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Extramammary Paget's disease: An analysis of plastic surgical treatment, clinical and histopathological characteristics, and prognosis ☆

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Introduction

Extramammary Paget's disease (EMPD) is a rare intraepithelial adenocarcinoma characterized by the presence of Paget cells with clear cytoplasm in the epidermis.[1] It accounts for approximately 1%-2% of vulvar cancers and typically affects older individuals aged 60–80 years, with a higher incidence seen in Caucasians than in other races. Studies have reported that the male-to-female sex ratio of patients with EMPD differs across races, with the proportion of female patients being higher among Caucasians and the proportion of male patients being higher among Asians (male-to-female sex ratio of 3:1).[2,3] Overall, the male-female ratio of EMPD is approximately 1.5:1, indicating that men are more commonly affected than women. EMPD is frequently present in areas with an abundance of apocrine sweat glands, such as the scrotum, penis, vulva, perineum, perianal region, groin, and axilla.[2] Its clinical manifestations are nonspecific and mainly include erythema, erosions, exudation, bleeding, ulcerations, and desquamation accompanied by itchiness or pain. The clinical manifestations of EMPD are nonspecific, primarily presenting as eczema-like lesions. Notably, EMPD is classified into primary (originating in the epidermis) and secondary (associated with underlying internal malignancies, e.g., genitourinary or gastrointestinal carcinomas) subtypes.[4] Clinically, EMPD is further stratified into epidermal-

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Abbreviations: EMPD, Extramammary Paget's disease.

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limited, microinvasive (<1 mm), and invasive (>1 mm) categories to guide therapeutic strategies and prognostic evaluation.[5]

In the early stage, EMPD is highly prone to misdiagnosis and missed diagnosis, and affected patients are highly likely to receive delayed treatment. Furthermore, the tumor cells of EMPD are often distributed in multiple clusters, and resection margins are difficult to determine owing to the irregularity of lesion boundaries.[1,3] Furthermore, subclinical extension of EMPD is a critical consideration in surgical planning. Subclinical extension refers to the spread of tumor cells beyond the clinically or dermatoscopically visible lesion boundaries, often requiring wider resection margins (e.g., ≥2 cm) to achieve clear margins. This phenomenon is distinct from the irregularity of lesion boundaries but contributes to the challenge of complete excision. Dermatosurgical studies have demonstrated that EMPD may extend several centimeters beyond the visible lesion, necessitating meticulous margin assessment.[35,36] The mortality rate of invasive EMPD (defined as tumor invasion depth >1 mm) is 66.7%.[3] In contrast, microinvasive disease (<1 mm depth), particularly in vulvar EMPD, has a mortality rate approaching zero, while significant outcome differences emerge when invasion exceeds 1 mm, as supported by meta-analyses[4]. Notably, mortality rates for in situ EMPD (<1 mm) remain very low.[4] Furthermore, prognosis varies by anatomic site. A recent study stratified outcomes of EMPD into perianal, vulvar, and penoscrotal subtypes, highlighting that penoscrotal EMPD with deep invasion (>1 mm) carries the highest mortality risk.[37] Consequently, wide local excision (WLE) remains the primary treatment for EMPD, postoperative recurrence rates vary widely, ranging from 27% to >60%,[21,22] primarily due to subclinical extension and challenges in margin assessment. Other modalities include photodynamic therapy, CO_2 laser, imiquimod cream, and chemoradiotherapy. Mohs micrographic surgery has emerged as the gold standard for EMPD due to its superior cure rates (>95%), enabled by real-time intraoperative frozen section analysis with immunohistochemistry to confirm margin clearance, thereby minimizing recurrence.[6,19,25,26] Radiation therapy is a viable alternative for inoperable or recurrent cases, achieving local control rates of 70%-80%.[6]

In the present study, the clinical and histopathological characteristics, immunohistochemical features, surgical methods, and recurrence factors in 64 patients with EMPD diagnosed and treated at our department were retrospectively analyzed to provide reference for the early diagnosis, treatment, and prognostic assessment of patients with EMPD.

Materials and methods

Study subjects

A total of 64 EMPD patients who came from the Plastic Surgery Department of Shandong Provincial Hospital between January 1, 2014, and January 1, 2024, were included in the study. They all had complete medical records, including the clinical and histopathological characteristics, immunohistochemical features, surgical methods, and prognosis (follow-up more than 6 months, median follow-up: 36 months). Detailed clinical history, relevant data and prognostic factors were retrospectively analyzed.

H&E and Immunohistochemical staining

Histopathological data were analyzed by dermatopathologists using H&E and immunostains for CEA, CK7, CAM5.2, CK8/18, CK5/6, S100, HMB45, and p40. Tumor invasion depth (>1 mm) was recorded. Specimens were derived from excisional (n = 48), punch (n = 12), and shave biopsies (n = 4). All immunostains were performed on formalin-fixed, paraffin-embedded (FFPE) excision specimens. Margin status was assessed on permanent sections with IHC; no frozen sections were used for margin analysis.

Statistical analysis

The data were analyzed using SPSS software (version 21.0; Chicago, IL, USA). The chi-squared test and Fisher's exact test for categorical variables were used to compare the recurrence factors between the case and control groups. This retrospective case-control study included 64 EMPD patients. Recurrent cases (n = 16) were compared to nonrecurrent controls (n = 48) matched by age, sex, follow-up duration, and anatomic site. Multivariate logistic regression and chi-squared tests were was used to analyze the independent risk factors. The 95% confidence intervals for crude odds ratios were also calculated. Statistical significance was set at $P < 0.05$.

Results

General data

The average age of the patients was 70.12 (range, 61-81 years), 2 were female and the rest were male. The disease duration at the time of consultation was 0.5-7.5 years, with a mean duration of 3.8 years. All patients were initially diagnosed in the dermatology department. Clinicians should maintain a high index of suspicion for EMPD in elderly patients with asymmetrical, refractory eczema-like lesions in apocrine gland-rich regions (e.g., vulvar, perianal, axillary).

Sixty of the 64 patients were misdiagnosed as having the following conditions: eczema, Bowen's disease, and squamous cell carcinoma, resulting in a misdiagnosis rate of 93.75%. Misdiagnosis was defined as a discrepancy between the initial clinical diagnosis (documented in physician notes) and the final histopathological diagnosis of EMPD. After various drug therapies were proven ineffective, confirmed diagnoses were made based on skin biopsy findings, and the subjects were transferred to the urologic surgery department or the plastic and aesthetic surgery department for further treatment.

Clinical manifestations

Among the 64 patients, 62.5% (n = 40) reported pruritus (itching), while 37.5% (n = 24) experienced pain (Table 1). Erythema (100%), crusting (81.25%), and scaling (50%) were the most common clinical features. Lesions were located at one or more sites on the mons pubis, penis, scrotum, and groin (Fig. 1) (Table 1). This study exclusively included EMPD cases involving the mons pubis, penis, scrotum, and groin. Patients with vulvar or perianal EMPD were excluded due to referral patterns (managed by gynecologic/colorectal departments).

Histopathological characteristics

Microscopic examination revealed epidermal parakeratosis and the presence of various numbers of Paget cells scattered in nest-like patterns. The cells were large and round or oval-shaped with abundant pale cytoplasm, large dark nuclei, and a certain degree of mitosis in the darkly stained parts of the nucleolii (Fig. 2). Infiltrative growth with appendage involvement was observed in 37.5% of patients (24/64): 18.75% (12/64) showed hair follicle involvement, 6.25% (4/64) had sweat gland involvement, and 12.5% (8/64) exhibited both. All wide local excision (WLE) specimens (n = 64) showed negative margins on final pathology, with no tumor cells detected at medial, lateral, superior, inferior, or deep margins. Initial biopsies (shave/punch) were excluded from margin analysis. Final permanent sections identified occult margin positivity in 8/64 cases (12.5%), missed by intraoperative frozen sections

Table 1
Clinical characteristics of EMPD subjects.

Age (years)		n (%)
	60-69	20 (31.25)
	70-79	36 (56.25)
	80-89	8 (12.50)
Age (Mean ± SD)	70.12 ± 5.48	
Misdiagnosis duration (years)	Range	0.5 ~ 7.5
	Mean	3.82
Localization		*n (%)*
	Scrotum	20 (31.25)
	Scrotum + Penis	16 (25.00)
	Penis	8 (12.50)
	Scrotum + Penis+ Mons pubis	8 (12.50)
	Scrotum + Penis+ Goin area	8 (12.50)
	Scrotum + Penis + Mons pubis + Goin area	4 (6.25)
Clinical manifestations		*N (%)*
	Erythema	64 (100.00)
	Incrustation	52 (81.25)
	Scale	32 (50.00)
	Erosion	28 (43.75)
	Exudate	24 (37.50)
Symptoms		
	Itching	40 (62.50)
	Pain	24 (37.50)
	Neither	16 (25.00)
Tumor boundaries	Well-defined	36 (56.25)
	Ill-defined	28 (43.75)

Table 2
Immunohistochemical characteristics of MPD subjects *n* (%).

	CEA	CK7	CAM5.2	CK8/18	CK(AE1/AE3)	CK34BE12	P63
Immunohisto-	64 (100.00)	64 (100.00)	64 (100.00)	64 (100.00)	12 (18.75)	12 (18.75)	8 (12.50)
chemistry	PHH3	CK5/6	S-100	HMB45	P40	ki-67+	
stainings	8 (12.50)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	>25%	10%~25%
						28 (43.75)	36 (56.25)

Among the 64 patients, 24 exhibited infiltrative growth of varying extents with appendage involvement. Furthermore, twelve had hair follicle involvement, 4 had sweat gland involvement, and 8 had both hair follicle and sweat gland involvement.

Immunohistochemistry staining

Immunohistochemical staining indicated that all 64 patients were positive for CEA, CK7, CAM5.2 (Fig. 2), and CK8/18 and negative for CK5/6, S100, HMB45, and p40. The percentages of subjects with p63, CK(AE1/AE3), CK34BE12, and PHH3 expression was 12.5%, 18.75%, 18.75%, and 12.5%, respectively. The Ki-67+ expression level ranged from 10% to 65%, with high expression (>25%) in 6 subjects (Table 2).

Treatment and sequelae

Treatment status

All patients underwent surgical treatment in our department with the following methods: wide excision followed by direct suture (8 cases), wide excision followed by skin flap transfer (thirty-six cases), wide excision followed by skin flap transfer and free skin grafting (twelve cases), and wide excision followed by free skin grafting (8 cases). Skin flap transfer was performed using scrotal flaps (sliding flap, scrotal bilobed rotation flap, scrotal bipedicle flap, and

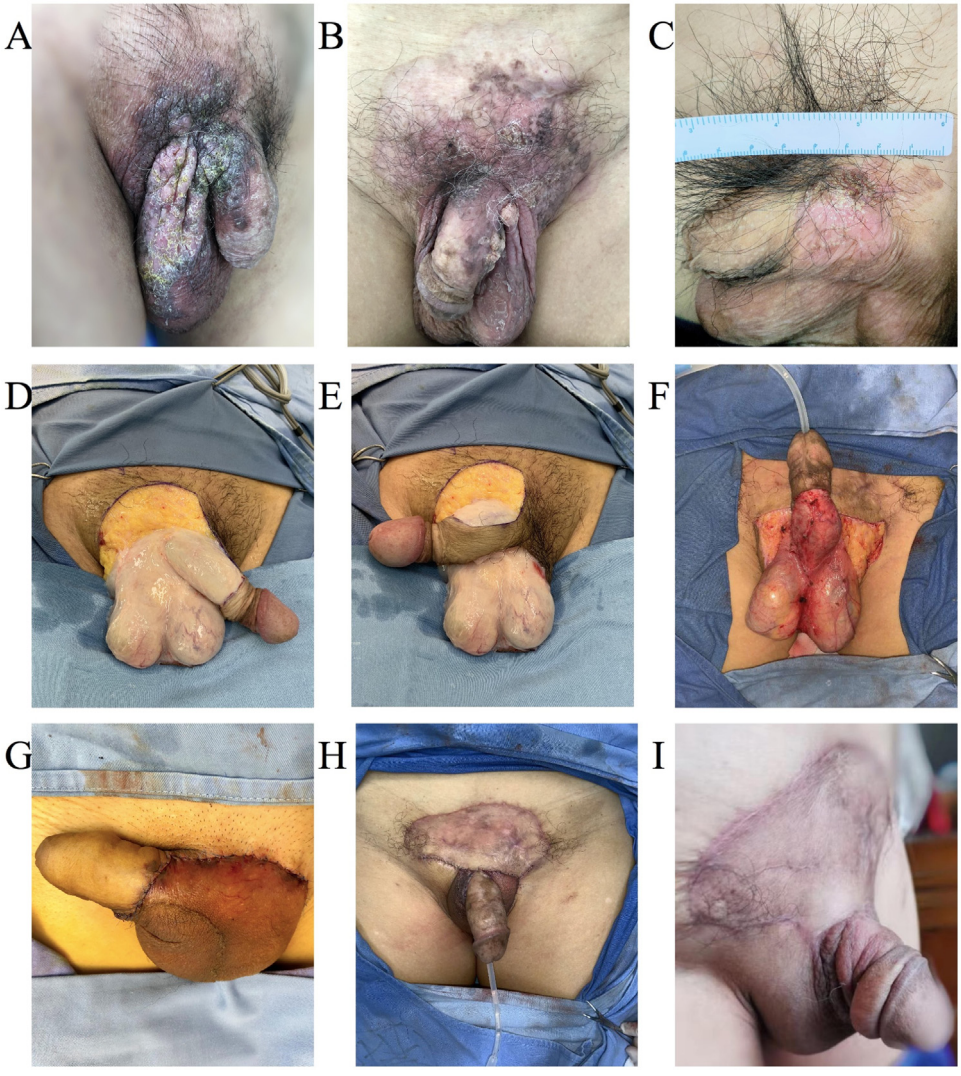

Fig. 1. (A-C) Clinical manifestations of EMPD subjects, mainly including erythema, erosions, exudation and desquamation; (D-F) The intraoperative views; (G and H) The immediate postoperative views; (I) The 3-month postoperative views.

preputial-scrotal flap), inguinal flaps, or lower abdominal wall flaps. Among the 8 patients in whom free skin grafting was performed, 3 received full-thickness skin grafts and one received a medium-thickness skin graft. Wide excision was performed with a minimum margin of 2 cm from the clinically visible lesion boundary, based on prior studies demonstrating subclinical extension in EMPD.[18,19] Margins were extended beyond 2 cm if intraoperative frozen sections suggested incomplete excision. All surgeries were performed by 3 senior plastic surgeons following a standardized protocol.

Intraoperative frozen sections of WLE specimens (n = 64) showed no tumor cells at resection margins. However, final permanent sections with immunohistochemistry (IHC) identified occult Paget cells in 8/64 cases (12.5%), all of which were missed on frozen sections. These cases were excluded from recurrence analysis. All pathological descriptions in this manuscript refer to WLE

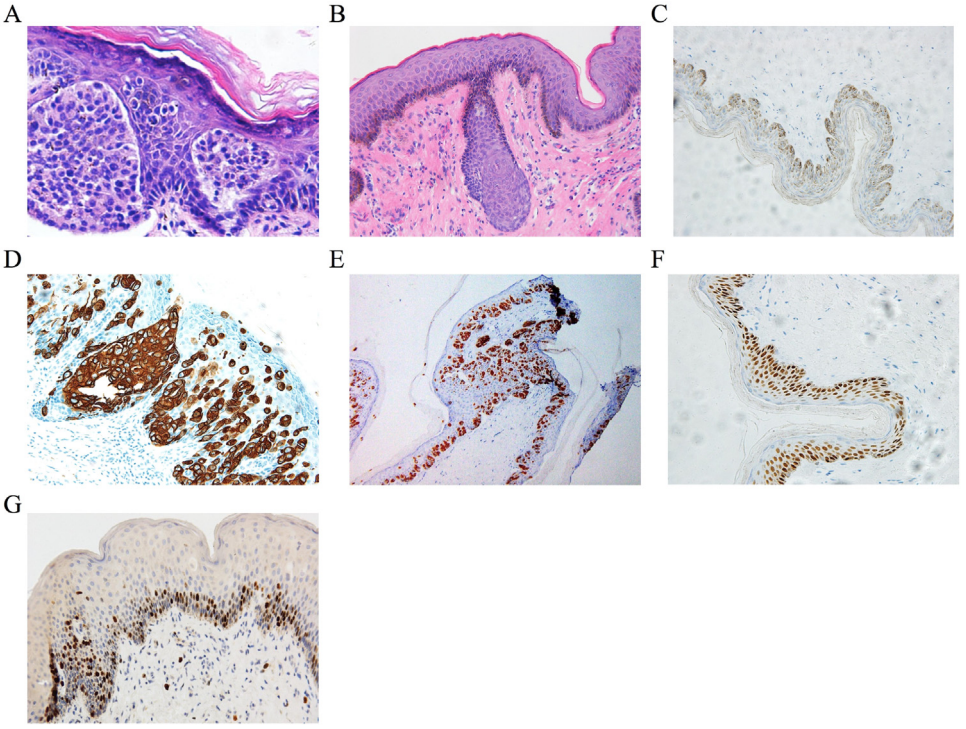

Fig. 2. (A and B) Paget cells were large and round with large dark nuclei, prominent nucleoli and large amount pale cytoplasm. The cells may be arranged in rows, nests or cords and extended in the basal and parabasal areas of the epithelium.(H&E × 200) (C) Paget cells highlighted by immunostaining for CEA (DAB stain × 200). (D) Paget cells highlighted by immunostaining for CK7 (DAB stain × 200). (E) Paget cells highlighted by immunostaining for CAM5.2 (DAB stain × 200). (F) Paget cells highlighted by immunostaining for CK8/18 (DAB stain × 200). (G) The expression of ki-67 in Paget cells (DAB stain × 400).

specimens unless stated otherwise. Sutures on the penis, scrotum, and external skin incisions at the periphery were removed at 7 days postoperatively and sutures at the graft recipient sites at 12 days postoperatively. The skin flaps and skin grafts of the 48 patients healed by primary intention. Postoperative hematoma occurred at the surgical site in 2 patients who underwent wide excision followed by skin flap transfer and free skin grafting. The surgical site was re-opened for examination, bleeding was stopped, a bandage was applied, and healing was achieved after dressing changes. Necrosis occurred in the scrotal flap of 2 patient, the distal part of the inguinal flap of 4 patients, and edges of the skin grafts of 8 patients, which healed after dressing changes during the hospitalization period. All patients were satisfied with the postoperative penile and scrotal appearance (Table 3). Urinary function was not affected, and the overall effects of surgery were satisfactory.

Recurrence

The median follow-up duration was 36 months (range: 6-60 months), with a distribution of 6 months in 16 patients, 12-36 months in 32 patients, and over 36 months in 16 patients. Between 12 and 60 months postsurgery, recurrences occurred in 8 patients at 60, 58, 36, and 35 months postsurgery. All sixteen patients experienced milder symptoms after recurrence, which mainly involved the appearance of erythema around the resection margins. Given that daily life and survival were not significantly impacted, none of the patients opted for reoperation, and recurrent cases were managed with topical imiquimod (75%, n = 12) or radiotherapy (25%, n = 4).

Table 3
The surgical methods of EMPD subjects n (%).

Surgical method		n (%)
Wide excision followed by direct suture		8 (12.50)
Wide excision followed by skin flap transfer		
	Sliding flap	12 (31.25)
	Scrotal bilobed rotation flap	8 (12.50)
	Scrotal bipedicle flap	8 (12.50)
	Preputial-scrotal flap	8 (12.50)
Wide excision followed by skin flap transfer and free skin grafting		
	Inguinal flaps	4 (6.25)
	Sliding flap	4 (6.25)
	Scrotal bilobed rotation flap	4 (6.25)
Wide excision followed by free skin grafting		
	Lower abdominal wall flaps	4 (6.25)
	Sliding flap	4 (6.25)

Analysis of factors affecting recurrence

The recurrence risk factors studied were first analyzed with a chi-squared test to remove the potential confound factors. The depth of infiltration, involvement of skin appendages, ill-defined lesion borders, and level of Ki-67+ expression were variables found to be significantly associated with EMPD recurrence ($P < 0.05$) (Table 4). Among dermal-invasive cases (n = 20), all recurrences occurred in patients with invasion ≥1 mm (12/12).

By using multivariate logistic regression analysis, Table 5 shows the results of the multivariate analysis: Involvement of skin appendages and level of Ki-67+ expression were independent recurrence risk factors for EMPD.

Discussion

Paget's disease (PD), a rare malignancy usually characterized by an eczema-like rash, is classified as mammary (MPD) or extramammary (EMPD). At present, the pathogenesis of EMPD remains unclear. A number of theories have been postulated, with the majority suggesting that EMPD arises from the apocrine sweat glands[5] and mainly occurs in areas with an abundance of apocrine sweat glands, such as the scrotum, penis, vulva, and perianal region.[6] EMPD has a low incidence rate, accounting for 1%-2% of vulvar cancers,[7] and is uncommonly encountered in plastic surgery.

EMPD typically affects older individuals aged 60-80 years and can develop in both men and women. Studies have reported that the male-to-female sex ratio of patients with EMPD differs across races, with the proportion of female patients being higher among Caucasians and the proportion of male patients being higher among Asians (male-to-female sex ratio of 3:1).[2,8] This study predominantly included elderly male patients (62/64, 96.9%), aligning with the age and sex distribution of EMPD in Asian populations.[2,10] Delayed diagnosis reflects both patient-related factors (e.g., healthcare-seeking barriers) and provider-related factors (e.g., misdiagnosis as eczema due to limited EMPD awareness).[22] In general, clinicians have an inadequate understanding of EMPD, as shown by the 93.75% of incorrect initial diagnoses in the patients with EMPD in this study. EMPD is frequently misdiagnosed as eczema, dermatitis, or Bowen's disease. Therefore, clinicians should maintain a high index of suspicion for EMPD in elderly patients presenting with asymmetrically distributed, solitary, refractory eczema-like skin lesions in apocrine gland-rich regions (e.g., vulvar, axillary, perianal), particularly when high-risk features—including dermal invasion ≥1 mm, appendage involvement, or elevated Ki-67 expression (>25%)—are identified, as these factors align with meta-analytic evidence on EMPD prognosis.[1,2]

The histohistopathological changes that occur with EMPD are mostly concentrated in the epidermis, with tumor cells extending down hair follicles or involving skin appendages, such as

Table 4
Analysis of factors affecting recurrence of EMPD subjects *n* (%).

Risk factors	Cases *n*	Recurrences *N* (%)	*P*
Age (years)			
>70	44	8 (18.18)	.861
<70	20	8 (40.00)	
Misdiagnosis duration (months)			
≥24	36	12 (33.33)	.147
<24	28	4 (14.28)	
The depth of infiltration			
Epidermis	44	4 (9.09)	.013
Dermis	20	12 (60.00)	
Involvement of skin appendages			
+	24	16 (66.67)	.001
-	40	0 (0.00)	
Tumor boundaries			
Well-defined	30	4 (13.33)	.037
Ill-defined	32	12 (37.50)	
Other tumors			
+	8	4 (50.00)	.437
-	56	8 (14.29)	
CK(AE1/AE3)			
+	24	8 (33.33)	.463
-	40	8 (20.00)	
CK34BE12			
+	12	8 (66.67)	.332
-	50	8 (15.38)	
P63			
+	8	0 (0.00)	.061
-	56	16 (28.57)	
PHH3			
+	8	4 (50.00)	.241
-	58	12 (21.43)	
Ki-67+			
>25%	28	16 (57.14)	.001
10%~25%	36	0 (0.00)	

Table 5
Multivariate logistic regression analysis on the recurrence risk factors of EMPD subjects.

Risk factors	*P*	OR	95% CI
The depth of infiltration Dermis	0.459	1.865	2.363-5.229
Involvement of skin appendages	0.027	5.123	0.851-17.981
Tumor boundaries Ill-defined	0.353	1.098	0.108-0.996
Ki-67+>25%	0.031	4.976	0.717-16.697
Age (>70)	0.098	2.342	0.936-1.195

sweat glands in certain patients, and with significant tumor cell invasion into the dermis occurring in other patients. The proportion of patients with appendage involvement is generally similar to that reported in previous studies.[11,12] Previous studies have found that the presence of skin appendage involvement in EMPD typically results in the extension of tumor cells towards the deeper dermal layers along the appendages rather than infiltration from the epidermis to the dermis.[11] In the present study, hair follicle involvement was the most common, followed by sweat gland involvement. In performing local treatment, the presence of tumor cells in the deeper dermal layers due to appendage involvement must be considered to avoid recurrence caused by incomplete lesion removal.

EMPD is histologically characterized by intraepidermal Paget cells, differentiated from Bowen disease and melanoma via immunoprofile (CK7+/CEA+/HMB45-).[13,14] Key immunohistochemical (IHC) profiles include: EMPD: CK7+/CEA+/EMA+/S100-/HMB45-; Bowen's disease: CK7-/CEA-;

Melanoma: S100+/HMB45+,[13,14]CK20 helps distinguish primary (CK7+/CK20-) from secondary EMPD (CK7+/CK20+),[14] CAM5.2 (CK8/18) and CEA highlight glandular differentiation. In this study, Ki-67+ expression correlated with recurrence (high Ki-67: >25%, $P < 0.05$), supporting its role in EMPD prognostication. Recent studies further suggest TRPS1 as a novel EMPD marker (sensitivity >90%).[15]

Currently, there are a variety of treatment modalities available for EMPD, with surgical excision being the mainstay of treatment.[16] Previous research has indicated that the adoption of antiandrogen therapy yields certain treatment effects.[17] In addition, adequate width and depth must be ensured during surgical excision. Studies have reported the adoption of wide excision with resection margins of 2-3 cm that extend down to the deep fascia. To ensure the negativity of resection margins and base of the excision, an intraoperative rapid frozen section procedure may be performed to enable an increase in excision width when resection margins are positive. Although this effectively reduces recurrence[18] accurate determination of lesion boundaries and complete excision of lesions may not be easily achieved as it is usually difficult to discern lesion boundaries with the naked eye. Recent research has advocated the use of Mohs micrographic surgery to achieve lower recurrence rates.[19] For centers lacking MMS expertise, preoperative mapping biopsies (e.g., scouting biopsies at 1-2 cm intervals beyond clinical margins) can delineate subclinical extension, optimize excision planning, and reduce operative time.[20]

The repair of wounds resulting from the resection of large lesions is a key challenge faced during EMPD treatment by wide excision, and defects may be surgically repaired by adopting methods such as direct suturing of the scrotal skin, skin flap transfer, and free skin grafting. Larger defects in the mons pubis and inguinal areas are repaired using lower abdominal flaps and inguinal flaps in addition to various scrotal flap transfer techniques. As most of the study patients were elderly men with lax scrotal skin, the penile and scrotal defects were mainly repaired using bipedicle scrotal flaps and multilobed rotation scrotal flaps. Therefore, skin flap repair methods are the mainstay of EMPD treatment in plastic surgery practice, as they satisfy the functional and aesthetic demands of patients. Through the full utilization of the laxity and elasticity of the scrotal skin and flexible application of skin flap creation techniques for the preparation of various types of scrotal flaps, defects can be effectively repaired.

The recurrence rate of EMPD has remained high, with studies in China and other countries reporting recurrence rates of 16%-44%.[21,22] The 25% recurrence rate in our cohort may reflect false-negative margins on frozen sections, which lack IHC. Mohs micrographic surgery (MMS) remains the gold standard for EMPD, achieving cure rates of 93%-97% through real-time margin control with CK7/CEA immunostaining on frozen sections.[20] In contrast, wide local excision (WLE) had a 25% recurrence rate in our cohort. The statistical analysis of the factors affecting recurrence in patients with EMPD revealed that the depth of infiltration, involvement of skin appendages, ill-defined lesion borders, and level of Ki-67+ expression were associated with EMPD recurrence ($P < 0.05$). Involvement of skin appendages and level of Ki-67+ expression were independent recurrence risk factors for EMPD. A number of studies have shown that different depths of dermal infiltration by tumor cells in patients with EMPD are associated with significantly different prognoses.[23-25] A study conducted by Hong Kong researchers found that dermal invasion by lesions led to an increase in patient mortality.[26] What's more, the mucosal invasion of EMPD lesions has been reported as an major risk factor for incomplete excision, local recurrence, and poor survival outcomes.[27-28] All patients with appendage involvement (24/64) developed recurrences, highlighting the critical role of adnexal invasion in EMPD progression. However, generalizability is limited to male-predominant cohorts, as vulvar/perineal EMPD may exhibit distinct behavior.[9]

Among the various immunohistochemical factors investigated in this study, high Ki-67+ expression level (>25%) was the only factor significantly related to EMPD recurrence, which is uncommon in previous studies.[29-30] Ki-67+, a nuclear antigen expressed during the G1, S, G2, and M phases of the cell cycle, is one of the most reliable indicators of tumor cell proliferative activity.[4] Given the limited sample size of this study, further large-sample studies are required to validate the effectiveness of Ki-67+. Other studies have reported that HER-2 is closely associated with tumor cell expression and prognosis in patients with EMPD,[31,32] which suggests the potential for its use as a therapeutic target in future treatment.[33] And, nectin cell adhesion molecule 4

(NECTIN4) has attracted attention as a potential therapeutic target for EMPD. The most EMPD lesions exhibited strong NECTIN4 expression, and high NECTIN4 expression was significantly associated with increased tumor thickness, advanced TNM stage, and worse disease-specific survival. These results support the potential use of NECTIN4-targeted therapy for EMPD.[34]

Conclusions

Extramammary Paget's disease (EMPD) predominantly affects elderly individuals, with a male-to-female ratio varying by geographic and racial demographics. While Asian populations show a male predominance (3:1), Caucasian cohorts report near-equal gender distribution. These differences likely reflect anatomic site preferences and healthcare-seeking behaviors rather than intrinsic biological predilection.[4]

In this study, the recurrence rate after wide local excision (WLE) was 25%, attributed to subclinical extension and false-negative margins on frozen sections. To mitigate recurrence, Mohs micrographic surgery (MMS) should be prioritized, achieving cure rates >95% through real-time immunohistochemical margin control For centers lacking MMS expertise, preoperative mapping biopsies and multidisciplinary collaboration are critical to optimize outcomes.

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Review Board of Shandong Provincial Hospital Affiliated to Shandong University.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Ran Huo and Jianhai Bi conceived and designed the study. Song Wang performed the data analyses and wrote the manuscript wrote the manuscript. Gunhyung Kee collected and analyzed the data. Renrong Lv reviewed and edited the manuscript. All authors read and approved the manuscript.

Declaration of competing interest

The authors have declared that no competing interests exist.

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