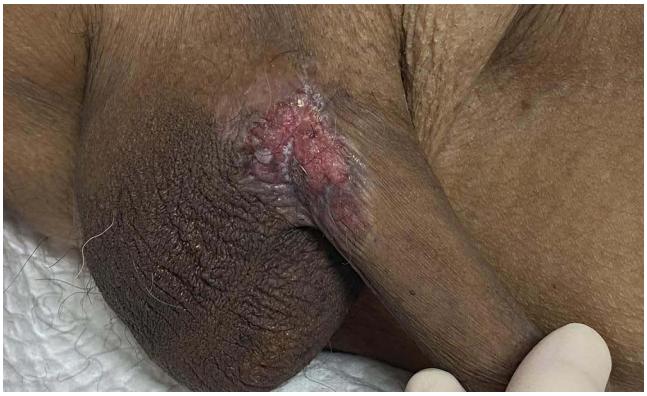

Figure 2 A raised surface with a nodule.

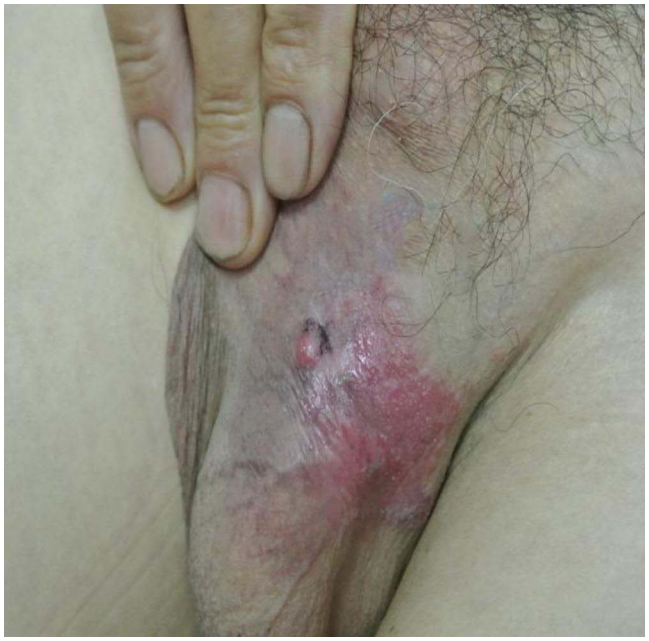

Figure 3 Exudation in the focus area can be noticed.

Clinical Manifestations Influence Postoperative Recurrence

In this research, we identified several clinical factors associated with recurrence of EMPD. Our findings evaluated the factors including age, gender, course of disease, history of immunosuppression, size of lesion, and misdiagnosis in diagnosis etc., although no correlation was found between these factors and recurrence. Intriguingly, univariate analysis showed that the postoperative recurrence rate of primary EMPD patients with ill-defined tumour borders, exudation and nodules was statistically significant ($P < 0.05$) as shown in Table 1. Multifactor analysis taking recurrence as the dependent variable (0 = No, 1 = Yes), whether there were ill-defined tumour borders, exudation and nodules was included in multivariate logistic regression analysis. The results showed that whether there were ill-defined tumour borders (OR=64.045, CI 3.252–1261.346), exudation in the focus area (OR=0.035, CI 0.003–0420) and the presence of nodules (OR=0.023, CI 0.001–0.494) were independent risk factors for the recurrence of primary EMPD (Table 2).

Discussion

With a global incidence of 0.4–0.6 per million person-years, primary EMPD was a rare disease. Unfortunately, the postoperative recurrence rate of primary EMPD was high, ranging from 20% to 60%.[11] In Western studies, the incidence was predominantly observed in females, with a male-to-female ratio ranging from 1:2 to 1:7. Conversely, in Asian populations, male patients were more prevalent.[12] Our study collected 40 cases with primary EMPD, among which 15 patients relapsed, reflecting a recurrence rate of 37.5%, aligning with previously reported figures.[8,13,14] The predominance of male patients in our cohort, constituting 77.5% of cases, echoed findings in Asian populations from other studies.[12,15] The median time to diagnosis was 48 months, ranging from 1 month to 20 years, primarily due to the nonspecific symptomatology of primary EMPD. Many patients presented solely with pruritus and erythema, resulting in delayed treatment.[16] Notably, 31 patients

Table 2 Multivariate Analysis of Factors Affecting Risk of Recurrence from Primary EMPD

Variable	β	SE	Wald	OR(95% CI)	*P*
Boundary	4.160	1.521	7.483	64.045(3.252, 1261.346)	0.006
Exudation	3.321	1.261	7.015	0.035(0.003, 0420)	0.008
Nodules	2.950	1.562	5.813	0.023(0.001, 0.494)	0.016

received misdiagnoses such as "eczema", "tinea cruris", and "eczema-like dermatitis", leading to localized corticosteroid use for itch relief. Given the genital area's common involvement, patients often resort to self-treatment, potentially delaying formal medical evaluation and treatment.[17] Owing to the limited effect of chemotherapy and the poor prognosis of patients with distant metastases,[18] surgery had become the first choice for treating primary EMPD. Primary EMPD mainly adopted wide local excision (WLE) and Mohs micrographic surgery.[15] Despite this, scant literature existed regarding postoperative EMPD recurrence, motivating our investigation into high-risk factors for such recurrences.

Our findings demonstrated that the ill-defined tumour borders of primary EMPD was an independent risk factor for postoperative recurrence, which was consistent with the study of Hu, J.[19] Paget's cells could involve mucosal areas (anal canal, vaginal and urethral mucosa) and infiltration of cutaneous appendages was a feature. Owing to primary EMPD had a skipping pattern and tends to be multicentric,[20] resection margins were often positive and local relapses were common. Even when intraoperative frozen biopsies were negative, they were more likely to lead to recurrence in patients because of the high false-negative rate.[21] Thus, the ill-defined tumour borders could be considered as a potential risk factor.

Additionally, the presence of exuding skin lesions also increased the probability of postoperative disease recurrence, which was consistent with a previous study.[17] The presence of exudation at the skin lesions might be associated with a local inflammatory response, and chronic inflammation has been shown to be one of the culprits in tumorigenesis and progression as well as recurrence.[22] A prolonged localized inflammatory response was more likely to lead to disease recurrence.

Furthermore, the presence of nodules on the lesion surface was associated with increased postoperative recurrence risk. We consider that the clinical nodules might be related to the pathological depth of infiltration, and at the same time, multivariate analysis also proved that the depth of invasion was an independent prognostic factor of primary EMPD. Clinical nodules were related to pathological infiltration depth, and simultaneously, multivariate analysis showed that invasion depth was an independent prognostic factor of primary EMPD. Based on previous studies,[17] tumour-specific survival was decreased with increasing depth of invasion, and some scholars reported that depth of invasion was the key factor affecting survival rate through multivariate analysis. Another study also pointed out that the depth of invasion was an independent prognostic factor of primary EMPD, and the invasion of the subcutaneous level or deeper level significantly shortened the cancer-specific survival period.[23]

While some researchers attribute disease site to recurrence risk, suggesting that the average disease-specific survival rate of patients with anorectal primary EMPD was significantly lower than that of patients with primary EMPD at other sites,[24] our study found no significant difference in overall survival rates among groups with different lesion sites, potentially due to the predominant perineal lesion location in our cohort, which was consistent with a study in Taiwan.[21]

Other researchers reported that the tumor size of primary EMPD affected the recurrence of the disease. However, such an association was not observed in our study. We found that tumour size and presentation as single or multiple lesions were not related to disease recurrence. Some studies had analyzed the effect of tumour size on prognosis. After reviewing the global cooperative database, Xu, C. and Safieddine, N. published a report that tumour size was not a prognostic factor for the disease.[25,26] They also analyzed the importance of assessing tumour size and concluded that tumour size had less impact than other tumour characteristics, which is in line with our research.

In our research, ill-defined tumour borders, exudation and nodules were high-risk influencing factors for recurrence of primary EMPD. In accordance with the studies of other scholars and our experience, patients with ill-defined tumour borders can expand the incision by 3 cm in the direction of ill-defined to avoid recurrence caused by residual cancer cells as much as possible. Moreover, the presence of localized nodules in the patient may represent a deeper infiltration of Paget's cell, but Paget's cell invasion of subcutaneous fat was rare, and the ability to cut to the depth of subcutaneous fat was sufficient to cure the disease.[27] The disease was easily misdiagnosed due to its unremarkable clinical presentation. In this study, 31 (77.5%) patients were misdiagnosed and they applied ointments were applied for a long period of time, resulting in erosion and exudation of the lesions. In case the patient's signs and symptoms did not improve, biopsy of skin lesions could be prioritized, and early diagnosis and surgical eradication of EMPD was the key to treatment.

Our study had some limitations. First, the data were retrospectively extracted from the electronic medical record system, which could lead to potential bias or misinterpretation in data extraction. In addition, the number of patients in this study was small. Secondly, we were a dermatology department. Finally, we might lose some patients to urology or

gynaecology, which might lead to bias in the selection of clinical features. Multi-centre studies with larger cohorts and longer follow-up were needed.

Conclusion

As the postoperative recurrence rate of EMPD was very high, we investigated the clinical features and risk factors for postoperative recurrence. Our study suggested that ill-defined tumour borders, exudation and nodules in the epidermis of primary lesions should be considered as independent risk factors for disease recurrence, which might provide useful suggestions for the diagnosis, treatment and follow-up of primary EMPD.

Ethical Approval

Ethical approval was given by the Medical Ethics Committee, the First Affiliated Hospital of Chongqing Medical University (number: K2023-335). This study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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