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NEWS, VIEWS, & REVIEWS

EXTRA, EXTRA, Treatment Approaches for EXTRAmammary Paget Disease

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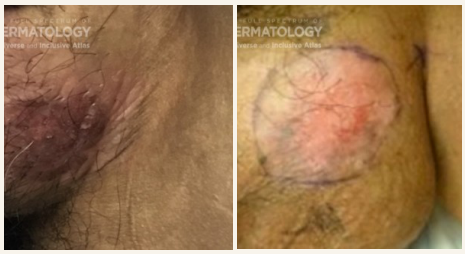
Introduction

Extramammary Paget Disease (EMPD) is a rare intraepithelial malignancy of pluripotent keratinocyte stem cells that presents on apocrine-rich skin of the perineum, vulva, and less commonly, axilla.[1] EMPD clinically presents as a slow growing, unilateral, strawberry-pink scaly patch or plaque, frequently impacting Caucasian women in their sixth to eight decades (Figure 1).[1,2]

Figure 1. Extramammary Paget Disease of the perineum and breast.[10]



While typically confined to the epidermis, EPDM can be invasive, associated with contiguous extension or upward pagetoid spread of underlying neoplasms or with distant synchronous malignancy.[3] The complexity of EMPD intertwined with the heterogeneity of the disease in its appearance, location, and depth of invasion, often requires a multidisciplinary approach to management (Table 1).[1]

There have been recent significant developments in further characterizing EMPD, such as identification of associated mutations in TP53, ERBB, NRAS, BRAF, PIK3CA, and AKT1 genes and overexpression of P16 protein and the HER2 and Androgen Receptor (AR) signaling pathways.[2] However, given EMPD is a rare disease, there are no established guidelines regarding diagnosis and treatment modalities.[2,3,4] Herein we review evidence and provide insight for non-surgical and surgical approaches utilized for EMPD.

Non-surgical Management

EMPD often elicits inherent surgical limitations due to its aggressive nature, ill-defined margins, and subclinical extension; therefore, conservative treatment approaches are ideal.[5,6]

Imiquimod

As a toll-like receptor 7 agonist, imiquimod induces innate and cell-mediated inflammatory responses and subsequent cell apoptosis.[2,3] Imiquimod can be used as monotherapy, adjunctive therapy before or after surgery, as well as part of a therapeutic combination with other management modalities. Complete remission (CR) when used as a single agent ranged from 52% to 72%, according to one study.[2,3] Eighty-five percent of patients experienced greater than 50% clinical regression; unfortunately,

Table 1. Treating Extramammary Paget Disease[2-8, 15,16,17]

Management	Modality	Best Clinical Use
I. ***Non-surgical Approaches***	Topical [eg, Imiquimod, 5-FU, Bleomycin]	Not well-established and limited evidence of its overall efficacy; high rates of recurrence and often toxic s/e
	Photodynamic Therapy	EMPD lesions of < 4 cm
	Radiation Therapy [Dosing: 10 Gy to 64 Gy]	Primary EMPD or adjuvant setting
	Holium Laser	EMPD limited to the dermis and epidermis areas
	Carbon Dioxide Laser	EMPD limited to the dermis and epidermis areas
II. ***Surgical Approaches***	Wide Local Excision [1 cm incision margins]	Well-defined EMPD lesions only
	Mohs Micrographic Surgery	1st line: primary excision or for recurrences from wide local excision
	Sentinel Lymph Node Biopsy	In cases where regional metastasis is present
III. ***Systemic Therapy***	Combination Chemotherapy of Low-Dose FP and Cisplatin	Advanced EMPD cases
	FECOM Therapy	Metastatic EMPD
	HER-2 Therapy	Deep invasion and lymph node metastasis as well as aggressive EMPD cases
	Trastuzumab	Metastatic EMPD
	Docetaxel + S-1	Metastatic EMPD
	Trastuzumab + Paclitaxel	Metastatic EMPD

40% of individuals with CR had disease recurrence, thus highlighting the importance of continued follow-up.[2]

5-Fluouracil (5-FU)

Topical 5-FU is a pyrimidine analogue that acts by inhibiting synthesis of DNA and RNA.[2] Despite being utilized as field therapy for actinic keratoses and topical treatment for both superficial basal cell carcinoma and squamous cell carcinoma in situ, its efficacy for EMPD is limited. One case series studied its application in combination with 0.005% calcipotriene twice daily for a twelve-week duration on patients with refractory EMPD. Although clinical lesions cleared, biopsy specimens following the treatment course showed persistent disease with no patient achieving CR.[2,8]

Photodynamic Therapy (PDT)

Patients undergoing PDT are exposed to photoreactive agents which are selectively taken up by tumor cells, and then exposed to appropriate wavelengths of light creating reactive oxygen species that allows selective destruction of neoplastic tissue.2[7] Multiple EMPD case reports revealed antitumor responses to PDT with one systematic review showing a complete response rate of 46.2% and recurrence rate of 33.6% to PDT alone. Overall results indicate that PDT can be beneficial when used as a palliative treatment to minimize EMPD associated symptoms.[2,3,6]

Radiation Therapy

Radiation therapy may be used as a first-line treatment in patients with inoperative primary EMPD, recurrent EMPD, as well as adjuvant therapy after surgery.[2] In one retrospective study, all primary EMPD tumors treated with radiation resolved by 2-to-9 months, yielding a 100% initial CR rate. Twenty-one percent of patients developed local recurrence after a median follow-up of 41 months, and local progression-free survival rates were 78% at 3 years and 69% at 5 years.[3] Another study found post-surgical radiotherapy with a median total dose of 59.4Gy achieved 100% local control after a median follow-up of 38 months and 55% attained progression-free survival at 5-year follow-up.[2,7,8] Furthermore, radiation is also routinely used to treat lymph node metastases, although minimal evidence of its efficacy exists.[2]

Surgical Management

Surgical excision remains the cornerstone treatment of choice for non-invasive EMPD, whether via wide local excision (WLE) with margins of 2-to-5cm or Mohs micrographic surgery (MMS), especially when definitive clearance is possible but can be limited by irregularities of borders, leading to positive margins, unresected satellite lesions, and high rates of local recurrence. Studies demonstrate that a clinically determined border of well-defined EMPD neoplasms permit adequate WLE with 1-cm surgical margins, whereas 2-cm margins are appropriate for ill-defined EMPD lesions.

There is growing evidence that MMS presents favorable patient outcomes with improved relapse-free survival (RFS) and recurrence rates of EMPD when compared to WLE.[2,7,8] MMS allows complete frozen section analyses of excised tumors, maximizing normal tissue conservation while optimizing cure rates.[3,11,12] Results from one retrospective study uncovered an estimated 5-year RFS rate of 91% versus 66% and an estimated 5-year overall survival rate of 79% versus 68% with MMS versus WLE, respectively.[4] Positive margins were reported in 3.4% patients after MMS compared to 33.3% of patients who underwent WLE.[4] A second study found a 37.4% recurrence rate of EMPD after non-MMS surgical excision versus 1.6% with MMS.[4,5]

Conclusion

Every case of EMPD is morphologically unique; the rarity of the disease and research to date supports that management varies vastly and evidence-based approaches are lacking. Future global collaborations with supportive groups can be imperative in designing EMPD clinical trials and effective database evaluation in hopes of establishing foundational EMPD practice guidelines and treatment interventions.[2]

Disclosure

The authors declare no conflicts of interest.

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