Extramammary Paget disease

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Abstract

In 1874, Sir James Paget first described Paget disease of the nipple, also known as mammary Paget disease. In 1889, extramammary Paget disease (EMPD) of the scrotum and penis was identified. Although mammary and extramammary Paget disease are both characterized by epidermal Paget cells and share a similar clinical presentation, their uniqueness lies in anatomical location and histogenesis. EMPD presents as an erythematous plaque on apocrine gland bearing areas (i.e. vulva, perineum, perianal region, scrotum, and penis) in older men and women. It can be a focal, multifocal, or an ectopic process. Immunohistochemical staining allows for differentiation between primary and secondary EMPD in addition to the many other disease entities that clinically resemble this malignancy. When diagnosing a patient with EMPD, a full history and physical should be performed given the possibility of an underlying malignancy. Surgical excision currently is first line therapy and the prognosis is often favorable. Recent advances within the field have examined the expression of chemokine receptors within tumors, which may be applicable in determining prognosis. This review addresses the history, epidemiology, pathogenesis, clinical presentation, histopathology, differential diagnosis, diagnosis, management, and new observations with respect to extramammary Paget disease.

Keywords: extramammary Paget disease

Introduction

Sir James Paget first described mammary Paget disease (MPD) in 1874 [1]. Paget noted a patient with a chronic eczematous disease on the skin of the nipple and areola that was associated with an intraductal carcinoma of the underlying mammary gland. MPD is a rare disease that corresponds to 1-4.3% of all breast cancers and is often associated with intraductal, in situ, or invasive neoplasms [2]. It typically affects postmenopausal women after the sixth decade of life, but can be seen in adolescent and elderly patients [3]. Involvement of the male breast is rarely reported. Patients with Paget disease frequently present with an insidious eczematoid, lichenified, moist, or crusted plaque beginning on the nipple and extending to the areola and surrounding skin [2]. The plaque is unilateral with

Abbreviations

5-ALA — 5-aminolevilunic acid
CDX2 — Caudal-Type Homeobox Protein 2
CEA — Carcinoembryonic antigen
CK — Cytokeratin
EMPD — Extramammary Paget disease
GCDFP-15 — Gross cystic disease fluid protein-15
HER-2 — Human epidermal growth factor receptor 2
M-ALA — Methyl-5-aminolevulinate
MMS — Mohs micrographic surgery
MPD — Mammary Paget disease
PAS — Periodic acid-Schiff
PCs — Paget cells
PDT — Photodynamic Therapy
RCAS1 — Receptor-binding cancer antigen exposed on SiSo cells
RT — Radiotherapy
SLNB — Sentinel lymph node biopsy
TCs — Toker cells
WLE — Wide local excision

irregular borders and may exhibit induration, scaling, secretions, bleeding, ulceration, or nipple invagination [4]. Breast cancer arises in 93-100% of MPD cases. Of these patients, half present with a palpable mass in the breast and the other half present without evidence of a mass [2].

There are two main theories about the histogenesis of MPD. The epidermotropic theory states that Paget cells originate from the underlying intraductal cancer and migrate through the basement membrane to the nipple. This scenario is supported by similar immunohistochemical staining between MPD and its associated intraductal cancer [2]. A second theory maintains that MPD is an in situ carcinoma, as Paget cells are keratinocytes that have undergone malignant transformation [5]. Whereas MPD and extramammary Paget Disease (EMPD) are both characterized by epidermal Paget cells, their differences lay in anatomical location and histopathogenesis.

Epidemiology

In 1889, EMPD involving the scrotum and penis was reported by Radcliffe Crocker who found similar histologic features to MPD [6]. Later, vulvar extramammary Paget disease was described in 1901 by William Dubreuilh [7]. Extramammary Paget disease is a rare condition. In the Netherlands, a population-based study found an incidence of 0.11 per 100,000 person-years [8]. EMPD often affects Caucasians, but it may occur less frequently in other races. EMPD most commonly appears in individuals aged 45-75 with peak age incidence varying based on anatomical location. For example, the onset of vulvar EMPD tends to occur in 50-65 year-olds, whereas scrotal and penile disease has a later onset in the 70s [9]. Interestingly, the prevalence of EMPD among different sexes seems to be reversed between Asian and Western populations. In Western studies, EMPD has been reported to have a female predominance with male-to-female ratios between 1:2 and 1:7 [10]. In 2014, Cheng et al. studied the nationwide database in Taiwan and found the EMPD male-to-female ratio was 3.5:1, which was comparable with multicenter studies in other Asian countries including Japan, Korea, and China [10]. It has been postulated that perhaps cultural differences such as conservatism in elderly Asian women may result in under diagnosis of female EMPD.

Clinical Presentation

Although MPD is known for its involvement of the breast (i.e. nipple, areola, skin) and EMPD for its occurrence in apocrine gland bearing areas (vulva, perineum, perianal region, scrotum, and penis), it is important to note that other types of Paget disease exist. EMPD can be focal (i.e. only one apocrine gland bearing area) or multifocal (i.e. more than one apocrine gland bearing area), commonly the groin and axilla [11].

The terms multifocality and multicentricity have been applied to cases in which there are multiple foci of EMPD that appear within a region, as determined by clinical or histologic evaluations (or both) [12]. Hendi et al. argues against the commonly held theory that EMPD is multicentric, as prior studies supporting this theory did not perform cytokeratin 7 (CK7) immunostaining, which helps identify Paget cells that might otherwise be clinically undetected. Instead, Hendi et al. emphasizes that like other tumors of the skin, EMPD too is unifocal. Its highly irregular growth pattern of subclinical, finger-like projections extending beyond the body of the main tumor might give the false impression of a multicentric tumor. Alternatively, multicentricity may be created via partial excision or treatment with topical agents [12]. Thus, further studies are needed to determine the focality of EMPD.

Clinically, lesions of EMPD are insidious and fairly nonspecific, presenting as multifocal, well-circumscribed erythematous or leukoplakic plaques or macules with occasional hyperpigmentation or hypopigmentation (**Figures 1 and 2**), [13]. Crusting, scaling, ulceration, and bleeding may also be observed. Occasionally, hard nodules, palpable masses, or lymphadenopathy may be discovered, which should raise suspicion for invasive disease. The majority of patients experience pruritus. However, burning, tenderness, and edema can also occur [14]. Additionally, roughly 10% of patients with EMPD are asymptomatic [15].

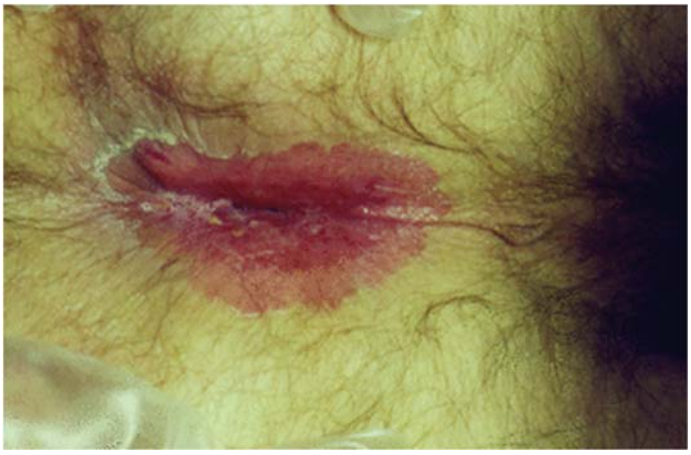

Figure 1. *Perianal Paget disease. Sharply defined, polycyclic erythema. Courtesy of Wagner et al. [30].*

Repetitive excoriation may modify the appearance of EMPD leading to misdiagnosis. Multiple topical therapies are often tried before a diagnosis is made. Subtle elevated sharp margins and lack of a response to topical anti-inflammatory ointments should prompt further investigation [16].

The vulva is the predominant site of EMPD, occurring in up to 65% of cases [14]. Other common locations include the perianal region (20%) and male genitalia including the scrotum or penis (14%), [17]. Rarely, EMPD has been noted in the axilla, buttocks, thighs, eyelids, external auditory canal, and other apocrine gland rich areas [17].

Histopathology

Similar to PD, EMPD is characterized by epidermal Paget cells (PCs), which are malignant glandular epithelial cells with abundant clear cytoplasm (usually containing mucin) and a pleomorphic and hyperchromatic nucleus [2]. Paget cells vary in number and are located throughout the epidermis in groups, with nest-like patterns or gland-like structures (**Figure 3**), [2]. Hyperkeratosis and parakeratosis are frequently present and invasion of adnexal structures can occur. Additionally, a dense inflammatory infiltrate composed of lymphocytes, histiocytes, neutrophils, eosinophils, and mast cells is commonly found in the upper dermis of EMPD [16]. Thus, this infiltrate may be the underlying root of the pruritus and eczematous appearance upon initial presentation [19].

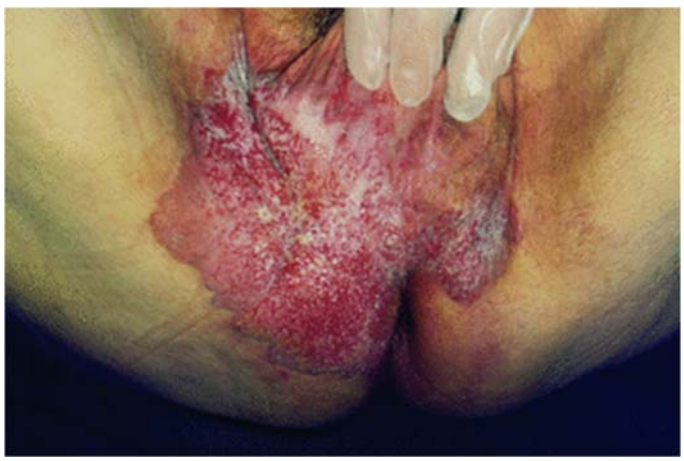

Figure 2. *Anogenital Paget disease presenting with a papular shape. Courtesy of Wagner et al. [30].*

The origin of PCs in EMPD remain unclear in current literature, however, one theory is that Toker cells (TCs) are a potential cellular precursor of primary intraepidermal MPD. Toker cells are most numerous in the epidermis of the nipple, immediately adjacent to the openings of lactiferous ducts, but are also found in the vulvar region and other apocrine gland-bearing areas of the skin [14, 18]. Of note, TCs have not been found in the penis, anus, or scrotum where EMPD is commonly found [19]. Toker cells are distinguishable from Paget cells by their round, bland nucleus with clear cytoplasm and smaller size [20]. However, when TCs rapidly proliferate or show cytological atypia, they are challenging to distinguish from PCs [20]. Toker cell hyperplasia in an areolar lesion has been described in in a 47-year-old woman with MPD without underlying adenocarcinoma, further supporting that MPD and EMPD confined to epithelial cells may be derived from Toker cells [21].

One counter argument to TCs being the origin for PCs was made by Fernadez-Flores in 2008. The argument explained that TCs are typically negative for S100 protein, cytokeratin (CK) 20, carcinoembryonic antigen (CEA), MUC2, MUC5AC, and usually gross cystic disease fluid protein-15 (GCDFP-15), but stain positive for CK7 and MUC1. This is opposite of anal Paget disease which is MUC2+ and the positive expression of GCDFP-15 in most cases of EMPD. Therefore, not all cases of MPD or EMPD have a similar phenotype to Toker cells, thus defying this origin hypothesis [22]. This was further

validated with a recent study by Fernadez-Flores et al. demonstrating MUC5AC positivity in all five cases of EMPD, which is typically negative in TCs [23]. However, some argue that the immunophenotype of TCs and the cells of Paget disease do not need to overlap as PCs should be considered the neoplastic counterpart of the TC.[22] Thus, there is plausible evidence supporting both sides, and the true origin of PCs remain unidentified.

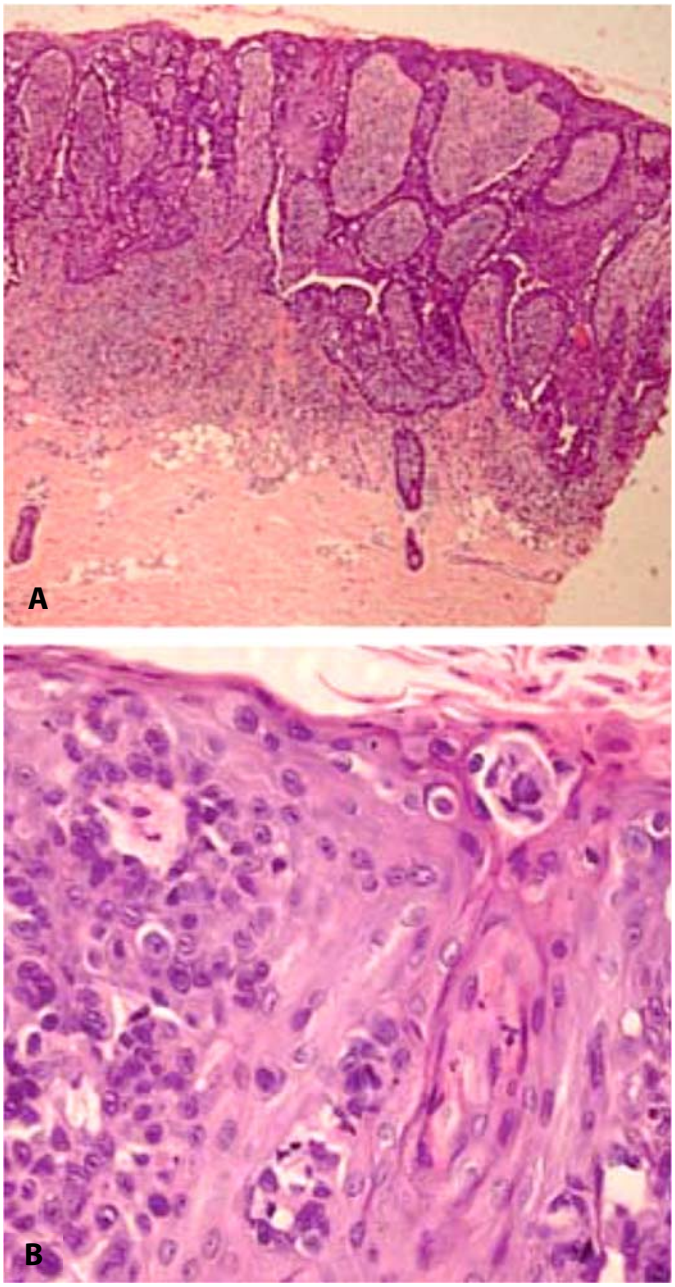

Figure 3. ***A)*** *Epidermis showing intense thickening due to the proliferation of atypical cells in Paget disease. H&E, 40×.* ***B)*** *Pagetoid migration of atypical epithelial cells, near the granular layer, some with a clear cytoplasm. H&E, 400×. Courtesy of Lopes et al. [2].*

Despite the aforementioned argument, there is still a need to differentiate TCs from mammary PCs due to their similarities previously discussed.

This can be achieved through recently described differentiating immunohistochemical markers. Although they share immunoreactivity to CK7, Park et al. demonstrated that there are substantial differences in expression of estrogen receptor (ER), c-erbB-2, and Ki-67 [20]. In mammary PCs, Ki-67 and c-erbB-2 were consistently positive, but almost always negative in TCs [20]. Also, ER was consistently positive in TCs [20]. Thus, these markers will aid in further understanding the underlying association of TCs with MPD and EMPD.

Immunohistochemical staining is also useful for separating Paget disease from other processes (**Figures 4 and 5).** This includes MPD and differentiating primary from secondary forms of EMPD. In general, Paget cells stain for low molecular weight cytokeratins (CK7 or CK20), GCDFP-15, periodic acid-Schiff (PAS), and CEA [9]. Although CK7 has great sensitivity (86-100%) for detecting Paget cells in EMPD and MPD, CK20 is more specific for EMPD [14]. Additionally, the tumor cells of EMPD contain more cytoplasmic mucin, staining positively with mucicarmine and PAS, whereas in MPD only 40% of cases stain for intracellular mucin and are weaker [13]. MPD cases are also more likely to be progesterone and estrogen receptor positive or have human epidermal growth factor receptor 2 (HER-2) protein overexpression compared to EMPD [14].

The most useful markers to distinguish between primary and secondary EMPD are GCDFP-15 and CK20 (**Figure 5**). GCDFP-15 is positive in up to 90% of primary EMPD, whereas CK20 is positive in up to 95% of secondary EMPD [14]. Caudal-type homeobox protein 2 (CDX2), which is sensitive and specific for gastrointestinal mucosa, can also be used to identify secondary EMPD [24]. Perrotto et al. examined the role of immunohistochemistry in discriminating primary from secondary EMPD [25]. The frequency of positivity for CK20 for primary EMPD was 22% and for secondary EMPD was 50% [25]. The frequency of

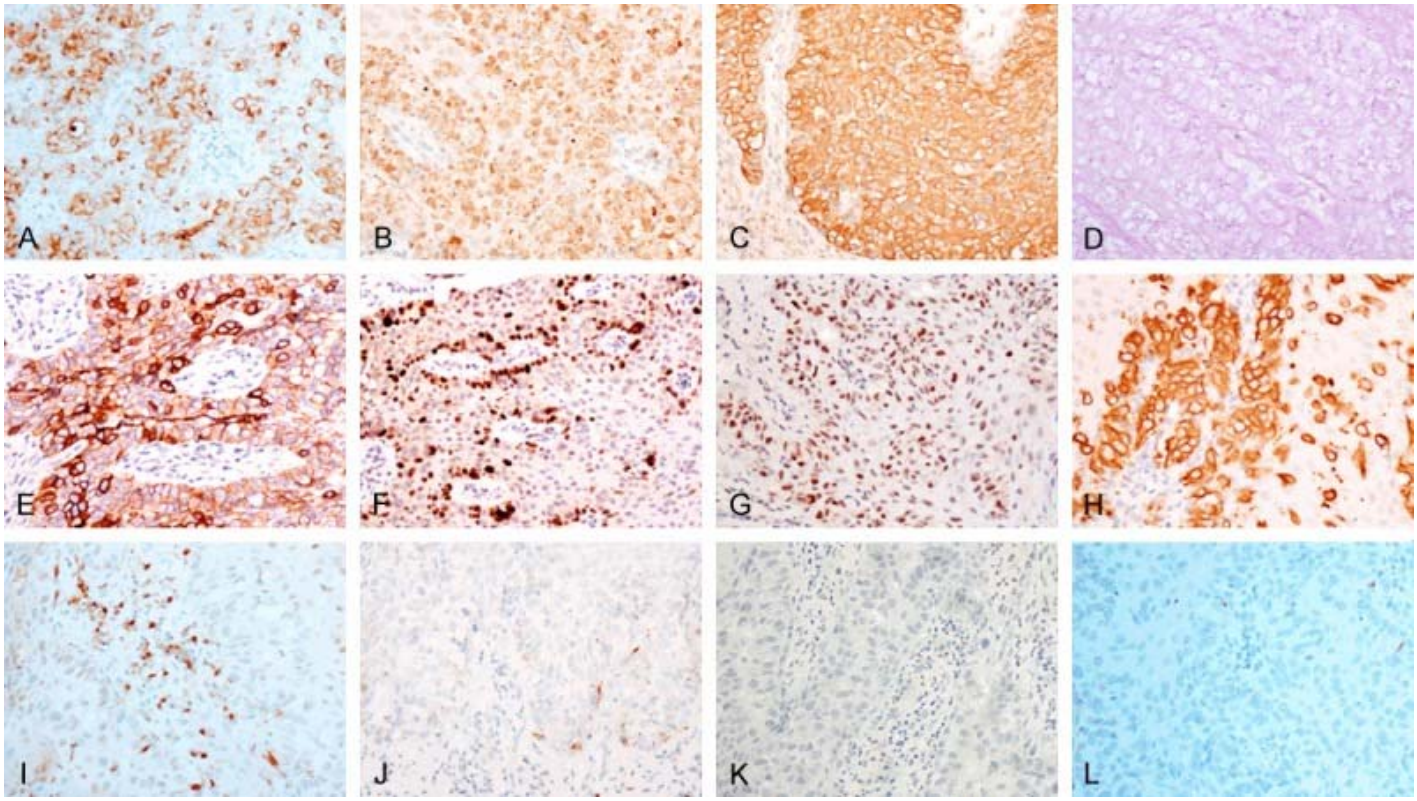

Figure 4. *Immunohistochemical staining of proteins expression in EMPD.* ***A)*** *Positive expression of EMA in EMPD section 200×.* ***B)*** *Positive expression of CEA in EMPD section 200×.* ***C)*** *Positive expression of CK7 in EMPD section 200×.* ***D)*** *Positive expression of PAS in EMPD section 200×.* ***E)*** *Positive expression of HER2/neu in EMPD section 200×.* ***F)*** *Positive expression of Ki67 in EMPD section 200×.* ***G)*** *Positive expression of P53 in EMPD section 200×.* ***H)*** *Positive expression of CK20 in EMPD section 200×. I) Partially positive expression of S100 in EMPD section 200×. J) Negative expression of LCA (leukocyte common antigen) in EMPD section 200×. K) Negative expression of VIM in EMPD section 200×. L) Negative expression of HMB45 in EMPD section 200×). Courtesy of Kang et al. [28] License: https://creativecommons.org/licenses/by-nc/3.0/us/legalcode.*

positivity for CDX2 for primary EMPD was 2% and for secondary EMPD was 33% [25]. Thus, an expanded immunohistochemical panel may be useful in distinguishing these two entities. Furthermore, in secondary EMPD, the phenotype is variable and depends on the nature of the underlying carcinoma. For example, secondary EMPD related to anorectal malignancy is CK7-/CK20+/GCDFP15-/CDX2+/p63-/MUC2+, whereas secondary EMPD related to urothelial malignancy is CK7+/CK20+/GCDFP15-/CDX2-/p63+/uroplakin3+ [26].

The use of immunohistohemistry is also required to exclude certain diagnoses that might mimic EMPD. p63 can be used to exclude pagetoid Bowen disease, which is positive for p63, but usually negative for CK7 [16]. p63 also distinguishes secondary EMPD related to urothelial malignancy from primary EMPD. S100 and HMB-45 are useful in differentiating EMPD from pagetoid melanoma, in which these markers are negative in EMPD, but positive in melanoma [16].

Recently researchers have postulated that certain tumor-related biomarkers may be useful to diagnose or monitor therapeutic efficacy in EMPD. In particular, the serum level of receptor-binding cancer antigen exposed on SiSo cells (RCAS1) was reported to be increased in patients with invasive disease and decreased after therapeutic remedies were administered [16]. Thus, RCAS1 might be used to stage and monitor treatment efficacy.

Additionally, ectopic EMPD continues to be exceedingly rare on the head and neck, with only two reports on the face in English literature [27]. In 2018, Hughes et al. found the third reported case of ectopic EMPD on the face and the first report of it on the nose. Interestingly this patient had another lesion on the left that was previously falsely

diagnosed as squamous cell carcinoma in situ instead of ectopic EMPD as well [27]. Thus, this study demonstrates new anatomical locations for ectopic EMPD and necessitates the need for having a broader differential diagnosis.

Differential Diagnosis

Diagnosis of EMPD is often delayed after a patient's initial presentation of the disease. In 2015, a retrospective review of 246 Chinese male EMPD patients found a significant delay in diagnosis for almost all patients, with a mean delay in diagnosis of 43.2 months after the onset of symptoms [28]. Interestingly, one patient's disease persisted for up to 30 years before confirming the correct diagnosis. Similarly, another retrospective review of 145 cases of EMPD in Japan found the average time to diagnosis was 39.7 months [29].

This inconsistency in the timeline from presentation to diagnosis is likely related to the diversity of symptoms of EMPD as well as the rarity of the disease [30]. The symptoms of EMPD overlap with several benign and malignant dermatologic conditions. Because of this, other dermatologic conditions are often considered first before a correct diagnosis is reached.

The clinical differential diagnosis for EMPD is very broad (**Table 1**), [2, 14, 31]. With respect to secondary EMPD, an underlying adenocarcinoma is usually the culprit behind the skin lesions. Thus, a thorough history and physical examination with appropriate diagnostic testing is indicated in all patients suspected to have secondary EMPD.

Diagnosis

A punch biopsy is necessary to confirm a diagnosis of EMPD. The presence of Paget cells can be confirmed through the use of histochemical stains such as Alcian Blue, colloidal iron, and mucicarmine Mayer, which stain the cytoplasm of the cells [2]. Additionally, immunohistochemical markers are useful in distinguishing primary from secondary EMPD and from other diseases or conditions as already discussed [14].

Determination of intraepithelial versus invasive EMPD is another important but controversial component in diagnosis. It is controversial because there is no algorithm for clinicians to follow when determining if a patient needs a sentinel lymph node biopsy (SLNB), [14]. Multiple studies have evaluated patients with intraepithelial, microinvasive (<1mm of invasion), minimally invasive (invasion to the papillary dermis), and deeply invasive (invasion to the reticular dermis and beyond) EMPD and determining efficacy and utility of SLNB [32]. These studies fail to prove consistency of finding lymph node invasion among minimally invasive disease and have even shown that patients with microinvasive EMPD can develop lymph node involvement [33]. Thus, we recommend SLNB for invasive disease routinely and minimally invasive disease if clinically indicated through history and physical examination.

Patient Evaluation

As EMPD sometimes presents in association with an underlying malignancy, a thorough review of systems is recommended, and a full physical examination should be performed on all patients. In addition to a complete evaluation of the skin, specific diagnostic investigations may be warranted depending on the initial presenting site of EMPD (**Table 2**) [14]. For example, in cases of vulvar EMPD, the following diagnostic tests may be performed: a complete pelvic examination with a pap smear and colposcopy, cystoscopy, abdominopelvic ultrasound, mammography, and colonoscopy [14]. For cases of perianal EMPD, screening for gastrointestinal and genitourinary carcinomas is recommended. For female patients, a mammography should also be performed [14]. These additional imaging modalities can be helpful in detecting the presence of metastasis or other underlying adenocarcinomas.

Pathogenesis

EMPD most commonly arises as an intraepithelial neoplasm of the epidermis (primary EMPD) with Paget cells likely originating from intraepidermal portions of apocrine glands or primitive basal cells [15]. Less frequently, EMPD may occur from epidermotropic spread of malignant cells or direct extension from an underlying internal neoplasm (secondary EMPD), [15].

Current literature postulates that EMPD is of apocrine origin. This is because it occurs in apocrine gland dense regions and stains with CEA and GCDFP-15, markers of apocrine differentiation [34]. Other suspected origins include eccrine glands (also stain with GCDFP-15), pluripotent stem cells, 'mammary-like' glands, or internal malignancy with contiguous spread [9]. It is also important to note that the location of EMPD has differing associations with underlying malignancies. For example, 70-80% of perianal cases arise secondary to invasive malignancy in the anus, rectum, or colon. Conversely, EMPD of the male genitalia is more frequently associated with internal malignancy (i.e. urethral, bladder, prostatic, and testicular neoplasms) than the vulvar region [9]. Vulvar EMPD may originate as a manifestation of adjacent primary anal, rectal, or bladder adenocarcinoma [35].

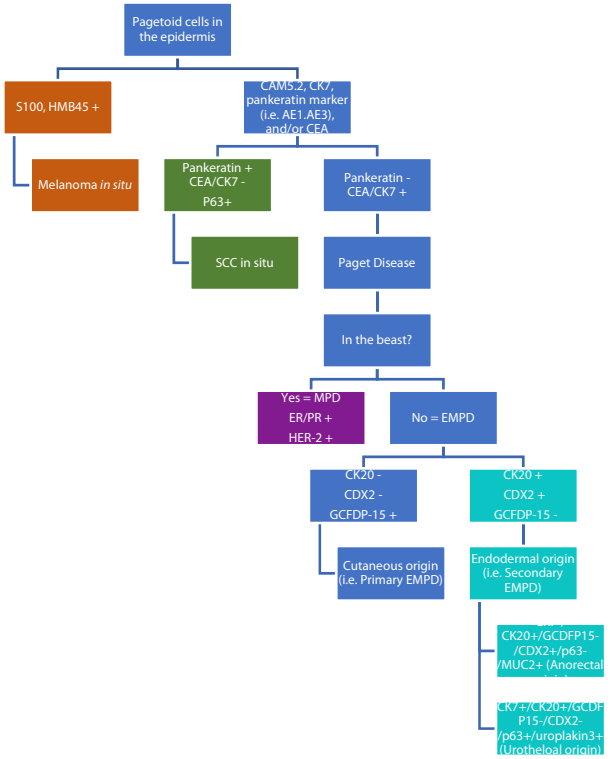

Figure 5. *Extramammary Paget disease. Histological differentiation of extramammary Paget disease. (HMB-45 = human melanoma black-45; CEA = carcinoembryonic antigen; CK = cytokeratin; AE1/AE3 and CAM5.2 = anti-cytokeratin antibodies; CDX-2 = caudal-type homeobox protein 2; GCFDP-15 = gross cystic disease fluid protein-15; SCC = squamous cell carcinoma; MPD = mammary Paget disease; EMPD = extramammary Paget disease; MUC2 = mucin 2), [31].*

Management

There are no guidelines for the treatment of EMPD. A lack of randomized controlled trials investigating different treatment options for EMPD and a small patient population owing to the low prevalence of the disease have limited the availability of conclusive evidence regarding treatment.

Currently, surgical excision of the lesion is the standard of treatment. Wide local excision (WLE) has traditionally been the surgical approach used, but Mohs micrographic surgery (MMS) has also been greatly documented in the literature. There is increasing support for MMS owing to lower rates of recurrence following excision [36, 37]. MMS allows the surgeon to microscopically visualize the entire tumor margin intraoperatively, which is more difficult to achieve when using a WLE approach [38]. MMS can be a challenging, lengthy process in the excision of larger lesions. To overcome these problems, some studies have adopted a technique known as peripheral MMS, in which the periphery of the tumor is marked and excised until clear margins are achieved. After the removal of the periphery, the leftover central part of the tumor is excised.

Despite the increasing support for MMS, a moderately elevated risk of recurrence still exists; thus, long follow-up periods with patients should be pursued. Disadvantages to surgical excision include cosmetic damage to the skin and anatomical and functional impairment of the treated area.

If surgery is contraindicated or if disease is limited, several alternative therapies exist, such as imiquimod 5% cream, photodynamic therapy (PDT), and radiotherapy (RT). Imiquimod 5% cream is an imidazoquinoline immunomodulator that is applied topically to the lesion [39]. One prospective study evaluated nine patients with EMPD treated with imiquimod 5% cream [40]. All nine patients responded to treatment, but only five achieved complete remission. Three of the five later experienced recurrence of their disease despite achieving complete remission. Owing to this possibility of recurrence, Sawada et al. emphasized the importance of a long follow up period if imiquimod 5% cream is chosen to manage EMPD.

Other reports evaluating the use of imiquimod 5% cream for EMPD exist; unfortunately they include shorter follow up periods. Feldmayer et al. reported a case of vulvar EMPD treated with imiquimod cream that showed complete remission one-year post therapy, but follow-up was not reported beyond this time. In this same report, seventeen other cases of EMPD treated with imiquimod 5% cream were analyzed, with 15/17 of the patients achieving complete clinical remission. However, the average follow-up time period was 11.2 months and the longest follow-up was 26 months [40, 41]. Additionally, Cohen et al. recommended application of imiquimod three times per week (non-consecutive days) for a minimum of 8 to 16 weeks after successful treatment of one patient with suprapubic EMPD [42].

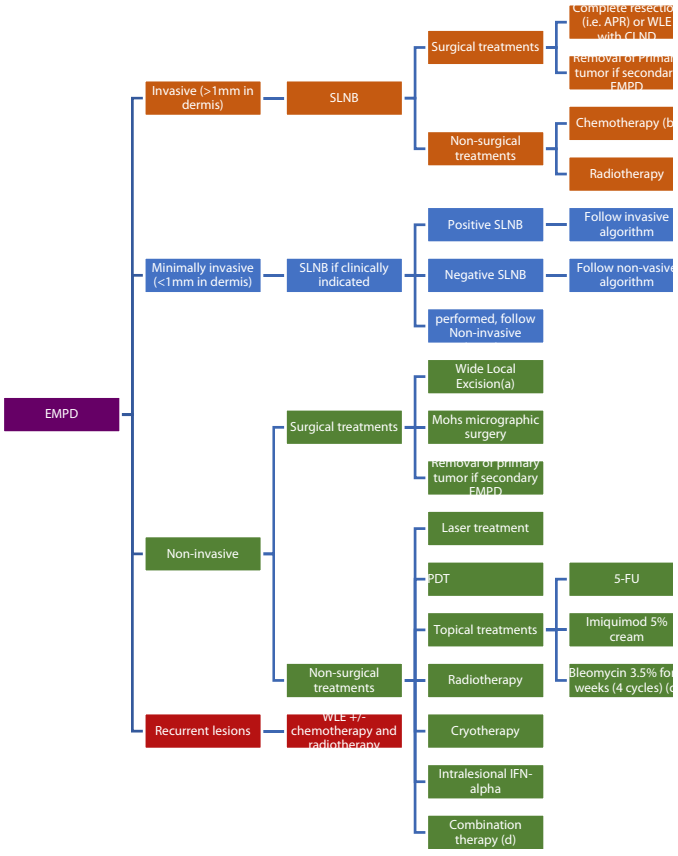

Figure 6. *Extramammary Paget disease. EMPD diagnosis and management algorithm. After diagnosis of EMPD, no matter the depth, all patients should have appropriate cancer screening based on symptoms and location as depicted in* **Table 2** *[33]. **A)** High recurrence rates despite use of 2-3cm epidermal margins and 0.5cm depth margins. **B)** Combination treatments include PDT for tumor margin delineation followed by CO_2 laser and 5-FU before and after WLE. **C)** Chemotherapy regimens include: 5-FU; 5-FU with mitomycin C; carboplatin with 5-FU; low dose 5-FU/cisplatin; low dose mitomycin C with etoposide and cisplatin; mitomycin with epirubicin, vincristine, cisplatin, and 5-FU; docetaxel [35]. **D)** 2 weeks of topical bleomycin 3.5% is followed by a 4-6 week rest period. **E)** All patients should have follow-up margin biopsies every year as well as appropriate cancer screening follow-up.*

Imiquimod 5% cream might also be beneficial as neo-adjuvant therapy by reducing the tumor size prior to surgical excision. By reducing lesion size prior to surgery, less cosmetic and functional damage would occur [43]. Further studies are needed to continue to look at the efficacy of this treatment option.

Photodynamic therapy is another alternative therapeutic regimen for EMPD. Topical photosensitizers, 5-aminolevilunic acid (5-ALA) and methyl-5-aminolevulinate (M-ALA), and an intravenous photosensitizer, porfimer sodium, have been employed in the treatment of EMPD. Housel et al. reviewed the treatment of PDT to 24 lesions of non-invasive EMPD that had previously been treated with other modalities [43]. Sixteen lesions were treated with 5-ALA and nine with porfimer sodium. Overall, 78% of the lesions treated with porfimer sodium achieved complete remission. In comparison, 50% of the lesions treated with 5-ALA achieved complete remission, but 3/8 of these lesions later developed recurrence. Therefore, porfimer sodium produced better short- and long-term outcomes, but the study was limited by short follow up periods and a small sample size.

Fontanelli et al. recently performed a clinical trial in which 32 patients with primary non-invasive EMPD were treated with PDT using M-ALA to consider its use as an alternative photosensitizer [44]. A previous pilot trial conducted by Fontanelli et al. treating seven cases of EMPD with M-ALA showed promising results [33]. In this more recent trial with 32 patients, only 3/32 patients demonstrated a complete response after three courses of treatment. The majority of patients (25/32) showed partial response to treatment, but 15 of these patients chose not to continue treatment further because they saw a satisfactory reduction in their symptoms and the cosmetic appearance of the lesions.

Table 1. *Extramammary Paget disease. The differential diagnosis for extramammary Paget disease.*

Clinical Differential Diagnosis	Histological Differential Diagnosis
Bowen disease	Malignant melanoma
Candidiasis	Mammary Paget Disease
Contact dermatitis	Mycosis fungoides
Crohn disease	
Eczema	
Erosive lichen planus	
Hidradenitis suppurativa	
Langerhans cell histiocytosis	
Lichen scleorsus	
Lichen simplex chronicus	
Mycosis fungoides	
Pemphigus vegetans	
Psoriasis	

Overall, these results suggest that PDT does not appear to be a curative treatment. However, more studies are necessary to compare treatment outcomes using M-ALA versus 5-ALA or porfimer sodium. Alternatively, PDT might be more helpful as an option for reducing symptoms of EMPD, especially those of which might greatly impact a patient's social life and well-being [44].

Side effects from PDT included pain and photosensitivity [43]. Pain typically lasts during the session and persists from hours to days following the treatment session. Over-the-counter analgesics are satisfactory for treating pain associated with PDT. With respect to photosensitivity, patients should be advised to avoid sun exposure and bright lights following treatment for several weeks, especially when sodium porfimer is selected as the photosensitizer.

Radiotherapy is another alternative therapeutic option as either monotherapy and or as adjuvant and neo-adjuvant therapy. Tolia et al. reviewed existing literature on RT and found no definitive recommendations on optimal radiation dose [45]. The total dose for radiation varied in each study that was reviewed, and the studies provided different conclusions on the effectiveness of radiotherapy.

One study examined the use of radiotherapy in the postoperative treatment of 21 patients with EMPD as a way to provide local control and prevent metastasis [44]. In 6/21 patients, the radiotherapy failed to provide local control and distant metastases developed. Notably these patients showed tumor invasion into the dermis and inguinal lymph node involvement prior to radiation therapy. The other 14 patients did not experience distant metastasis. The study concluded that that radiotherapy could be useful as postoperative adjuvant therapy to provide local control in cases of EMPD that have not already invaded the dermis and involved inguinal lymph nodes [44].

Chemotherapy is an additional therapeutic option in advanced or refractory EMPD. A majority of the studies are case reports, making the role of chemotherapy in the management of EMPD unclear. For example, Kariya et al. reported a patient with advanced EMPD treated with combination therapy including 5-fluorouracil and cisplatin. After six weeks of therapy, the primary genital lesion had disappeared, and a CT scan revealed a partial response in metastatic disease as well. The patient passed away from multiple organ failure 18 months

Table 2. *Extramammary Paget disease. Suggested diagnostic and screening recommendations based on location of EMPD or gender of patient. (CEA = carcinoembryonic antigen; PSA = prostate-specific antigen).*

Clinical Location	Clinical Exam and Diagnostic Tests
All locations	Complete history and review of systems; complete cutaneous examination; evaluation of lymph nodes, liver, and spleen
All Women	Breast examination; Mammography
Invasive EMPD	Serum CEA levels
Penoscrotal EMPD	Colonoscopy; cystoscopy +- urogram; consider PSA and CEA
Perianal EMPD	Upper and lower endoscopy +/- CT scan; cystoscopy +/- Urogram; Mammogram (women); consider CEA and PSA (men)
Vulvar EMPD	Complete pelvic examination with Pap smear and colposcopy; cystoscopy +/- CT scan urogram; abdominopelvic ultrasound +/- CT scan

later, but the chemotherapy might have prolonged the patient's survival [33].

Additionally, a retrospective review of 18 cases of metastatic EMPD treated with docetaxel therapy reported a disease control rate of 83%. This rate included cases that showed a complete response, partial response, and stable disease. No patient exhibited signs of a complete response, but docetaxel might be useful in establishing stable disease status [45].

Alternatively, use of trastuzumab in cases of EMPD that overexpress human epidermal growth factor receptor 2 (HER-2) demonstrated promising results. One case report of a 58-year-old woman with a history of breast cancer suffering from relapsed advanced vulvar EMPD that stained positive for HER-2 was treated with trastuzumab and paclitaxel. CT scans showed a decrease in the primary tumor and disappearance of inguinal lymph node metastases following six months of therapy. At the time of the report's publication, the patient had been on the chemotherapy regimen for two years and was continuing therapy as it was providing adequate control of the disease [46].

Another patient with advanced EMPD staining positive for HER-2 was treated with trastuzumab monotherapy and within ten infusion treatments, imaging showed disappearance of all lesions except for one metastatic lesion in the lung. Notably the lesion in the lung decreased in size from 13.4×11.8mm to 3mm [47].

Another patient with advanced EMPD of the scrotum and inguinal region that stained positive for HER-2 was treated with trastuzumab and paclitaxel therapy. Overall, there was a decrease in the number of skin lesions and diminished tumor cells in the lymph nodes and dermis. However, the patient ended up succumbing to the disease following metastasis to the brain [48]. Although the data on HER-2 positive EMPD is limited, these case results suggest that immunohistochemistry stains evaluating overexpression of HER-2 might be helpful in guiding therapy.

Overall, management of EMPD remains difficult. It is further complicated by the lack of an official TNM staging and grading system. Surgery continues to be the mainstay for treatment. There is hope that other alternative therapies might arise or current alternative therapies, given as monotherapy or in conjunction with surgical excision, might be helpful in the treatment of EMPD.

Prognosis

Typically, the course of EMPD is indolent. In these cases, EMPD lesions remain localized within the epidermis. Occasionally, however, the lesions will invade the dermis and there is potential for metastasis to distant locations. When this occurs, the prognosis is much worse.

In one review of 145 cases of EMPD in Japan, the 5-year survival rate for those with tumor thickness lesser than or equal to 1mm was 99.1%. For those with tumor thickness equal to or greater than 3mm, the 5-year survival rate was 57%. Metastasis to one or more lymph nodes was associated with a worse prognosis. Dermal invasion showed a statistically significantly worse 5-year survival rate than when the lesion was confined to the epidermis or exhibited only superficial dermal invasion [39]. Serum carcinoembryonic antigen (CEA) markers correlated with a worse prognosis as well. Similarly, Hata et al. analyzed factors affecting survival outcomes in 76 patients with EMPD and reported depth of invasion as the most significant factor affecting survival [42]. The study also evaluated the measurements of serum CEA levels, which carried a worse prognosis when elevated. Therefore, serum CEA levels might be useful in detecting patients who carry a worse prognosis. Another large retrospective review evaluated 495 male patients with EMPD and determined that the presence of metastasis had worse survival outcomes and was associated with an 60% increase in mortality using multivariate Cox regression analysis [46].

Overall, the prognosis for EMPD appears to depend primarily on tumor thickness, depth of invasion, and the presence or absence of metastasis. It is important to take into consideration that EMPD is a disease that often affects an older population and this may play a role in a patient's prognosis or affect their ability to receive treatment.

What's new in the diagnosis and management of EMPD

Recently Chang et al. has evaluated the expression of chemokine receptors, CXCR4 and CXCR7, in a series of EMPD patients and correlated their expression patterns with clinicopathological characteristics and patient outcomes. They found that either high expression of CXCR4 or CXCR7 was indicative of lymphovascular invasion, regional lymph node metastasis at diagnosis, and a poor prognosis [49]. Additionally, high expression of CXCR7 was correlated with greater depth of invasion, whereas patients overexpressing both CXCR4 and CXCR7 experienced the worst prognosis [49]. Thus, these reliable biomarkers can be helpful to distinguish malignant potential and are potentially useful therapeutic targets for patients with EMPD moving forward.

Additionally, ectopic EMPD continues to be exceedingly rare on the head and neck, with only two reports on the face in English literature [27]. In 2018, Hughes et al. found the third reported case of ectopic EMPD on the face and the first report of it on the nose. Interestingly, this patient had another lesion on the left that was previously falsely diagnosed as squamous cell carcinoma in situ instead of ectopic EMPD as well [27]. Thus, this study demonstrates new anatomical locations for ectopic EMPD and necessitates the need for having a broader differential diagnosis.

Conclusion

The field of dermatology has come a long way with respect to the diagnosis of EMPD mainly through the use of immunohistochemical staining. Additionally, the literature reveals an enhanced understanding of the pathogenesis of EMPD. The discovery of new prognostic indicators is also helpful in further classifying patients with EMPD and predicting patient outcomes. However, the management of EMPD still lacks a standard and effective treatment regimen. Further studies are needed to find new and more effective treatment modalities for this difficult-to-treat disease.

Potential conflicts of interest

The authors declare no conflicts of interests.

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