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Case Report

Genitourinary extramammary Paget's disease: review and outcome in a multidisciplinary setting

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Abstract: Background: Extramammary Paget's disease (EMPD) is a rare malignant disease originating from the apocrine glands involving the perineum, vulva, axilla, scrotum, and penis. Objective: To study the clinical presentation, extent of disease, efficacy of treatment, and survival outcomes of the cases in a single institution. Methods: Retrospective observation data analysis of 19 EMPD cases was performed. Demographic information, clinical management records, and histopathologic data of individual cases were obtained from the inpatient hospital data registry. Results: The mean age (years) at time of diagnosis was 62.4 with equal gender distribution. Synchronous tumors were detected in 6 cases (31.5%). 18 out of 19 patients underwent definitive surgical management in the form of wide local excision (WLE) and reconstructive surgery. Positive margins were found in 11 (68.8%) cases and 7 out of these 11 cases underwent second look surgical intervention to achieve oncological clearance or adjuvant oncology treatment. Follow-up period for living patients varied depending on time of diagnosis and definitive treatment. 10 out 19 cases (52.7%) were alive at the time of the study. Among the 7 cases of mortality from cancer, 5 cases died from progression of underlying associated malignancy and only 2 cases died with advanced stage of EMPD. Conclusion: EMPD can be quite aggressive, especially in the secondary form, and surgical management is challenging with a high rate of residual tumor at the surgical margin. EMPD can easily mislead the clinician and patient, leading to unnecessary delay prior to definitive effective management.

Keywords: EMPD, Extramammary Paget's Disease, clinicopathologic, Malaysia

Introduction

Extramammary Paget's Disease (EMPD) is a rare malignant disease originating from the apocrine glands involving the perineum, vulva, axilla, scrotum, and penis. EMPD of the scrotum and penis was first described by Crocker in 1889 [1, 2]. EMPD typically appears as vague dermatological symptoms at initial presentation and has a long latency period before evidence of cancer or metastasis appears. Depending on the origin of tumor and association of underlying tumor, EMPD has a wide spectrum of management and an unpredictable incidence of recurrence, leading to different curative and survival outcomes [1-4]. Depending on the presence or absence of associated underlying malignancy such as malignancy of the gastrointestinal tract or urogenital tract, EMPD can be primary or secondary [5-7]. There may be underlying primary or non-cutaneous malignancy in up to 42% of EMPD cases. However, the exact relationship between EMPD and an associated malignancy is uncertain [8, 9].

Histologically, EMPD is characterized by the presence of Paget cells which have abundant pale cytoplasm, pleomorphic nucleus, and prominent nucleolus. They are distributed either as single cells or in small clusters with variable extent (**Figure 1**). The cytoplasm often contains diastase-resistant periodic acid-Schiff (PAS)-positive or mucicarmine-positive material. Invasion to underlying structures is characterized by the presence of scattered and dyscohesive neoplastic Paget cells infiltrating the underlying dermis or submucosa [10, 11]. EMPD can be confirmed by several diagnostic immunohistochemical markers such as CK7, BerEp4, high molecular weight cytokeratin (HMWCK), and p63. In our center, immunohistochemical markers such as CK20 and CK 7 were used to confirm the diagnosis (**Figure 2**).

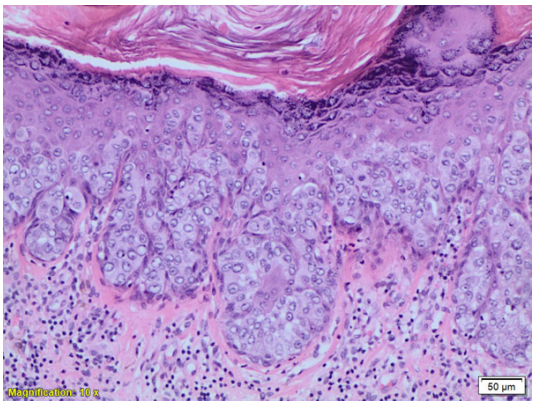

Figure 1. Squamous epithelium demonstrating clusters of Paget cells in the basal layers. The Paget cells exhibit pleomorphic vesicular nuclei, with occasional distinct nucleoli and abundant pale pink cytoplasm (Hematoxylin & eosin stain, original magnification ×10 objective).

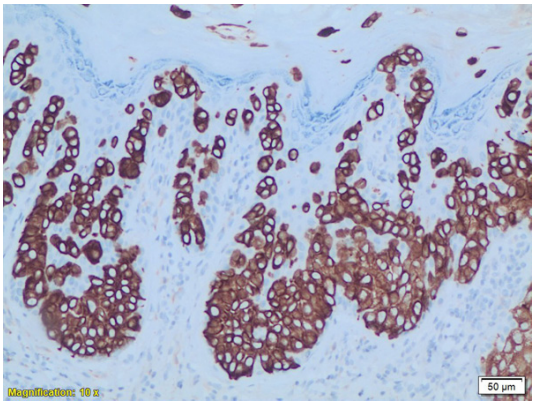

Figure 2. Malignant Paget cells stain strongly positive for CK7 while non-neoplastic squamous epithelium is negative for CK7 (CK7 antibody, original magnification ×10 objective).

Most available literature reports the epidemiology, diagnosis, and management of EMPD in a relatively small number of data sets or case reports due to rarity of the disease. This disease is characterized by the nonspecific initial presentation, presence of an underlying malignancy, aggressiveness of tumor, and high tendency of recurrence after surgical resection. Timely and appropriate medical care to get early diagnosis and effective management is very important to ensure a better outcome. In our case series, besides epidemiology, clinical presentation, modality of the treatment and outcome, we will review the point of patient's first consultation and the latency time before reaching a definitive diagnosis and treatment.

Material and methods

This study retrospectively reviewed the data of all EMPD cases involving the genitourinary area treated at University Malaya Medical Centre (UMMC), Kuala Lumpur from 1994 to 2019. Institutional Ethical Board approval (MECID.NO 2019619-7539) to review all records of these patients was obtained. Medical records of all patients were reviewed for demographic information, clinical data such as initial presenting symptoms, and primary area of involvement, year of diagnosis, latency period prior to getting the definitive diagnosis, primary clinician for the patient's first consultation, and definitive treatment modality including adjuvant therapy. Patients' oncological outcome was also reviewed.

Final histopathologic reports for all our cases were retrieved from UMMC Pathology department database to get the final histology report of the involved area, surgical margin status, and lymph node involvement. At the time of diagnosis, all patients received intensive staging with pelvic examination, transvaginal ultrasound, PAP smear in females, chest X-ray, mammography, cystoscopy, and colonoscopy to rule out associated malignancy in other areas. All surgical management was under the combined care of relevant clinical teams from the Urology, Gynaecology, and Plastic and Reconstructive team of UMMC. Data for recurrence post-surgical intervention, requirements of adjuvant systemic treatment, and survival status were obtained from patient's medical record. We retrieved the cause of death for deceased patients whether it was related to advanced disease progression or an unrelated cause for all our patients.

Results

A total of 19 cases of EMPD were identified at UMMC from the period 1994-2019. The mean age (years) at the time of diagnosis was 62.4. The male to female ratio of cases was almost 1:1 with 10 females and 9 male patients. The majority of the patients in our study were of Chinese ethnic group (**Table 1**).

The most common presenting symptoms were pruritus, swelling, and an erythematous lesion over the involved area (**Figure 3**). Among males, the primary site of lesion was the inguinoscro-

Table 1. Patient demographics and clinical presentation

Demography and patient characteristics	Number (%)
Total number of cases	19
Gender	
Male	9 (47.3%)
Female	10 (52.7%)
Primary site of tumor	
Vulva	9 (47.3%)
Penoscrotal	9 (47.3%)
Inguinal	1 (5.2%)
Primary team for first consultation (available data for 7 cases)	
Gynecology	2 (28.5%)
Primary care	3 (42.8%)
Dermatology	1 (14.2%)
Internal medicine	1 (14.2%)
Mean latency period to definitive diagnosis (range in months)	6.2 (range 2-12)
Regional lymph node involvement	3 (15.7%)
Associated malignancy	6 (31.5%)
Ovary	1
Bladder	1
Prostate	1
Vulva	1
Caecum	1
Breast	1

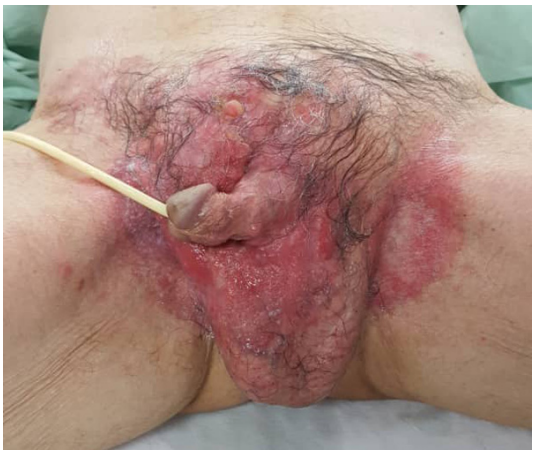

Figure 3. Erythematous lesion over the inguinoscrotal region.

tal region, while females presented with a lesion on the vulva, except for one who had a lesion in the inguinal area. Most of the patients had initial consultation with either the gynecologist, primary care physician, or dermatologist. The mean time interval between presentation and definitive treatment was 6.2 months (**Table 1**). At the time of diagnosis, 3 patients had regional inguinal lymphadenopathy which required them to undergo lymph node dissection during primary surgery. We found associated underlying malignancy in 6 out of 19 (31.5%) cases with the involvement of prostate, bladder, ovary, vulva, and caecum reported.

After establishing the diagnosis with biopsy in all cases, 18 patients underwent wide local excision (WLE) and reconstructive surgery, with one patient who refused definitive management and opted to seek alternative treatment. Patients also underwent vulvectomy (n=3) and penectomy (n=2) in addition to WLE. The patients with clinically evident regional lymphadenopathy (n=3) underwent regional lymph node dissection during primary surgery (**Table 2**). Patients with underlying associated malignancy underwent definitive treatment for their respective conditions except one patient with muscle-invasive bladder cancer who was offered definitive treatment in the form of radical cystectomy or radical radiotherapy and chemotherapy, but the patient refused. Histopathologic outcome was available only for 16 of the 18 patients who underwent definitive surgical intervention. Positive margins were detected in most of the patients (n=11, 68.8%). Patients who underwent regional lymph node dissection were all confirmed to have positive lymph node involvement. Patient with positive margins subsequently underwent surgical re-intervention (n=4) to achieve clearance with another 3 patients receiving adjuvant systemic chemotherapy and radiotherapy. The remaining 4 patients with positive margins declined further surgical or oncological intervention. They were put on surveillance (**Table 2**).

Survival outcomes of patients in this report showed that 7 out of 19 cases died due to can-

Table 2. Clinical management and survival outcomes

Treatment and survival outcome	Number (%)
Total number of cases	19
Definitive treatment	
WLE + Reconstructive surgery	13 (68.4%)
WLE + Reconstructive surgery + vulvectomy	3 (15.7%)
WLE + Reconstructive surgery + Penectomy	2 (10.5%)
Local excision + alternative treatment	1 (5.2%)
Regional lymph node dissection	3 (15.7%)
Treatment of associated malignancy	6 cases
Ovary	TAH + BSO
Bladder	TURBT (offered RT/RC + chemotherapy)
Prostate	ADT
Vulva	Vulvectomy
Caecum	Right hemicolectomy
Breast (triple negative)	Chemotherapy
Histopathology (Margin status)	16 available data
Positive	11 (68.8%)
Re-intervention (out of 11 positive margin cases)	
Surgical intervention	4 (36.3%)
Systemic treatment (Chemotherapy/Radiotherapy)	3 (27.2%)
Clinical surveillance	4 (36.3%)
Survival status	
Alive	10 (52.7%)
Deceased	9 (47.3%)
Disease progression (from associated malignancy)	5 (55.5%)
Disease progression (from EMPD)	2 (22.2%)
Unrelated (Non oncological)	2 (22.2%)

WLE-wide local excision, TAH + BSO-total abdominal hysterectomy and bilateral salpingo-oophorectomy, ADT-androgen deprivation therapy, RT-radiotherapy, RC-radical cystectomy, TURBT-transurethral resection of bladder tumor.

cer. Among them, 5 patients died from progression of underlying associated malignancy. Only 2 patients died with an advanced stage of EMPD disease. Another 2 patients died from non-oncological causes like cardiac and respiratory Illnesses. The living patients have been followed-up for a period varying from 6 months to 6 and half years depending on the time of treatment received. All cases receiving ancillary treatment in the form of re-surgical intervention or adjuvant systemic treatment showed a survival rate longer than 5 years.

Discussion

Generally, EMPD is a rare, slow-growing intraepithelial adenocarcinoma and is more common in post-menopausal women [1, 2]. In our cohort, we found that half of our cases were of female gender and all of them were post-menopausal.

Diagnosis

EMPD patients present with non-specific and vague symptoms such as pruritus, erythematous skin patch, and focal swelling that can result in delayed diagnosis. With these misleads, most of these patients consult different groups of medical professionals for their first consultation. From our review, the main initial presenting symptoms were erythematous itchy lesions over the affected area. About 90% of our patients had symptoms involving the genitourinary system including the vulva and penoscrotal area, followed by inguinal region. With these symptoms, most of the cases initially consulted gynaecologists, primary care physicians, and dermatologists to get medical advice. In our study cohort, the average latency period from the first presentation to definitive diagnosis was about 6 months. This highlights

the role of the primary physician to get the diagnostic clues and to keep a high index of suspicion when dealing with a rare tumour to avoid delay in initiating definitive management [8, 12-14].

These patients, upon diagnosis of EMPD, should undergo preoperative thorough and systematic staging with imaging, endoscopy, tumor markers, and immunohistochemistry to help explore the presence a secondary form of EMPD that can have underlying associated malignancy. In our case series, at least 1/3 of our patients had an underlying malignancy from a different organ system. A review of literature showed that an associated malignancy is common in ovaries, vulva, vagina, prostate, bladder, and rectum [15]. The association between the underlying malignancy and EMPD is not well-understood but very scant literature mentioned possible epidermotropic spread of malignant cells or direct extension from an internal malignancy [16]. This emphasizes the importance of staging investigation with complete imaging and proper endoscopic investigations to diagnose and exclude the underlying malignancy before treatment of EMPD is initiated, as the associated condition should also be treated radically.

Management

There is no validated guideline for management of EMPD to date due to the lack of randomized control trials to draw conclusive evidence regarding the best treatment protocol. Multiple treatment options are available for cases of EMPD, from non-invasive topical treatment such as imiquimod, radiation therapy, and photodynamic therapy to aggressive surgical management such as Mohs microsurgery and wide local excision; with each having variable outcomes and success rates. With the locally aggressive nature of the disease and high chance of positive surgical margin after excision, wide surgical excision and reconstructive surgery for wound coverage remain the standard of care [17, 18]. Despite radical surgical excision, the incidence of residual tumor at surgical margin and the rate of local recurrence are still very high. This is due to the nature of the lesion which is characterized by its multifocality and skip lesions with asymmetric involvement of the tumor [19, 20]. The involvement of the surgical margin obtained from final histopathologic report is very important and may influence the outcome of oncological clearance and chances of recurrence. In our case series, the standard of care was to subject the patients to aggressive surgical interventions in the form of wide local excision and reconstruction, vulvectomy, and penectomy. Due to positive surgical margin, some of our patients had to undergo a second-look wide excision. Most literature reports show that margin status of the initial specimen from primary surgery carries no significant impact on chance of recurrence [21]. With a relatively small number case load with variable follow-up periods, there is a lack of strong consensus as to the need of secondary exploration to achieve free margins. Interestingly, in our cohort, the patients who underwent surgical re-excision of the involved area due to positive margins showed a better survival rate of longer than 5 years without any recurrence.

It has been demonstrated that 15-30% of patients with invasive EMPD have positive involvement of the regional lymph nodes [15]. Presence of regional lymph node involvement is a key feature in determining the poor prognosis of EMPD patients [22, 23]. Our patients with clinical regional lymphadenopathy, underwent nodal dissection and they were found to have a poorer prognosis compared to patients with localized disease with patients dying within 18 months of primary surgery. They all had proven disease progression in the follow-up period.

The role of adjuvant chemotherapy and radiotherapy after primary WLE with or without reconstruction, remains controversial with varying outcomes reported in many series [24]. Among our patients who had positive surgical margins and declined a second look surgery, they were offered adjuvant chemoradiotherapy. It was noted that the survival outcome in these patients was good and they were all free of recurrence. However, there is no direct comparison between surgical re-intervention and adjuvant systemic treatment [10] thus far. The choice of chemotherapeutic agents used varies from center to center. Many regimes have been reported, with some common ones being FP regime (low-dose 5-fluorouracil (5-FU)/cisplatin), FECOM regime (5-FU, epirubicin, carboplatin, vincristine, and mitomycin C) and PET regime (cisplatin, epirubicin and paclitaxel). Other known agents that have been used to treat

metastatic or invasive EMPD are docetaxel monotherapy, S-1 monotherapy, and docetaxel and S-1 combination therapy [24-28]. However, the overall survival of the patients who needed systemic treatment is very poor with the survival period reported to be about one and half years only [24]. In our series, patients who had a positive surgical margin and refused surgical reintervention were administered adjuvant chemotherapy. The regime used in our center is FP regime and we noted that their survival was up to 2 years (RT).

Evolving knowledge of tumor micro-environment from translational research and greater understanding of genomic analysis and cellular signaling in tumor immunity have given rise to novel approaches such as immunotherapy, genomic remodeling, and targeted therapy for metastatic EMPD. However, significant survival improvement with robust and valid data on these novel therapies are not available [29, 30].

Outcomes (survival and recurrence)

Though EMPD may be associated with aggressive underlying malignancy, the natural survival outcome of primary EMPD (without secondary malignancy) is good [31]. The prognosis of patients with primary EMPD is better than those with associated malignancy. Higher mortality figures come from the more aggressive secondary form [32]. Concordant with these results, half of the deaths in our series were from advanced stages of associated underlying malignancy. Regarding the invasion and progression of primary EMPD cases, 10% of our cases had disease invasion and progression.

There is a lack of validated guidelines for the follow-up protocol in EMPD cases currently. In our cohort, according to the time of diagnosis and definitive treatment, the follow-up periods varied. We found that more than half the surviving patients in our series achieved a 5-year survival period.

Limitations

With rarity of the disease, collection of data for our cohort must be based on patient demographic and clinical data over a 25 year period. With the above limitation in our retrospective data analysis, we encountered some difficulties in extraction of clinical data and some of the missing data may affect the strength of our study especially in the interpretation of data for management outcome.

Since this was a retrospective study, we did not have advantage of a uniform follow up protocol with regards to follow-up duration and surveillance measures; hence, survival and recurrence data derived from our cohort might be varied.

Conclusion

EMPD is a rare, aggressive cutaneous malignancy with anatomic involvement of the genitourinary area. The disease is frequently underestimated as patients commonly present with vague and misleading features that cause a significant delay in diagnosis and initiation of definitive treatment. Skip-metastasis and multifocal presentation that are associated with EMPD pose serious challenges to effective management, especially in cases of secondary and invasive EMPD. There is currently a lack of validated guidelines for patient identification and diagnosis of EMPD, as well as absence of a blueprint for treatment with follow-up protocols. We feel that multicenter, prospective studies are needed to address the aforementioned challenges and limitations.

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Disclosure of conflict of interest

None.

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