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Extramammary Paget disease of the vulva

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ABSTRACT

Extramammary Paget disease (EMPD) is a rare neoplasm with uncertain histogenesis, usually presenting in the anogenital area, most commonly in the vulva. The disease is characterized by slow grow and high recurrence rates. This article reviews the epidemiological, clinical, morphological, genetic and treatment features of EMPD of the vulva reported in recent years.

Introduction

In 1874, Sir James Paget reported a series of 15 cases of chronic skin eruption of the nipple and areola, associated with an intraductal carcinoma of the mammary gland, a condition that is now referred to as mammary Paget disease.[1] In 1889, shortly after James Paget's report, Crocker described the first case of Paget disease involving the extramammary (penoscrotal) skin.[2] The first case of Paget disease of the vulva was described by William Dubreuilh in 1901.[3]

Epidemiology

EMPD is rare, representing approximately 1% – 2% of neoplasms in the anogenital area..[4-6] The disease usually involves the anogenital area, most commonly the vulva.[6,7]

The overall European incidence of EMPD is 0.7 per 100,000 persons per year.[7] EMPD incidence is increasing by 3.2% every year, affecting hormonally-targeted tissues such as the vulva and scrotum.[8]

Classification

The EMPD can be classified into primary or secondary forms, the latter representing intraepithelial spread of an underlying carcinoma arising in the urogenital or gastrointestinal tracts.[9–12]

A majority of primary EMPD are intraepithelial neoplasms. When invasion into the dermis occurs, they are designated as invasive or microinvasive carcinomas. The latter defined as stromal invasion to a depth of no more than 1 mm below the basement membrane.[13]

Pathogenesis

The histogenesis of primary EMPD is uncertain. Cutaneous adnexa, clear cells of Toker, pluripotent stem cells in the epidermis, keratinocytes and anogenital mammary-like glands (AGMLG) have been proposed as possible sites of origin.[9,14–27]

Primary EMPD originates in the skin (EMPD in sensu stricto) and is analogous to mammary Paget disease (MPD). Unlike primary EMPD, in MPD, there is almost always an underlying in situ or invasive carcinoma and the intraepidermal Paget cells are assumed to be the result of upward migration and epidermotropism from the underlying neoplasm. In very rare cases lacking any underlying carcinoma, the Toker cells of the nipple are considered to be the source of the disease.[9]

By analogy with mammary Paget disease, rare cases of primary EMPD may originate in ductal carcinoma in situ (DCIS) or invasive carcinoma in anogenital mammary-like glands (AGMLG) with a subsequent upward migration of the neoplastic cells into the epidermis and possible later breach through the basal membrane. Ductal changes usual and atypical ductal hyperplasia in AGMLG can then be regarded as earlier precursor lesions of primary EMPD.[9,15,28]

The authors have disclosed that they have no relationship with, or financial interest in, any commercial companies pertaining to this article.

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Clinical features

Vulvar EMPD is reported to occur most often in postmenopausal Caucasian women, with the median age at presentation ranging from 70 to 75 years..[29–31] In women, 81.3% of EMPD cases are related to the vulva; the most common location is the labium majus followed by the labium minus and clitoris (Fig. 1).[8,32]

The clinical presentation of EMPD has no pathognomonic symptoms or specific clinical aspects. It presents as a relatively well-demarcated erythematous plaque with typical white scaling known as "cake-icing scaling". There often may be scaling, excoriations, and/or crust with a papillomatous surface (Fig. 1). Rarely, hyperpigmentation, hypopigmentation, or depigmentation may be seen. The extent of disease varies considerably with average size about 5 cm (range from 1 to 20 cm).[9,30,33–37] EMPD may cause itching, burning sensation, tenderness and pain. EMPD is a slow growing malignancy with symptoms are typically present for an average of almost 2 years before the diagnosis is made.[21,38–40] Local recurrences may result in involvement of large area, beyond the vulva (Fig 1).

Rarely, patients present with multicentric EMPD. These cases show a striking male predominance and are rare in white individuals.[41–44]

Pathological features

Paget cells are large and pleomorphic, characterized by vesicular nuclei, prominent nucleoli and abundant pale, clear, basophilic or amphophilic cytoplasm (Fig. 2A). They are usually spread as single cells throughout the epidermis or confined to the lower and middle epidermal layers. Neoplastic cells may form well-demarcated rounded solid nests or gland-like structures adjacent to the basement membrane (Fig. 2A, 3). The latter are usually small and simple, but sometimes have a more complex architecture including cribriform growth and large glandular formations with apocrine secretion.[9,30,45–47]

In cases where large intracytoplasmic mucin droplets displace the nucleus eccentrically, Paget cells assume signet-ring cell appearances (Fig. 2B). Rare cytological variations of Paget cells include cells with hyperchromatic nuclei, multinucleation, partially scalloped nuclei imitating sebocytes, and cells with intracytoplasmic inclusions. Mitotic figures may be seen, but are uncommon[9,30,45]

In some cases, there are reactive epidermal changes including

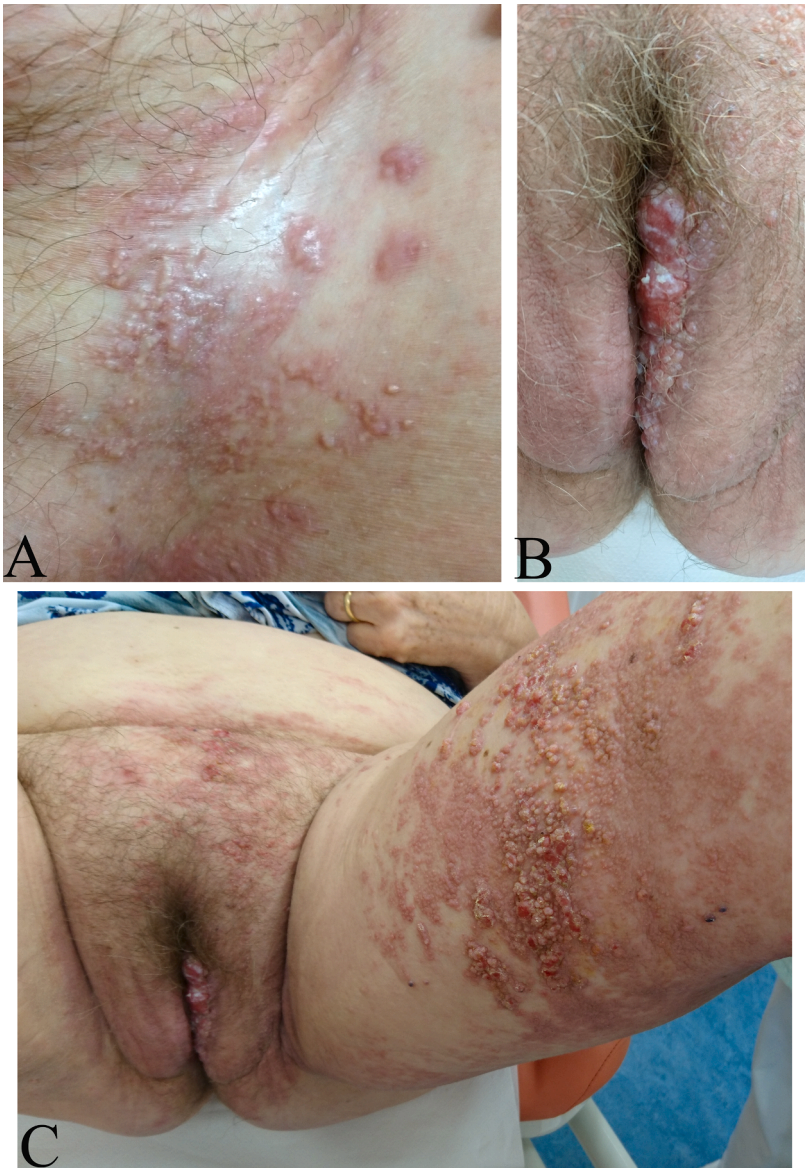

Fig. 1. Clinical presentation of the EMPD in the anogenital area. The disease manifests as relatively well demarcated areas (A, B) and progressed over years beyond the anogenital areas with locoregional metastases (C).

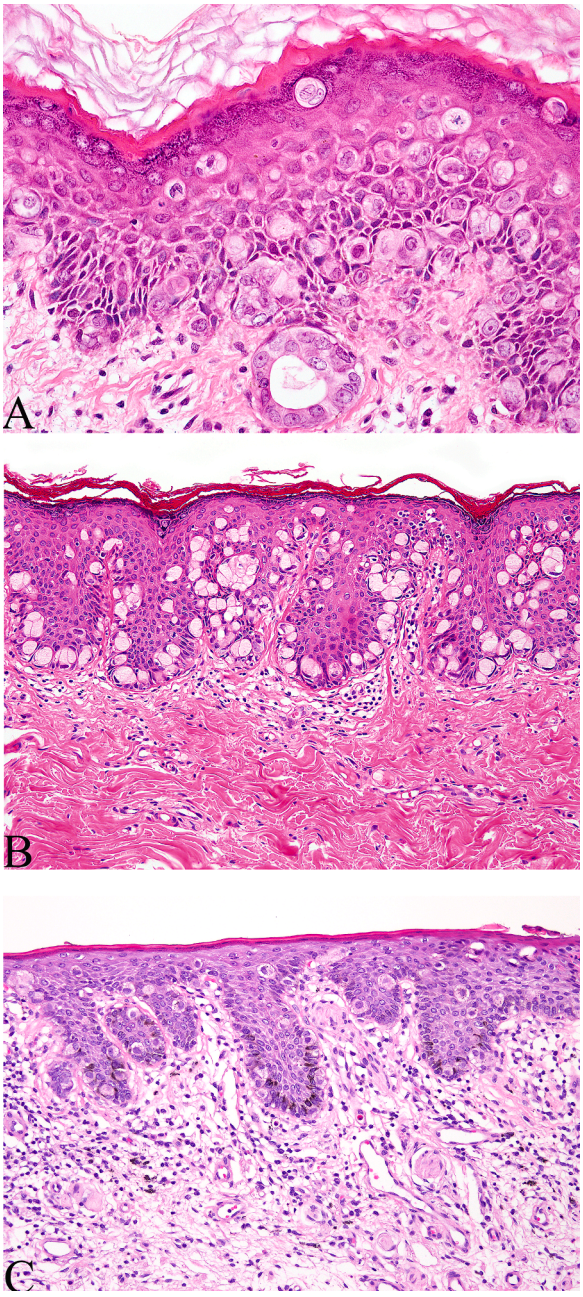

Fig. 2. Large and pleomorphic Paget cells with vesicular nuclei, prominent nucleoli and abundant pale, clear cytoplasm. Note a gland-like structure (A). Signet-ring cell appearances of Paget cells in EMPD (B). Pigment variant of EMPD with melanin pigment occurs in the cytoplasm of neoplastic cells (C).

fibroepithelioma-like changes, papillomatous hyperplasia, squamous and psoriasiform hyperplasia. In the upper dermis there may be a dense inflammatory infiltrate with small capillary proliferation.[9,30,46–48] A relatively uncommon EMPD may morphologically demonstrate resemblance to syringocystadenocarcinoma papilliferum in situ.[9,49]

Hyperpigmentation clinically seen in rare cases results from an increased number of dendritic melanocytes, abundant intracytoplasmic melanin in pagetoid cells, or presence of melanophages in the underlying dermis (Fig. 2C).[50–52]

Involvement of adnexa is a very common feature (>90% of cases of primary EMPD), likely contributing to the spread of carcinoma into deeper tissues.[15,26,53,54,55] Hair follicles (Fig. 4) and eccrine ducts are the most common colonized adnexa; several patterns of adnexal involvement have been described.[56] The maximal depth of involvement found

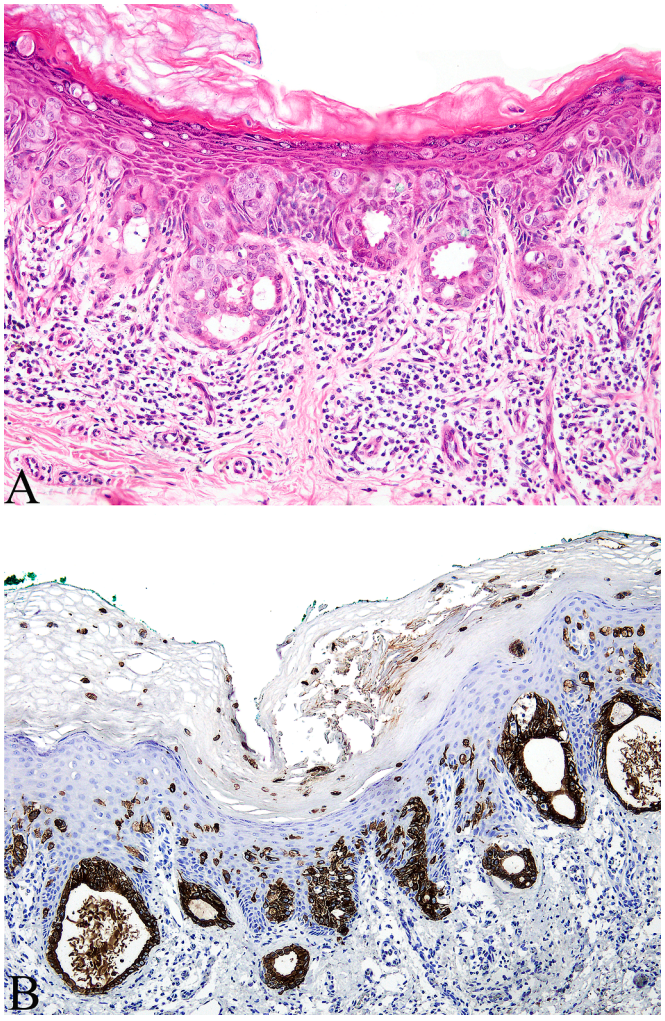

Fig. 3. Prominent glandular structure with apocrine secretion in EMPD (A, B). Staining for CK7 (B).

in one study was 3.6 mm, with median for each adnexal structure ranging from 0.93 mm (eccrine ducts) to 2.55 mm (eccrine secretory coils).[9,56]

Association of EMPD with an underlying mammary-type carcinoma is a rare event (<5% cases) and often characterized by a more aggressive behavior.[11,40,57,58] These carcinomas are identical to their breast analogs, most have features of invasive ductal (no special type) carcinoma and most likely originate in anogenital mammary-like glands..[28,59,60,58,61,62] Some are DCIS..[63,61] Carcinomas with mixed ductal and lobular features and lobular carcinomas are extremely rare associated with EMPD.[9,64,65,66]

EMPD rarely coexists with melanoma,[67,68] vulvar intraepithelial neoplasia (VIN)/squamous cell carcinoma (SCC) in situ,[69,70,71,72] invasive squamous cell carcinoma,[48] basal cell carcinoma,[73] condyloma accuminatum,[74,75] and hidradenoma papilliferum.[76,77,78]

Histochemistry and immunohistochemistry

Paget cells usually contain mucin that stains with mucicarmine (Fig. 5A), periodic acid Schiff reagent, aldehyde fuschin, and zirconyl haematoxylin.[79] Alcian blue is the stain of choice for mucin-staining EMPD. Electron microscopic studies showed that there are secretory and nonsecretory (lacking secretory granules) cell types in the neoplasm.[80]

Numerous immunohistochemical markers have been studied in

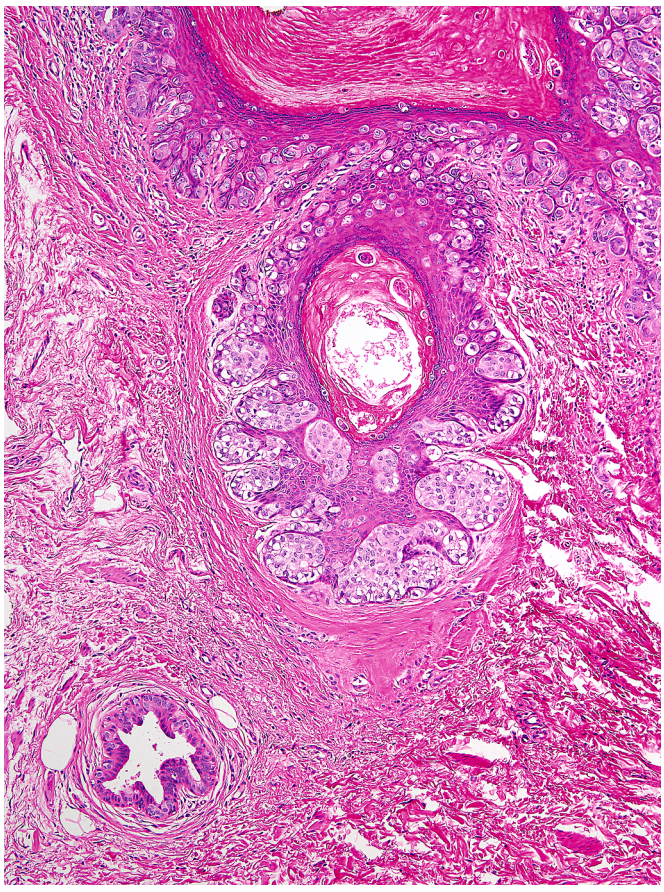

Fig. 4. Involvement of hair follicle in EMPD.

EMPD, but diagnostic and prognostic applying of these markers remains minimal. For practical purposes, neoplastic cells in primary EMPD consistently react with CK7 (Fig. 5B) and often express CEA and GCDFP-15. A combination of certain markers can be used in the distinction between primary EMPD and secondary EMPD arising from other sites and few markers related to prognosis (these are discussed below).[81,82]

In recent years the information about targetable biomarkers in EMPD has been published.[83, 84] Tessier-Cloutier et al. demonstrated that breast cancer subtyping can be applied to vulvar EMPD.[85] Her2/neu positivity has been reported in 20% to 80% of patients[86,87,88,89] Androgen receptor expressed in the majority of EMPD and often positive immunostaining with estrogen receptors may be seen in EMPD. Several cases of positive PD-L1 VPD were reported in the literature.[83,90]

Differential diagnosis

Due to the non-specific presentation, the clinical differential diagnosis of VPD consists of eczema, vulvovaginal candidiasis, psoriasis, lichen simplex chronicus, lichen sclerosus, VIN, SCC, histiocytosis, and others.[29,37,91]

The histological differential diagnosis mostly concerns tumors and diseases with pagetoid pattern of a spread in the epidermis.[40,46,91]

The most important issue is distinction between primary and *secondary EMPD,* the latter being the result of intraepithelial spread from a visceral carcinoma (reported incidence of such an association varies from 5% to 30%).[38] Secondary EMPD originates mostly from a malignancy of the gastrointestinal tract (distal colon, rectum) or the urogenital tract (urinary bladder).,[45,92] or rarely, vulvar EMPD may arise from a Bartholin gland carcinoma.[93]

Tumors secondary to colorectal carcinoma resemble gastrointestinal glands with stratified columnar cells, signet-ring cells, goblet cells and intraluminal dirty necrosis and are often immoreactive for CK20, CDX2 and GCDFP15.[92,94,95,96] In the rare cases of CK7+/CK20- colorectal carcinomas causing secondary EMPD, CDX2 is very useful IHC marker.[97] Of note, secondary EMPD may arise in association in-situ colorectal lesions[98]

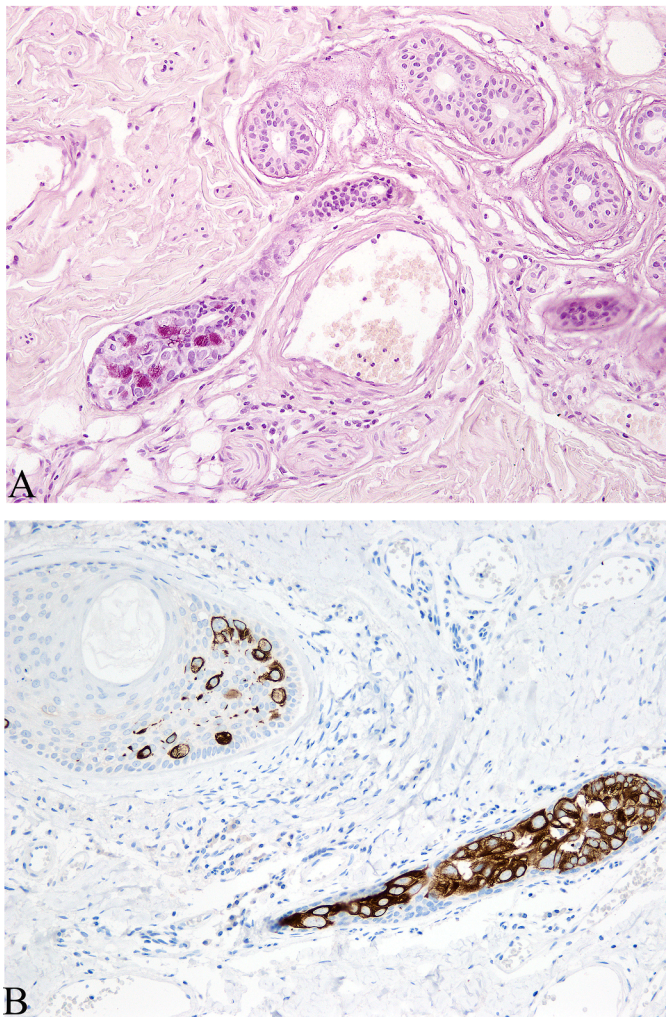

Fig. 5. Involvement of eccrine/apocrine ducts (A, B) and hair follicle (B) in EMPD. Staining for mucicarmine (A) and CK7 (B).

Paget cells in cases secondary to urothelial carcinoma resemble high-grade urothelial cells with anaplastic nuclear features, variable nuclear shapes, coarse irregular chromatin, infrequent or non-prominent nucleoli and have a high mitotic rate.[91] Uroplakin-III expression helps establish urothelial carcinoma as the cause of EMPD.[99]

Vulvar Toker cells may be confused with Paget cells especially when hyperplastic and/or forming glandular structures. Toker cells typically occur as an incidental finding accompanying a lesion other than EMPD.[9] Willman et al. reported one case showed hyperplasia of Toker cells overlying an AGMLG without atypical cytological features.[16] The immunoprofile of vulvar Toker cells has not been adequately studied. Although several studies of mucin core protein expression indicated these may be a helpful diagnostic markers,[100,101,102] a subsequent study has shown a lower specificity of their positive immunostaining.[103]

Mucinous metaplasia of the vulvar surface squamous epithelium is characterized by the uniformity of the surface mucinous epithelium replacing rather than infiltrating the original squamous epithelium, the absence of cellular atypia and a pagetoid pattern.[104,105]

VIN (including HSIL/squamous cell carcinoma in situ*) and melanoma*, especially if exhibiting a pagetoid pattern of involvement, must also be

distinguished from EMPD. The histological and immunohistochemical differential diagnosis between these tumors is presented in the Table 1.,[29,46,91,106–108]

Pagetoid dyskeratosis is another potential mimic of EMPD that represents a reactive process whereby collections of normal keratinocytes are induced to proliferate, possibly secondary to friction.[111,112] Pagetoid dyskeratosis cells have clear-to-pale, finely granular cytoplasm, distinct cytoplasmic borders, and pyknotic nuclei surrounded by clear halos. They are mucin-negative and do not express EMA, CEA, or low-molecular-weight keratins.[113]

EMPD may also be difficult to distinguish from exclusively or predominantly *epidermotropic metastasis* of visceral carcinoma wherein the metastatic cells are confined to the epidermis and spread in a pagetoid manner.[114,115]

Clear cell papulosis is a rare condition with unknown cause characterized by multiple hypopigmented macules or palpable papules sometimes in a linear arrangement distributed in the pubic area, lower abdomen and anterior trunk occurs predominantly in otherwise healthy Asian children younger than 6 years. Microscopically, it is characterized by round cells with ample clear cytoplasm and pale, sometimes grooved nuclei, distributed among the basal keratinocytes, sharing a similar immunoprofile with EMPD.[116,117,118,119,120,121,122]

Langerhans cell histiocytosis is a disease with a broad spectrum of clinical presentations. Few cases revealed the unique presentation limited to the genitalia and the morphological similarity to EMPD have been published.[29,123]

Syringomatous ductal proliferations and syringoma-like structures can be associated with several inflammatory and neoplastic conditions in the vulva including EMPD and represent another pitfall.[124]

Molecular biology

Mutations in genes encoding PI3K/AKT cascade have been found in EMPD.[90,125,126,127, 128] Takeichi et al. identified *FOXA1* mutations, a *GAS6-FOXA1* fusion gene, and somatic hotspot mutations in the *FOXA1* promoter region in 11 of 48 EMPD patients (23%).[129] Genetic alterations in MMR genes,[130] in the key genes of RAS/RAF pathways,[128] *MUTYH, TP53 genes*[90] may be involved in the pathogenesis of this disease. Kiniwa et al. identified somatic mutations in 9 genes, including seven pathogenic (*CDK11B, ERBB2, ESRRA, NUP93, PIK3CA, TP53*, and *ZFHX4*) and two frameshift mutations (*UHRF1* and *ZFYVE19*).[131]

A study using comparative genomic hybridization revealed that the most recurrent change was amplification at chromosomes Xcent-q21 and 19, and loss at 10q24-qter.[132]

Results of HER2/neu gene amplification studies are conflicting the rate ranging from 7%[133] to 43%.[89] TOP2A gene amplification was detected in 16.7% of EMPD.[90]

Therapeutic options

The diagnosis of EMPD must trigger a laboratory work-up aiming to detect/exclude an underlying malignancy.[7] In cases of secondary EMPD, the therapeutic management is determined by the origin of the visceral carcinoma and its histological types.,[45,134,135]

The knowledge regarding the natural course of primary vulvar EMPD is limited. The 'Radiumhemmet series' of 28 women contained 4 untreated women, of whom two were inoperable and two women refused surgery. Both inoperable patients died of other causes. One of the patients who refused surgery had progressive disease and the other patient died of a squamous cell carcinoma of the vagina..[136]

Despite the fact that numerous treatment modalities are available for EMPD, there are no standardized therapeutic guidelines. Surgical treatment is still considered to be the gold standard.[108,137]

In case of non-invasive EMPD, wide local excision is the treatment of choice. Because sometimes EMPD extends diffusely beyond the visible clinical extent it becomes very difficult to make margin controls.

Table 1
The histological and immunohistochemical differential diagnosis between EMPD, SCC in situ/HSIL and superficial spreading malignant melanoma.

	EMPD	SCC in situ/HSIL	Superficial spreading malignant melanoma)
Basal cell layer	Often intact beneath aggregates of Paget's cells	Usually involve in the neoplastic process; effacement of the basal layer	Typically involver
Pagetoid cells	Above the dermo-epidermal junction	At the full-thickness of the epidermis	At the dermo-epidermal junction
Usually predominant in the epidermis	Single cells	Full-thickness atypia	Nests of cells
Involvement of adnexa	++	∓	+
Glandular formation	±	–	–
Paget cells in cornified layer	++	∓	±/+
Clefts in the epidermis	Between Paget cells (individual or aggregates) and surrounding keratinocytes	–	Between aggregates of melanocytes and surrounding keratinocytes
Dyskeratotic cells in the spinous layer	–	+	–
Acid mucopolysaccharide in cytoplasms	+	-**	–
Signet ring cells	±/+	–	–
Melanin in the cytoplasm	Uncommon in Paget cells, when present sparse and as large granules	∓	Fine granules throughout the cytoplasms of the pagetoid cells
Mitotic figures	++	+	±
Epidermal hyperplasia	++	+	±
Ulceration	+	±	∓
Spontaneous regression changes	–	–	+
Lichenoid infiltrate in papillary dermis	+	∓	∓
Neutrophils in epidermis	+, especially in foci of necrosis and/or ulceration	±	∓
CK7, CEA, GATA3, GCDFP15	+	-*	–
HMB45, Melan-A	–	–	+
P16	∓	+	–
P40 (p63)	–	+	–

* CK7 is typically absent in VIN, but there have been reports of VIN with CK7 positive cells.[106,109] VIN associated with mucinous differentiation and positivity with CK7 and CEA is another potential pitfall.[110].

** Very rare. These cases may be regarded as the vulvar analogue to cervical SMILE (Stratified mucin-producing intraepithelial lesion).[110].

Therefore, Mohs micrographic surgery has emerged as the gold standard for the excision of EMPD lesions. Recurrence rates of 23% for MMS versus 33% for conventional excision with margin control have been reported.[138] Patients with an underlying adnexal adenocarcinoma or stromal invasion more than 1 mm need more aggressive treatment, with excision to the fascia coupled with lymphadenectomies.[46,108,137] Nonetheless, patients treated with wide local excision had a significantly longer survival than patients treated with other more radical treatments.[11]

There are no well-established guidelines relating to the extent of surgical excision required or depth of pathological sampling. However, the depth of secondary adnexal involvement (up to 3.6 mm) and the depth of location of AGMLG (up to 3.9 mm) should be taken into account.[9,56,139]

EMPD is characterized by high recurrence rate despite surgery as well as the potential morbidity, tissue loss and functional impairment that may result from surgical intervention. Thus, alternative therapies are being investigated.

Radiation treatment can be utilized for inoperable lesions, in patients with an underlying adenocarcinoma or as an adjunct to surgery in order to prevent local recurrence or.[46] Karam et al. reported that patients who received radiation, alone or in combination with site directed surgery, did not fare any better than patients who underwent surgery alone.[140]

Photodynamic therapy is another non-invasive method of therapy that might be used as a primary treatment approach or as an adjunctive therapy to surgical and/or medical interventions. It involves the light activation of a photosensitizer in tumor cells.[141]

Laser therapy has been applied in non-invasive cases as a primary modality but is limited to the treatment of superficial lesions alone, as the depth of photon penetration is only a few millimeters.[142]

Systemic chemotherapy can be used if patients with contraindications to surgery and radiotherapy and for treatment of metastatic EMPD. These chemotherapeutic agents (5-FU, Cisplatin, Carboplatin, Docetaxel and others) have been used as single agents or in combination with varying degrees of success.[46,91,143,144,145] Targeted therapy is a new therapeutic strategy in cases of EMPD showing the overexpression of Her-2/neu. Trastuzumab can either be used as a single agent, resulting in significant disease regression, or in combination with other agents such as Paclitaxel.[146]

Local application of cytotoxic drugs (bleomycin, 5-fluorouracil) alone is not sufficient. However their usage may decrease the margins of the lesions or assist in visualization, making surgical resection more efficacious.[147,46]

Imiquimod, the topical immune-response modifier, can be considered an alternative to surgery, an adjunct before or after surgery, and even part of a therapeutic combination with other treatment modalities. When associated cancers and invasive growth are excluded, imiquimod appears to be a safe and effective.[108,148,149,150] Imiquimod and radiotherapy are thought to be the most appropriate nonsurgical modalities for EMPD treatment.[151,152] Trofymenko et al. concluded that there was no difference in survival for surgically and nonsurgically treated patients.[153]

Prognosis and behavior

The prognosis of primary EMPD, in particular for non-recurrent cases and those with no invasive component, is generally good. In the group of patients with EMPD in situ, five-year survival rate was from 98 to 100%.[140,154]

However, the 5-year disease specific survival is 94.9% for localized disease, 84.9% for regional disease and 52.5% for distant disease[140] and 33.3% in EMPD with the invasion to the reticular dermis.[154]

Patients with clitoral involvement had a higher incidence of death from disease[11] and perianal location of Paget's disease is associated with more adverse prognosis.[155,156,157,158] The presence of a nodule on the primary lesion, the level of tumor invasion, presence of lymph node metastases were found to be a significant prognostic factors in EMPD[159,160] along with tumor thickness.[155]

Among various immunohistochemical markers it have been shown that overexpression of p53[161,162,163] and loss of expression of E-cadherin correlate with stromal invasion.[164] The proportion of Her2/neu positive cases was higher in recurrent lesions, suggesting more aggressive behavior.[88] Aoyagi et al. observed Ki-67 and cyclin D1 to be expressed at significantly higher levels within invasive lesions when compared to in situ lesions.[165] The pattern of mucin expression may vary according to the presence or absence of (micro)invasion in EMPD.[101] In addition, chemokines CXCR4 and CXCR7 can be used as prognostic biomarkers and prediction of aggressiveness of EMPD.[166] Furthermore, *PIK3CA* and *AKT1* mutations were significantly correlated with CDH1 hypermethylation which could explain why the majority of EMPD cases with mutant*PIK3CA* and *AKT1* were invasive.[128]

EMPD has a high recurrence rate of 12% to 58% (mean 32%–33%).[30,40] Several factors including site of involvement and treatment modality affect recurrence.

The data about the relation of positive surgical margins and their size with high recurrence rate is controversial.[11,30,34,161,167,168] Recurrences have also been attributed to multicentricity[167] and skip areas. Adamsons and Reisfeld showed that tumor cells can be demonstrated histologically well beyond the grossly visible margins of the lesion.[169] Anther report showed that clinically determined border of well-defined lesions of EMPD corresponded well to the histopathologic border.[170] Local invasion and lymphovascular invasion have also been shown to correlate with recurrent disease[161] along with epidermal acantholysis.[30]

Conclusion

EMPD is a rare condition with uncertain histogenesis that poses difficulties of clinical and histopathological diagnosis and management. The correct diagnosis is sometimes delayed by years. EMPD may be associated with an underlying carcinoma. Hence, following the microscopic diagnosis, an extensive search for an associated malignancy should be initiated. Patients with EMPD have a high rate of recurrence with many factors suggested to be associated with recurrences. In recent years the information about targetable biomarkers in EMPD has been published. Thus, further large studies are needed to clarify molecular mechanisms in EMPD and to identify individual patients with targetable molecular alterations.

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