REVIEW

Extramammary Paget's disease: what do we know and how do we treat?

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Introduction: *Extramammary Paget's disease (EMPD) is a rare and complex condition, for which no established guidelines exist regarding diagnosis and management. There have been recent improvements in the diagnosis and management in EMPD, largely due to an enhanced understanding of its underlying pathogenesis.*
Materials and methods: *A literature search on PubMed including articles that describe pathogenesis, clinical diagnosis, treatment modalities, and future treatment were selected and included to build this review.*
Results: *Recent studies would suggest the expression of HER2 and androgen receptors which could be useful targets for future treatment strategies. Carcinoembryonic antigen as a biomarker for EMPD has shown the potential to aid in the detection of metastatic EMPD and assessment of treatment response. Studies have also demonstrated the initial site of EMPD can be predictive of secondary malignancies, which helps guide initial work up and evaluation.*
Conclusions: *Significant developments in understanding the pathogenesis of EMPD have been made, especially of the genomic aberrations associated with EMPD. This has allowed for the development and use of therapeutic options which may improve outcomes for patients with EMPD.*

Key Words: extramammary Paget's disease, novel therapy, cell-free DNA, immunotherapy

Introduction

The complexity of Extramammary Paget's Disease (EMPD) has been apparent for decades with minimal improvements in diagnostic and therapeutic options. This rare carcinoma generally afflicts individuals greater than 60 years old and more often Caucasians than any other ethnicity.[1] There are a multitude of case series, case reports, and retrospective studies, offering various treatment protocols; however, there is insufficient evidence for clear management guidelines. The heterogeneity of this disease in its presentation, location, depth of invasion and its typical multidisciplinary approach to management make it difficult to treat. The association with other malignancies is a well-described phenomenon and should inform treatment and long term management.[2] Use of biomarkers shows promise in diagnosis and treatment monitoring. As immunotherapy (IO) is becoming a mainstay for many cancers, there is growing support for the use of these agents in advanced EMPD patients.

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Pathophysiology of EMPD

Studies show EMPD development is associated with increased P16 protein expression. This protein is implicated in the pathogenesis of human papilloma virus (HPV). Interestingly enough, the upregulation

of P16 in EMPD does not appear to be caused by HPV. This HPV-independent pathway has been described in a study where the mean P16 expression was only 33.3% (range: 10%-80%) in scrotal EMPD samples.[3] In the described study, none of the samples had any HPV staining via immunohistochemistry (IHC) nor fluorescent in situ hybridization (FISH).

Another mechanism for the pathogenesis of EMPD has been described via the HER2/neu amplification pathway. A study of 103 patients found that 15% (n = 16) had increased HER2 expression and amplification of the *ERBB2* gene. Furthermore, these HER2-positive EMPD cases conferred a more aggressive biology.[4] This mechanism may provide a potential target with HER2-directed therapeutics. Additional studies found that in approximately 90% of patients with metastatic EMPD, there is concordance in the HER2 expression and *ERBB2* gene amplification from primary and lymph node metastases.[5] Additionally, HER2 overexpression activates both the *RAS* and *PIK3CA* pathways, which offer more actionable targets.[6]

Alterations in either the *RAS* or *PIK3CA* pathways appear to be mutually exclusive in the pathogenesis of EMPD. In a gene sequencing-based study of 144 samples, *RAS* or *RAF* alterations were detected in 19% (n = 27) of samples and *PIK3CA* or *AKT* alterations were detected in 35% (n = 50) of samples.[7] Both of the *RAS/RAF/MEK/ERK* and *PIK3CA/AKT/mTOR* pathways have multiple agents targeting various drivers along these pathways and additionally there are clinical trials developing more drugs directed to these targets. The importance of identifying actionable targets in EMPD affords the possibility to find more patient-specific treatment options.

In another cohort of EMPD patients, androgen receptor (AR) signaling has been implicated as a mechanism of pathogenesis. In a study analyzing AR, HER2, and estrogen receptor (ER) positivity, more patients had AR positive disease than HER2 or ER combined. Almost 80% (18/23) of patients had AR-positive EMPD, whereas HER2 was positive in 52% (12/23), and only 4% (1/23) of patients had ER-positive disease.[8] There are multiple agents targeting AR approved in prostate cancer as well as multiple agents targeting other androgen pathway related molecules. Another study found that AR, 5-alpha hydroxylase,

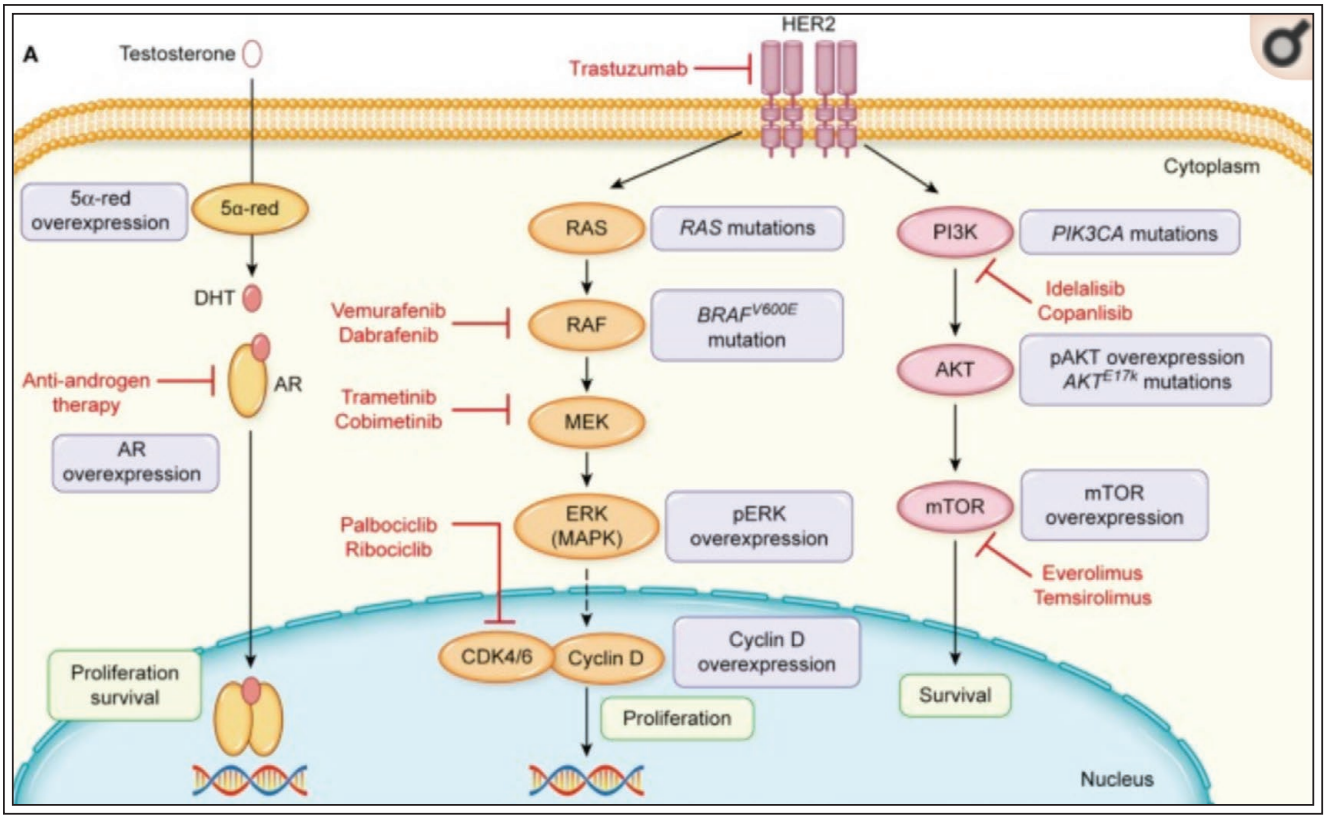

Figure 1. Signaling pathways involved in EMPD progression. Excessive activation of the HER2 signaling pathway and androgen receptor can induce proliferation and survival of Paget cells, leading to EMPD. There are numerous targets within signaling pathways that can serve as targets for therpautic agents. Frontiers in Oncology (Fukuda et al, 2018).[6]

and 17-beta dehydrogenase type 5 significantly increased immunoreactivity in invasive compared to non-invasive EMPD ($p < 0.0001$).[9] Agents targeting all of these receptors with exquisite specificity exist and are approved in other conditions offering additional potential treatment options, Figure 1.

Diagnostic evaluation

Patients with EMPD typically present with well-demarcated, persistent and non-resolving erythematous, eczematous plaques that may have associated crusting, scaling, papillomatous lesions, lichenification, ulceration or bleeding, Figure 2. Deep ulceration is typically indicative of invasive disease and poor prognosis.[10] The most common associated symptom is pruritis, followed by irritation, burning, and pain.[11] Regional lymph nodes may be enlarged and clinically palpable, which may represent metastasis versus reactive lymphadenopathy.[11] The differential diagnoses for EMPD include: contact dermatitis, lichen sclerosis, melanoma, psoriasis, mycosis fungoides, and fungal infections.

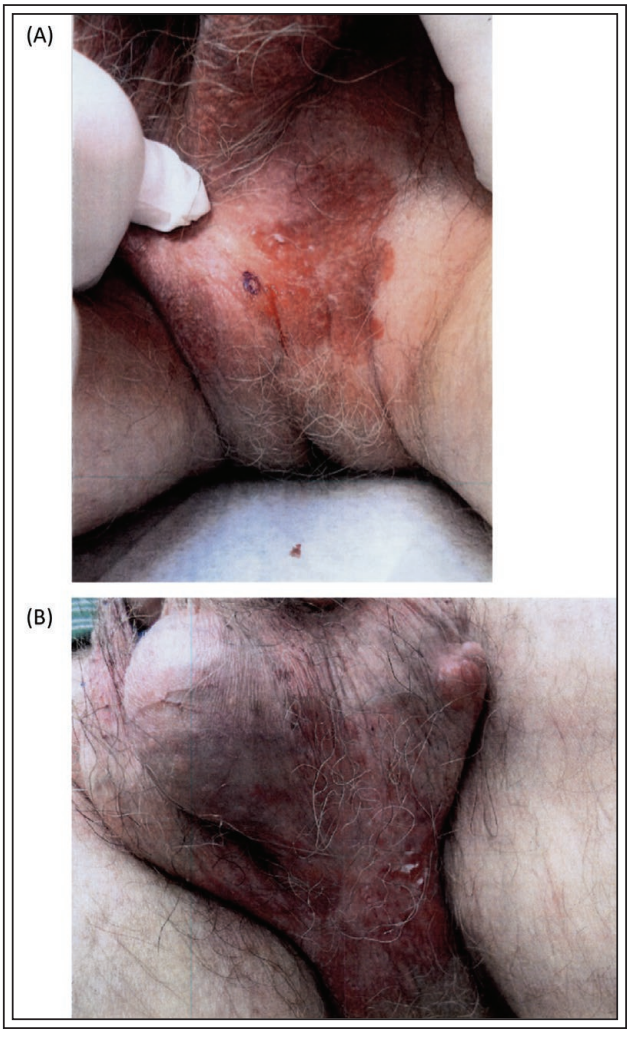

Figure 2. (A and B) Representative photos of patients with penoscrotal EMPD lesions affecting large surface area.

EMPD is strongly associated with the presence of co-existing adnexal and other visceral malignancies. Chanda et al reviewed 196 EMPD cases from 1962-1982 and reported the rate of adnexal carcinoma to be 24% and the rate of visceral malignancy to be 12%.[12] More recently, the incidence has been reported to be as high as 25%-35%.[13] Perianal EMPD has a higher frequency of associated cancer than genital EMPD.[14] Many studies have shown that the initial site of disease predicted the site of secondary malignancies, i.e. patients with colorectal, anal, vulvar, and scrotal EMPD showed an increased risk of colorectal, anal, vulvar/vaginal, and scrotal malignancies, respectively, Table 1.[14] A thorough work up for occult malignancy should be performed on all patients with biopsy proven EMPD. As described by Shmitt et al, patients with EMPD should undergo a full physical examination to evaluate for multifocal disease including digital rectal examination, as well as breast and lymph node examinations.[15] Additionally, for all male and female patients, work up should include urine cytology, office cystoscopy, chest x-ray, axial imaging of the abdomen and pelvis (CT or MRI), and colonoscopy. For female patients, practitioners should also consider Papanicolaou smear and mammography. For male patients, PSA blood testing should be included.[15]

EMPD is usually limited to the epidermis, but in some instances may progress to invasive disease. For this reason, a diagnosis is first confirmed by biopsy of

TABLE 1. **Most common sites of visceral malignancy in extramammary Paget's disease**

Rank	Site	Number of cases
1	Colorectum and anus	32
2	Male genital system	22
3	Female genital system	20
4	Breast	20
5	Lung and bronchus	9
6	Urinary bladder	7

Number of secondary malignancies at secondary sites recorded over 120+ months from most common (rank #1) to least common.[14]

the skin lesion that has shown persistence in the form of eczematous or erythematous plaque on the penoscrotal skin. The optimal method of biopsy has not been standardized, although typically is done by punch biopsy to establish a diagnosis. Handheld reflectance confocal microscopy (HRCM) has been investigated as a tool assist evaluation and management of EMPD given it has been used in the past to evaluate skin tumors, its non-invasive nature, and its ability to provide results in a timely manner when compared to traditional biopsy methods.[16-19] While there is relative paucity of data regarding HRCM and EMPD, it has shown the potential to be useful in assisting the diagnosis of EMPD and determining surgical margins intraoperatively.[17] Currently, mapping biopsies are often conducted to aid in the determination of surgical borders due to tumors commonly extending beyond the clinically apparent lesion. Though, it has been proposed mapping biopsy may not be required for well-defined lesions and ill-defined lesions where 1 cm and 2 cm lesions can be obtained, respectively.[20]

At the Moffitt Cancer Center, we have instituted a novel mapping biopsy technique to better determine border for surgical resection. The skin surrounding the lesion is marked in the 1 through 12 o'clock positions like a clockface. Next, 2 mm punch biopsies are obtained along each line of the clockface in 1 cm intervals up to 5 cm from the visible edge of the lesion, Figure 3. Each is individually sent for surgical pathology, and the biopsy sites are closed in interrupted fashion with 4-0 biosyn sutures.

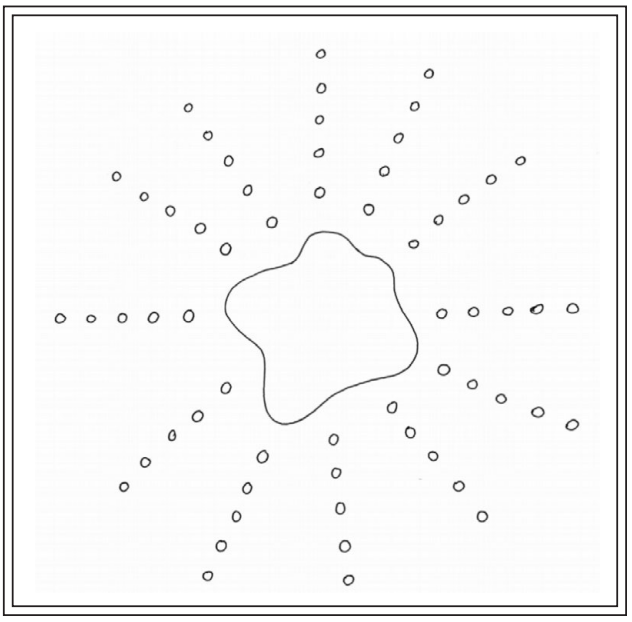

Figure 3. The skin surrounding the EMPD lesion is marked at the 1 through 12 o'clock positions from 1-5 cm at 1 cm intervals. Then 2 mm punch biopsies are taken at each site.

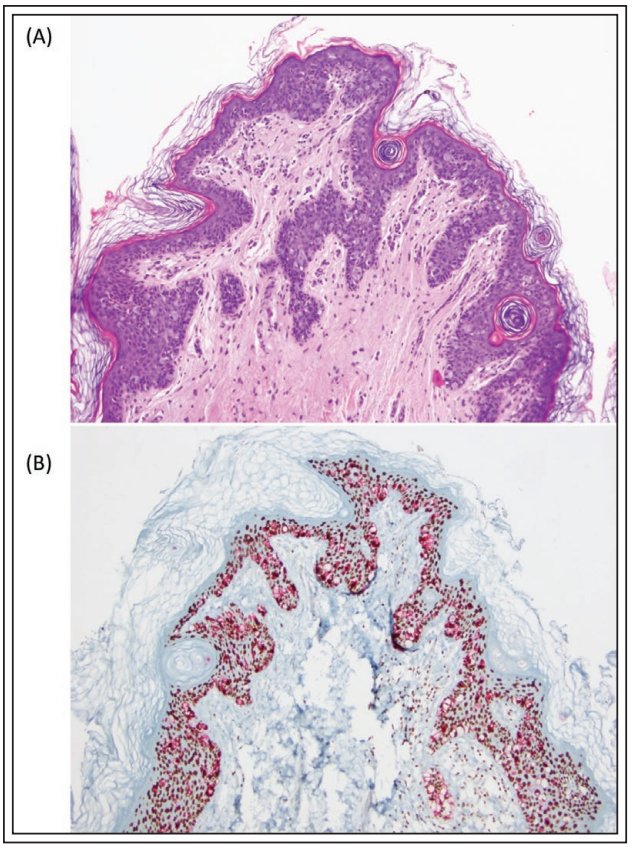

Figure 4. (A) H&E staining: The tumor cells are present as large, individual cells with abundant amphophilic cytoplasm within the epidermis (10x). **(B)** IHC dual staining: Dual immunohistochemical stain CK7 + GATA3 highlights the Paget cells that stain positive for CK7 (cytoplasmic stain red in color) and GATA3 (nuclear stain brown in color) (10x).

Various histopathologic characteristics have been identified as predictors of invasive disease in EMPD, Figure 4. A study of 41 patients with invasive penoscrotal EMPD revealed that all cases had a carcinoma in situ pattern and a large majority showed evidence of nodular growth patterns and glandular formation.[21] Other factors found to be strongly correlated with poor prognosis included delay in diagnosis, depth of invasion greater than 1 mm, lymphovascular invasion, and lymph node metastasis at diagnosis.[21]

Treatment options

There is a lack of consensus among therapeutic strategies, in part due to the variety of specialists treating EMPD. Each approach carries varying levels of evidence as to

TABLE 2. **Treatment options summary for non-metastatic extramammary Paget's disease (EMPD)**

Treatment option	Study size	Reported outcomes	Median follow up (range)	Best clinical use
Imiquimod[24]	63	CR = 73% Recurrence rate = 5.7%	12 (0.5-53) months	Neoadjuvant or adjuvant with excision
Photodynamic therapy and 20% topical 5-aminolevulinic acid[27]	17	CR* = 62.5% (< 4 cm) CR* = 33.33% (4-8 cm), CR* = 0% (> 8 cm); Overall recurrence rate = 50%	24 months (range not reported)	EMPD lesions < 4 cm
Radiotherapy[31]	41	OS = 93% at 3 years OS = 68% at 5 years	41 (2-174) months	Primary or adjuvant settings
Holmium laser[30]	61	Mean operation time: 43.3 vs. 86.65 min; Mean wound healing time 17.2 vs. 7.61 days[a]	Median not reported, (5-60) months	Disease limited to the dermis and epidermis
Wide local excision[35]	124	RFS = 66% at 5 years OS = 68% at 5 years	1.9 years (1 day-20.5 years)[b] 2.6 years (49 days-18.7 years)[c] 4.2 years (1 day-18.8 years)[d]	1st line – primary excision
Mohs micrographic surgery[34]	81	Recurrence rate = 12.2%	27.5 (2-174) months	1st line – primary excision, also recurrences from wide local excision

A list of treatment options for non-metastatic EMPD along with reported outcomes in series using those options. CR = complete response rate; *CR is defined in each lesion size, [a]laser therapy vs. traditional surgical excision; [b]for patients without recurrence; [c]for patients with recurrence; [d]for patients alive at last follow up; RFS = recurrence-free survival; DSS = disease-specific survival; OS = overall survival

its effectiveness and tolerability. Common treatments include topical immunomodulators, photodynamic therapy, laser ablation, radiotherapy, wide local excision (WLE), and Mohs micrographic surgery (MMS), Table 2.

Topical imiquimod therapy is indicated in non-invasive EMPD with reported complete response (CR) in 56% of select cases.[22] Acting as a toll-like receptor agonist, it stimulates the Th1 acquired immune response and cytokine release of tumor necrosis factor alpha, interferon alpha, interferon gamma, interleukin-2 and interleukin-12.[23] Its safety and efficacy has been proven for various skin malignancies and is typically prescribed as a 5% cream applied topically, 3-4 times weekly for various durations.[24] Imiquimod has been used extensively in vulvar disease as neoadjuvant or adjuvant treatment with primary lesion excision.[24] It can be considered for primary non-surgical treatment in the elderly population with high surgical risk. Notably, a handful of case reports have shown CR to topical imiquimod alone where patients had no evidence for visceral malignancy.[25]

Imiquimod, when used concurrently with photodynamic therapy, has led to CR in select cases of EMPD.[26] For scrotal lesions < 4 cm in diameter, photodynamic therapy with 5-aminolevulinic acid, once weekly for 3 weeks, has shown CR rate of 66.6%, but is not recommended as first line for most in situ EMPD.[27]

Laser ablation therapy is a less invasive option for superficial EMPD compared to surgery. There are case reports using CO2 and neodym:YAG laser therapy with success.[28,29] The holmium laser showed no significant difference in a study of 61 patients with EMPD versus surgery for recurrence-free survival (RFS) ($p = 0.77$) and disease-specific survival ($p = 0.279$).[30] Although, for lesions > 6 cm^2, there was a statistically significant increase in healing time for patients who were treated with the holmium laser. It is also worth noting, with laser ablation it is not possible to confirm via histologic examination whether cancerous tissue has been completely ablated, theoretically increasing the risk for recurrence. However, the aforementioned studies documenting successful utilization of laser therapy is reassuring.[28-30]

Radiotherapy (RT) is another option that has been used successfully as primary and adjuvant treatment of EMPD. In a study by Hata et al, 41 patients underwent

RT for EMPD (24 as primary therapy, 17 as adjuvant therapy following surgical excision with positive or close margins) with 23 patients undergoing RT using 4-15 MV X-rays to the local tumor site and regional lymph node area followed by local radiation boost to the gross tumor site with 6-13 MeV electrons.[31] Eighteen patients underwent treatment with either 4-15 MV X-rays or 6-15 MeV electrons to the tumor site alone.[31] RT was delivered in total doses of 45-80.2 Gy (median of 60 Gy) in 23-43 fractions (median = 33 fractions) over 31-69 days (median = 49 days). Radiation fields included the gross tumors along with tumor beds, including positive and close margins, and each radiation field had a margin of 2-5 cm.[31] The overall survival (OS) rates at 3 and 5 years were 93% and 68%, respectively. However, 39% of patients developed recurrence, with 12.2% experiencing tumor progression within the radiation field, and 29.3% experiencing lymph node and/or distant metastasis outside the radiation field (median follow up = 41 months, range for follow up = 2-174 months).[31] Reported adverse reactions, from most common to least common, included dermatitis (100% of patients), hematologic reactions (leukopenia = 39% of patients and anemia = 9.8% of patients), diarrhea (34% of patients), and GU tract reactions (29.3% of patients). All adverse reactions were grade 1-2 reactions per National Cancer Institute Common Terminology Criteria for Adverse Events.[31] Additionally, it was demonstrated that tumor invasion into the dermis and regional lymph node metastasis could be useful prognostic factors for OS and distant metastasis.[31]

Surgical excision remains the cornerstone of non-invasive EMPD treatment, whether via WLE or MMS, but is limited by irregularities of borders, leading to positive margins, satellite lesions that are not resected, and high local recurrence rate.[32] The definition of "wide" in WLE is not well established, however, most agree a clinical tumor-free margin between 2-5 cm is reasonable.[33] Yet, a recent study conducted by Kaku-Ito et al has shown pre-determined 1 cm and 2 cm margins may be adequate for well-defined and ill-defined EMPD lesions, respectively.[20] When large lesions are removed, a significant skin deformity is created. Split-thickness skin grafting is often required for scrotal and inguinal reconstruction, Figure 5. While WLE remains the treatment of choice, the MMS technique has gained popularity since its development in the late 1990s due to improved RFS and lower rates of false-negative margins. It is more expensive and time consuming than WLE, but allows tissue sparing via frozen section analysis for positive margin until a negative margin is achieved.[34] Due to the rarity of EMPD, small study sample sizes limit useful statistical analysis in comparing the two techniques.

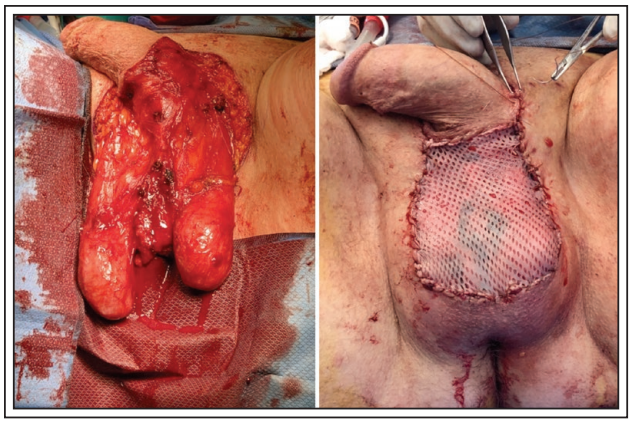

Figure 5. Scrotal reconstruction with split-thickness grafting. **(A)** Scrotal EMPD lesion completely excised. **(B)** Scrotal reconstruction with split-thickness skin graft from upper thigh. Split thickness grafts and local myocutaneous flaps are often required for scrotal and inguinal reconstruction.

In 2017, results from a large retrospective cohort review of EMPD patients treated between 1961-2012, with either WLE or MMS, found estimated 5 year RFS rate of 91% versus 66% and an estimated 5 year OS rate of 79% versus 68% with MMS versus WLE, respectively.[35] Another study retrospectively reviewed 302 EMPD tumors, all male patients, with tumors of the penoscrotal and perianal region. Of 278 primary tumors, recurrence rates after non-MMS surgical excision versus MMS were 37.4% and 1.6%, respectively. Twenty-four patients with recurrence after non-MMS surgery underwent definitive MMS, noting a 4.2% (1/24) recurrence rate at 75.3 month follow up, supporting the efficacy of MMS in treating primary EMPD and also as salvage therapy.[36]

Several studies show association between margin status and recurrence. Margin status was evaluated in 154 cases of EMPD, analyzing variables including gender, provider specialty, and disease site for likelihood of positive margins. Females were more likely than males to have a positive margin (odds ratio (OR), 8.1, 95% CI 2.7-24.6), and positive margins were more common after WLE than MMS (OR 13.8, 95% CI 1.8-105.8). Patients with positive pathologic margins had 3.5-fold increased risk of recurrence compared to those with negative margins (95% CI 1.7-7.2; $p < 0.001$). Since none of the women in the study underwent MMS, male patients were included in a subgroup analysis, finding a higher rate of negative margin with MMS and a 2-fold increased risk of recurrence with WLE versus MMS.[37]

For patients with invasive EMPD (invasion beyond the epidermis) who are surgical candidates, the current

standard of care is to perform surgical excision of the primary lesion with the necessity for lymphadenectomy being dependent on the status of the patient's inguinal lymph nodes.[38] For patients with clinically positive inguinal lymph nodes, a therapeutic inguinal lymph node dissection is recommended.[38] However, for patients with invasive disease without clinically positive regional lymph nodes there is no consensus at this time.[38] Some have recommended prophylactic lymph node dissection for patients with invasive EMPD regardless off lymph node status,[39] while sentinel lymph node biopsy has been explored as an option to assess lymph node status.[40]

Metastatic and unresectable EMPD is difficult to treat with poor OS. The most effective chemotherapeutic regimen for metastatic disease is not well established. Numerous monotherapies as well as combination chemotherapies have been proposed, Table 3.

In a study of 8 patients with metastatic EMPD using docetaxel and cisplatin, the authors reported a mean progression-free survival (PFS) of 9.9 months and mean OS of 28.9 months.[41]

A series of 7 patients with metastatic EMPD were treated with a combination chemotherapy regimen including epirubicin, mitomycin C, vincristine, carboplatin, and 5-fluorouracil (5-FU). The study reported PFS of 6.5 months and OS of 9.4 months with 1 year OS of 43% (3/7 patients). Of note, 57.1% (4/7) patients were evaluable with RECIST criteria, and all were seen to have partial responses (PR) to therapy.[42]

One patient with penoscrotal EMPD, found to have multifocal synchronous metastases at time of diagnosis, underwent treatment with topical 5-FU and systemic pemetrexed. Treatment imaging at 6 weeks demonstrated a PR.[43]

TABLE 3. **Review of case reports/series of proposed systemic therapies for metastatic extramammary Paget's disease**

Therapeutic option	Number of patients tested	Primary lesion location	Median overall survival (range)	Median progression free survival (range)	Major side effects
ADT5[4]	1	Pubic region	12 months	2 months	NR
5-fluorouracil, epirubicin, carboplatin, vincristine, mitomycin C[42]	7	Scrotum (5) Penis (1) Vulva (1)	9.4 months	6.6 months	Myelosuppression
Paclitaxel5[5]	1	Perineum	NR	At least 3 months	Myelosuppression
Lymph node dissection, 5-FU and docetaxel[45]	1	Penoscrotal	At least 12 months	At least 12 months	Neutropenia, leukopenia, anorexia
Trastuzumab[48]	1	Scrotal and perianal	At least 12 months	At least 12 months	Fatigue
5-FU and cisplatin[44]	8	NR	18 months	6 months	Fatigue, numbness
Docetaxel and cisplatin[41]	8	Scrotal skin	28.9 months (11-53 mo)	9.9 months (3-18 mo)	Myelosuppression
Cisplatin, epirubicin and paclitaxel[46]	5	Scrotum (4) Vulvar (1)	20.1 months (3.8-36.5 mo)	8.0 months (0.5-10.4 mo)	Myelosuppression, alopecia, nausea, fatigue, anorexia
Pemetrexed monotherapy and 5-FU topical[43]	1	Penoscrotal	NR	At least 4.2 months	Well tolerated, mild fatigue

A summary of systemic therapies as well as the location of the primary lesion, median overall survival, median progression free survival, and major side effects of therapy
ADT = androgen deprivation therapy; 5-FU = 5-fluorouracil; NR = not reported

Kato et al retrospectively reviewed 17 patients with treatment of advanced EMPD. Nine patients received best supportive care, and 8 received combination 5-FU with cisplatin. Four of the patients receiving 5-FU with cisplatin had PR, 2 with stable, and 2 with progressive disease. In patients receiving 5-FU with cisplatin, the median PFS was 6 months and median OS was 18 months ($p = 0.08$).[44]

A patient with penoscrotal EMPD with positive bilateral inguinal lymph nodes and distant nodal metastases (left external iliac lymph node) was treated successfully with wide local excision and sentinel lymph node biopsy followed by surgical excision of the bilateral inguinal lymph nodes and treatment with a 5-FU derivative and docetaxel. Following 3 cycles of treatment, he had a significant decrease in the size of the left external iliac lymph node (12 mm to 6 mm) and was disease free at 1 year follow up.[45]

The combination chemotherapy regimen cisplatin, epirubicin, and paclitaxel was employed in 5 patients with metastatic EMPD. In this study, 80% (4/5) had PR with median PFS of 8 months and median OS of 20.1 months, including 2 patients with disease previously refractory to taxane monotherapy or platinum-based regimens.[46]

Interestingly, the *HER2* oncogene is expressed in 15%-60% of EMPD.[47] A retrospective study of 73 EMPD tissue samples found HER2 positivity using IHC staining, FISH, and applied the American Society of Clinical Oncology algorithm for breast cancer (combines IHC and FISH). The combined algorithm of IHC and FISH showed higher rates of HER2 detection than either test alone. In these patients, anti-HER2 targeted therapies could potentially be used as a therapeutic strategy.[47] Finally, in a case of recurrent, multifocal metastatic EMPD, single-agent trastuzumab provided a CR with no evidence of disease at follow up of 1 year.[48]

Future insights

Metastatic EMPD has been shown to be associated with elevated carcinoembryonic antigen (CEA) levels compared to non-metastatic disease having lower levels (median 10.6 versus 2.6, respectively; $p = 0.005$).[49] When the CEA levels were ≥ 20 ng/mL, they correlated to disease burden on positron emission tomography-computed tomography (PET-CT) scans. This is a useful tool in monitoring disease progression and response to treatment in metastatic disease. The value of CEA levels in metastatic EMPD was further validated in a 72-patient study spanning 13 years. This study showed that metastatic EMPD was significantly associated with elevated CEA levels ($p < 0.0001$); however, in stages I-III there was no significant association with CEA levels ($p = 0.6867$).[50] This again shows the utility of CEA levels for detecting metastatic EMPD.

In efforts to identify a biomarker for early stage disease, a study using cell-free DNA (cfDNA) found a significant association with disease state. This study showed that cfDNA of patients with non-metastatic EMPD was significantly higher than in healthy controls (71.8 ± 80.6 versus 24.3 ± 10.1 ng/mL, respectively).[51] Furthermore, this study reported that patients with metastatic EMPD had elevated cfDNA levels that were not significantly higher than their non-metastatic cohorts and that cfDNA could be a reliable biomarker in all EMPD patients regardless of clinical stage disease.[51] This finding is especially important for early stage disease and offers a mechanism for monitoring response to treatment.

In looking for additional treatment options, IO are a continually attractive option as they offer more tolerable side effect profiles compared to traditional chemotherapies. However, programmed cell death-1 (PD-1) positivity is not associated with disease-free survival nor OS ($p = 0.13$ and $p = 0.87$, respectively).[52] Although this target may not yield significant benefit for patients, EMPD tissue expresses significant amounts of indoleamine 2,3-dioxygenase (IDO) ($p < 0.01$).[52] The IDO molecule serves to inhibit the function of CD8+ T cells, and in these patients the proportion of peritumoral CD8+ T cells was inversely related to OS (HR 5.03; 95% CI 1.03-24.4; $p = 0.045$).[52] This finding may offer a successful approach in treating EMPD via inhibiting IDO and restoring CD8+ T cell function.

Mismatch repair genes (MMR) (*MLH1*, *MSH2*, *PMS2*) have also been analyzed in EMPD patients in efforts to potentiate the role of IO. A study of 172 patients found that 34.3% of patients had germline alterations in MMR genes and that 13.4% of tumors had somatic mutations.[53] In addition to providing insight into the pathogenesis of EMPD, these findings also substantiate the claim that perhaps there may be a role for IO in these patients, even if PD-1 may not play a major role in disease evolution. The benefit of IO in EMPD is unclear, yet there are strong indications that various immunostimulatory modalities may provide benefit; however, randomized controlled trials are imperative to discern their efficacy.

Conclusions

There have been significant developments in understanding the pathogenesis of EMPD which have allowed for noteworthy improvements in its diagnosis and management. In particular, a better understanding

of the genomic aberrations associated with EMPD has allowed for the development and use of therapeutic options which may improve outcomes for patients with EMPD. Furthermore, the use of biomarkers has the potential to enhance the ability to detect disease earlier and monitor response to treatment. While EMPD lesions biopsy is pivotal in determining surgical margins, no standardized template has been produced. However, development of standardized templates, such as the one used at Moffitt Cancer Center, have the potential to improve the initial diagnostic evaluation of EMPD.

At this time, there are no established guidelines regarding treatment modalities for EMPD. There are various treatment options for localized EMPD; however, less is known about the best treatment modalities for metastatic disease. Neoadjuvant or adjuvant therapy with topical imiquimod or radiation therapy, in addition to surgical resection, may be beneficial for patients with localized disease. For metastatic disease, there is a paucity of evidence to make recommendations for systemic therapy and randomized controlled trials are imperative in order to determine how to provide optimal care and treatment guideline for these patients. □

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