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Adnexal Involvement in Primary Extramammary Paget's Disease

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ABSTRACT

Primary extramammary Paget's disease (EMPD) is a rare intra-epidermal neoplasm originating from apocrine gland duct cells or pluripotent keratinocyte stem cells. It clinically manifests as asymmetrical white and red plaques, often leading to delayed diagnosis due to its rarity and non-specific features. This study aimed to elucidate the clinical and pathological characteristics, particularly focusing on adnexal involvement patterns. Twenty cases were prospectively analyzed from September 2021 to July 2023. A slight male predominance was noted, with vulva and scrotum being the most commonly affected areas in females and males, respectively. Histopathological analysis revealed Paget cells as a universal feature, with in situ disease observed in 80% of cases and dermal invasion in 20%. Adnexal involvement was common, notably with hair follicles being the most frequently affected structure. This study underscores the significance of recognizing adnexal involvement in primary EMPD, with implications for diagnosis and treatment planning.

Keywords: EMPD; Adnexa; Histopathology

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INTRODUCTION

Mammary Paget disease (MPD) is an adenocarcinoma localized within the epidermis of the nipple or areola of the breast. Extramammary Paget disease (EMPD), in turn, is a rare subgroup of cutaneous neoplasm, with similar histologic appearance to MPD, occurring on apocrine gland-bearing skin. Histogenesis of EMPD is unclear. In contrast to MPD, only a small proportion of EMPD cases are associated underlying internal malignancy.[1] Primary EMPD is thought to be an intra-epidermal neoplasm that originates from cells of apocrine gland ducts or pluripotent keratinocyte stem cells.[2] Currently, Toker cells, are thought to be the possible benign precursors of Paget cells.[3] Clinically, EMPD commonly presents as an asymmetrical, painful or pruritic, white and red plaque. This accounts for the frequent misdiagnosis of EMPD as other inflammatory cutaneous conditions, which accounts for significant delay in therapeutic intervention.[4] Extramammary Paget disease, is histopathologically, characterized by presence of Paget cells in epidermis and the epithelium of cutaneous adnexal structures. Disease progression may lead to dermal invasion and subsequent metastasis.[1] Previous studies have demonstrated the frequent adnexal involvement in EMPD. Also, adnexa is implicated as a route for carcinoma spread to deeper tissues.[3,5] Hence, this study was carried out to elaborate the clinico-pathological features and patterns of adnexal involvement, of this rare but frequently misdiagnosed cutaneous neoplasm.

MATERIALS AND METHOD

A prospective hospital-based study was carried out at outpatient department of Shanghai skin hospital (Tongji University) from September 2021 to July 2023. All cases clinically and histopathologically suggestive of primary EMPD were included in our study. All relevant epidemiological and clinical data were recorded as per a pre-designed proforma. Patients with infectious dermatoses, pseudo-tumors, secondary lesions, or survival time less than one month were excluded. Participants provided informed consent approved by the hospital's ethics committee. Relevant laboratory and imaging studies were performed to exclude any underlying malignancy. Hemotoxylin and eosin (H&E) and Cytokeratin 7 staining of skin biopsy specimens from lesion were performed after informed consent. Histopathological features and patterns of cutaneous adnexal structures involvement were evaluated. All data were recorded using Microsoft Excel, and descriptive analysis was performed using IBM SPSS software version 23. The study was approved by the ethics committee of the Shanghai skin hospital (Tongji University).

RESULTS AND DISCUSSION

Our study included twenty histopathologically proven cases of primary extramammary Pagets's disease (EMPD). The mean age of our patients was 69.25 (±12.86 SD) years, with a

range of 40-94 years. Maximum number of our patients belonged to age group 61-70 and 71-80 years, with each age group comprising 30% (n=06) of our study population. A slight male preponderance (n=11; 55%) was observed in our study.

The mean duration of EMPD at diagnosis was 29.25 (±40.95 SD) months. Majority of our patients were previously misdiagnosed as cases of eczema (n=12; 60%) or candidiasis (n=04; 20%). All the lesions encountered in our study were solitary and occurred in the anogenital area. In females, vulva (n=08; 40%) and the perianal area (n=01; 05%) were the initial affected areas. (Figure 1) In males, scrotum was the most frequently affected initial site (n=06; 30%). The perianal area (n=02; 10%), penile shaft (n=01; 05%), pubic area (n=01; 05%) and groin (n=01; 05%) were the other affected sites. (Figure 2) Majority of lesions appeared as erythematous patch or flat plaques, with variable amounts of scaling, excoriations, oozing and crusting. The average size of lesions at presentation was 09.05 (±6.79 SD) cm. The major symptom upon presentation was pruritis (n=14; 70%). Burning sensation (n=04; 20%) and pain (n=01; 05%) were the other encountered symptoms.

The universal feature amongst all histopathological specimens analyzed in our study was the presence of Paget cells. Typically, Paget cells, were observed as large, round cells with abundant pale-staining cytoplasm and large nuclei with prominent nucleoli, upon routine staining. (Figure 3) Positive Cytokeratin 7 staining was obtained in all specimens. (Figure 4) Acantholysis was observed in four specimens (20%). In situ EMPD was present in 16 specimens (80%) and dermal invasion occurred in four cases (20%). Microdermal invasion (invasion to papillary dermis) occurred in three cases. Whereas, dermal invasion (invasion to reticular dermis or deeper), was present in one case. Inguinal lymph node metastases was not encountered in our study. Adnexal involvement was frequently encountered in our biopsy specimens. Hair follicle was the most frequently involved adnexa (n=10; 62.5%), when present on histopathological specimen (n=16). Patterns of adnexal involvement are summarized in Table 1.

Table 1: Patterns of adenexal involvement

Adenexal Structure	Involved (n)	Present (n)	Percentage with involved adenexa (Involved/Present)
Hair follicle	10	16	62.5%
Sebaceous gland	02	04	50.0%
Eccrine gland	01	10	10.0%
Apocrine gland	00	01	00.0%
Adenexal ducts			
Eccrine duct			
Acrosyringium	02	04	50.0%
Straight/Coiled	01	04	25.0%
Apocrine duct	00	01	00.0%
*Ducts NOS**	01	03	33.3%
*NOS: Not otherwise specified			

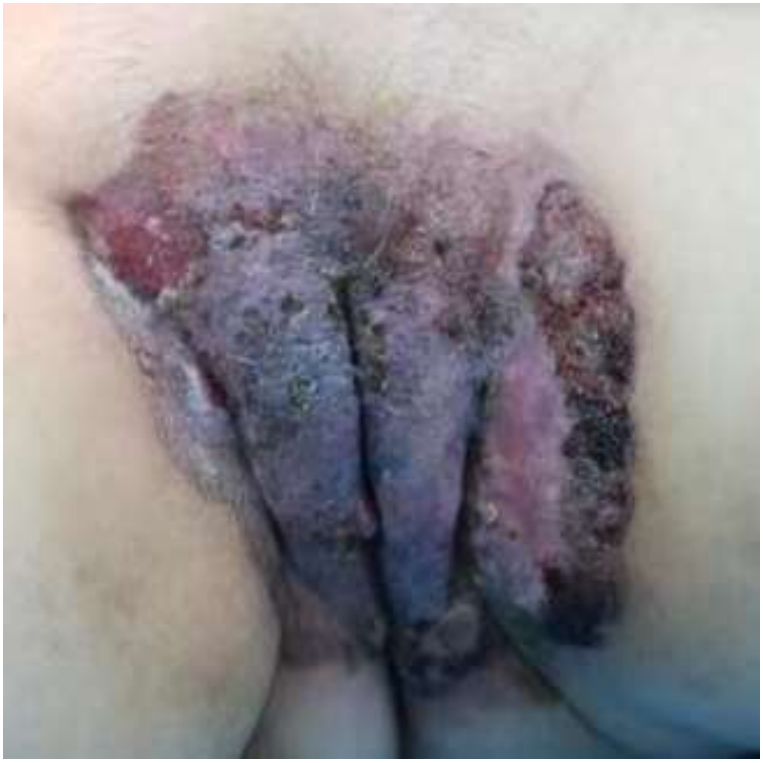

Figure 1: A 49 year old female with erythematous, excoriated and lichenified plaque on vulval area

Figure 2: A 40 year old male with an erythematous plaque on pubic area and penile shaft

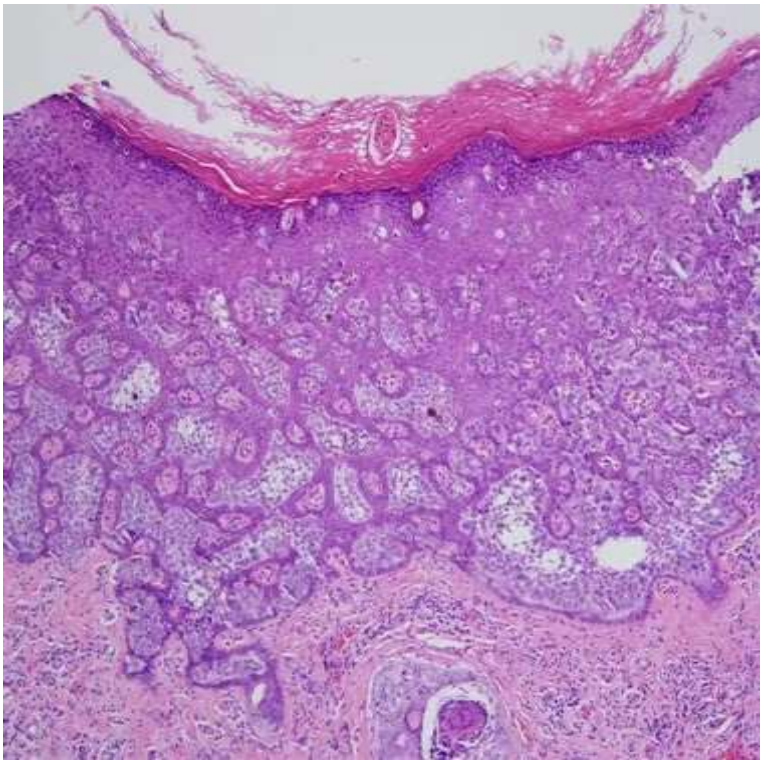

Figure 3: Histopathological section of skin depicting Paget cells (Hemotoxylin and eosin stain; 100x magnification)

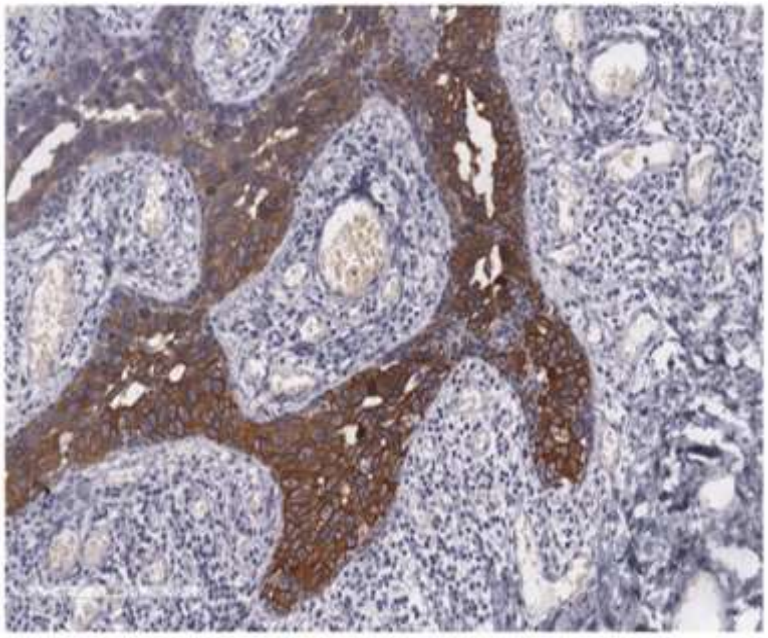

Figure 4: Histopathological section of Extramammary Paget disease (Cytokeratin 7 stain; 100x magnification)

Extramammary Paget's disease (EMPD) is a rare cutaneous neoplasm that has a predilection for areas with a high density of apocrine glands.[1] A peak incidence of disease is usually seen around 65 years.[6] In accordance, mean age of our study population was 69.25 years. Previous studies, conducted predominantly in western countries, describe EMPD as a disease occurring predominantly in elderly Caucasian women.[7,8] However, a slight male

preponderance was seen in our study. Several studies, based on Asian population, have also found a nearly 1:1 male-to-female ratio.[9,10]

Our study highlighted the large interval been onset of disease and diagnosis, with the mean duration of EMPD at diagnosis of 29.25 months. Pruritis was the most prevalent symptom in our study. Majority of lesions appeared as erythematous patch or flat plaques, with variable amounts of secondary changes. Owing to the nonspecific clinical manifestations and relative rarity of EMPD, rather unsurprisingly, majority of our patients were previously misdiagnosed as cases of eczema (60%) or candidiasis (20%).

Extramammary Paget's disease most commonly occurs on apocrine rich skin of genital skin or the axilla. Rare case reports mention EMPD occurring on the eyelid[11], ear canal[12] and umbilicus[13]. In our study, all lesions of EMPD were confined to the anogenital region. In accordance with several studies, vulva and scrotum were the most frequently affected initial sites in females and males, respectively.[7,14]

Intra-epidermal proliferation of Paget cells, which is the classical histopathological manifestation of EMPD, was observed in all our histopathological specimens. Classic type (Type A) of Paget cell is characterized by vesicular nuclei with prominent nucleoli and abundant pale cytoplasm. Whereas, signet ring type (Type B) is characterized by an eccentrically displaced nucleus with large cytoplasmic mucin droplets.[5] Cytokeratin 7 (CK 7), carcinoembryonic antigen, epithelial membrane antibody, HER-2/neu and gross cystic disease fluid protein-15 (GCDFP-15) are the major immuno-histochemical markers expressed in EMPD. In our study, all the histopathological specimens of EMPD consistently expressed CK 7. Cytokeratin 7 is considered to be a reliable immune-histochemical marker in EMPD specimens.[15] Due to unavailability of facilities, other immuno-histochemical stains were not performed.

Our study showed in situ EMPD in 16 specimens (80%) and dermal invasion in four cases (20%). Hatta et al. classified dermal invasion in EMPD as microdermal (invasion to papillary dermis) and dermal invasion (invasion to reticular dermis or deeper).[9] Microdermal invasion occurred in three specimens. Whereas, dermal invasion was present in one case. Several studies have demonstrated an increased risk of death for tumors with dermal invasion compared with in situ or microdermal invasive tumors.[9,16] Acantholysis was observed in four specimens (20%). A study by Zeng et al. found that dermal invasion was significantly more common in cases with acantholytic EMPD, when compared to cases with non-acantholytic EMPD.[17] Interestingly, in our study, all specimens showing acantholysis, also had some degree of dermal invasion.

Several studies have documented frequent involvement of adnexa by Paget cells in EMPD cases.[3,5] In our study, too, adnexal involvement was frequently present in our biopsy

specimens. In agreement with above mentioned studies, hair follicle was the most frequently involved adnexa (62.5%). Some studies have suggested that the adnexa may serve as a route for carcinoma spreading to deeper tissues. This may, in turn, affect the efficacy of local therapeutic agents like imiquimod, 5-fluorouracil and retinoic acid in management of EMPD.[3,5] Hence, further studies are required to highlight this important clinical aspect of EMPD, so as to facilitate formulation of proper therapeutic plan. There are very few studies of this disease on Asian population. Our study has highlighted several important aspects of this rare cutaneous neoplasm.

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