Metastatic Primary Extramammary Paget Disease: A Case Series

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PRACTICE **POINTS**

- Invasive primary extramammary Paget disease has a higher risk for lymph node metastasis.
- Consider extramammary Paget disease in patients presenting with erythematous pruritic plaques in apocrine-rich areas that fail to respond to topical steroids or antifungals.
- Prompt diagnosis can expedite comprehensive malignancy work-up and multidisciplinary management, potentially impacting patient outcomes.

Extramammary Paget disease (EMPD) is an uncommon cutaneous malignancy that manifests with pruritic erythematous plaques within apocrine-rich areas such as the axillae and anogenital region. Dermal invasion is a known risk factor for metastasis, which is associated with poor outcomes. We present 2 cases of invasive EMPD on initial biopsy with rapid disease progression. The patients died secondary to metastatic EMPD without additional underlying malignancy. We review the literature and highlight key clinicopathologic features, management considerations, and the potential for rapid disease progression in cases of invasive EMPD.

Extramammary Paget disease (EMPD) is a rare cutaneous malignancy typically seen in apocrine-rich areas, including the axillae and anogenital region. It presents as a slow-growing, erythematous patch or plaque that commonly is misdiagnosed as an infectious or inflammatory condition.[1,2] Primary EMPD occurs as a intraepithelial neoplasm, whereas secondary EMPD occurs due to epidermotropic metastases or direct extension of an underlying adenocarcinoma into the skin.[1] Most commonly, primary EMPD occurs in situ; however, when present, dermal invasion and metastases from the skin are associated with poorer outcomes.[3] Given the rarity of metastatic disease, existing literature is limited to case reports and case series.

We present 2 patients with metastatic primary EMPD who had evidence of invasion on initial biopsy and died secondary to metastatic EMPD. We conducted a comprehensive review of the literature for invasive and metastatic EMPD to highlight key clinicopathologic features, treatment considerations, and the potential for rapid disease progression in cases of invasive EMPD.

Case Series

Patient 1—A 68-year-old White man with a history of breast cancer (in remission) presented to our clinic for further management of biopsy-proven scrotal EMPD. Prior to biopsy, he described a 6-month history of worsening scrotal rash treated with topical antifungals, oral antibiotics, and topical steroids due to presumed diagnosis of intertrigo, cellulitis, and dermatitis, respectively. Clinical examination showed indurated, erythematous, ulcerated plaques involving the bilateral groin, genitalia, and perineum (Figure 1). Skin biopsy confirmed a diagnosis of EMPD with both dermal and lymphovascular invasion. An immunohistochemical profile was positive for CK7 and carcinoembryonic antigen (CEA) and negative for CK20 (Figure 2).

At presentation, the patient had palpable lymphadenopathy and scrotal edema concerning for inguinal and iliac lymph node metastases. Workup for an underlying adenocarcinoma included computed tomography (CT) of the chest, abdomen, and pelvis; urologic consultation with cystoscopy; and a screening colonoscopy. The

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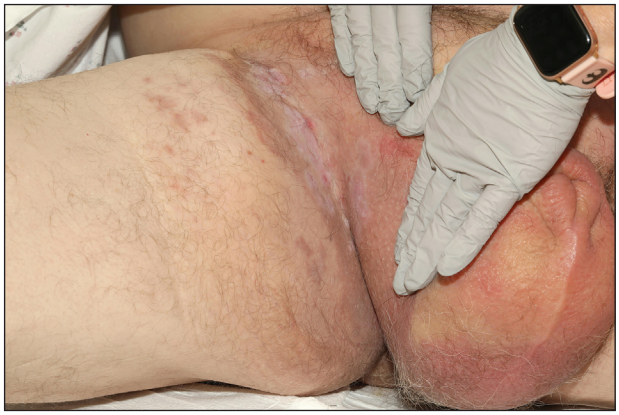

FIGURE 1. Extramammary Paget disease with an indurated erythematous plaque involving the right inguinal fold and edematous genitalia (patient 1).

CT scan revealed multiple enlarged inguinal and external iliac lymph nodes. Fine-needle aspiration revealed CK7- and CEA-positive neoplastic cells consistent with metastatic EMPD. The patient was treated with 6 cycles of carboplatin-paclitaxel, palliative radiation therapy, and pembrolizumab with minimal response to treatment and development of osteolytic vertebral lesions concerning for disease progression. He died 1 year after the initial diagnosis secondary to the disease.

Patient 2—A 79-year-old White man presented for further management of an outside diagnosis of superficially invasive primary EMPD of the bilateral inguinal folds and scrotum that had been present for 5 months prior to biopsy and diagnosis. Clinical examination at initial presentation revealed erythematous patches of the bilateral inguinal folds and scrotum, as well as an erythematous scaling plaque in the right axilla. There was no palpable clinical lymphadenopathy. Biopsy of the axilla and groin were both consistent with invasive EMPD with positive staining for CK7 and negative staining for CK20 and CDX2. Workup for underlying adenocarcinoma with whole-body positron emission tomography/CT, mammography, esophagogastroduodenoscopy, serum CEA, colonoscopy, and cystoscopy were all negative for a metastatic adenocarcinoma. There was no imaging or clinical evidence of lymphadenopathy. Complete circumferential peripheral and deep-margin assessment was performed in a staged manner on both sites, and negative margins were obtained.

Surveillance imaging 6 months after surgery revealed suspicious hepatic lesions. Fine-needle aspiration of the hepatic lesions demonstrated positive staining for CK7 and negative staining for CK20, CDX2, prostate-specific antigen, and thyroid transcription factor 1, consistent with metastatic EMPD. Oncology recommended carboplatin and docetaxel or docetaxel monotherapy chemotherapy. The patient was further managed by an outside oncologist due to ease of travel but died secondary to the disease 15 months following the initial diagnosis.

Comment

Extramammary Paget disease is an uncommon cutaneous malignancy that manifests as pruritic erythematous plaques within apocrine-rich areas such as the genitalia, axillae, or anal region. It most commonly occurs in patients older than 65 years, with White women and Asian men being affected at disproportionately higher rates.[1,4] Delay in diagnosis is common, as EMPD can mimic other benign inflammatory or infectious conditions, including contact dermatitis, seborrheic dermatitis, tinea, candidiasis, and eczema.[1]

Metastatic and multifocal cases of primary EMPD are especially rare. According to a search of PubMed articles indexed for MEDLINE published through December 2023 using the terms *extramammary Paget disease, EMPD, neoplasm metastasis, invasive extramammary,* and *neoplasm invasiveness,* we identified 5040 cases of invasive EMPD and 477 cases of metastatic EMPD.[5-37] Of the reports that disclosed patient demographic information, 3627 patients were female 1410 were male, and the mean age was 67 years. Sites of metastases included regional lymph nodes, liver, lungs, cervix, bladder, bone, brain, skin, kidney, and adrenal glands.

Workup for EMPD—The initial steps for workup of EMPD include a thorough physical examination and lymph node assessment. A skin biopsy also should be performed for patients presenting with refractory, pruritic, and eczematous rashes in apocrine-rich areas to evaluate for EMPD.[1] Characterization of large and complex tumors is better achieved through multiple biopsies with particular focus on nodular or thickened areas, as these may indicate invasive disease.[2] Primary EMPD is characterized by pagetoid cells with abundant pale cytoplasm proliferating in a single-cell or nested pattern within the epidermis or dermis in invasive disease and often is accompanied by dermal lymphocytic inflammation.[1] Immunohistochemistry demonstrates positive staining for CEA, CK7, and CK8, with negative staining for indicators of secondary EMPD including CK20 and CDX2.[1,2]

As part of the workup, it is critical to distinguish between primary disease and secondary EMPD.[1] Beyond skin and clinical lymph node examination, additional workup should be based on age-appropriate and location-directed malignant neoplasm screenings, including colonoscopy, cystoscopy, prostate examination, mammography, and Papanicolaou test. Advanced imaging such as CT, positron emission tomography, or magnetic resonance imaging can be used to assess for metastatic disease if internal malignant neoplasms are present on initial screening or clinical lymphadenopathy is identified.[2] Additionally, it can be helpful in the evaluation for nodal disease in cases of invasive EMPD.

The likelihood of associated underlying carcinomas varies depending on the site of involvement.[38,39] For example, vulvar involvement constitutes approximately 65% of EMPD cases, with 11% to 20% of cases being associated with underlying gastrointestinal or genitourinary

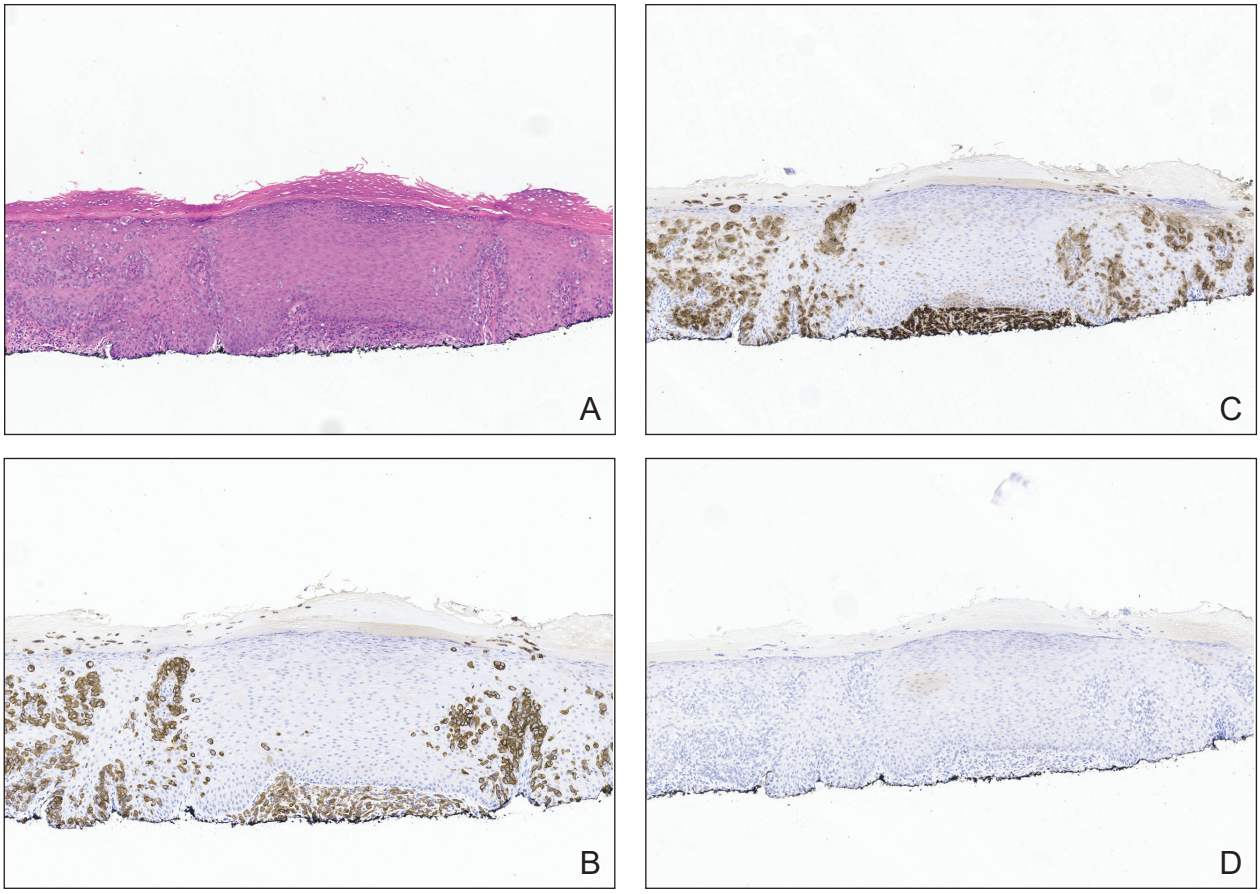

FIGURE 2. Shave biopsy from patient 1 demonstrated extramammary Paget disease with diffuse pagetoid epidermal involvement and dermal invasion (A; H&E, original magnification ×10), positive staining for CK7 (B; H&E, original magnification ×10) and carcinoembryonic antigen (C; H&E, original magnification ×10), and negative staining for CK20 (D; H&E, original magnification ×10).

carcinomas. Involvement of the male genitalia, as in our 2 patients, is rare, accounting for approximately 14% of cases, 11% of which are associated with prostate, testicular, and bladder carcinoma. Perianal involvement comprises 20% of EMPD cases and has the greatest risk for underlying malignancy with an incidence of 33% to 86%, the majority of which are rectal or tubo-ovarian cancers.[38,39] Consideration of the frequency and types of underlying carcinoma of respective sites of involvement can be helpful when ruling out secondary EMPD.

In both of our patients, palpable lymphadenopathy at the time of original diagnosis and histologic invasive disease on initial biopsy warranted thorough imaging and laboratory workup; there was no evidence of primary malignancy. Given the absence of an underlying carcinoma, both patients were classified as having metastatic primary EMPD.

Assessment of lymphadenopathy is an essential aspect of disease workup, as it is associated with a statistically higher rate of lymph node metastases. A study by Fujisawa et al[20] demonstrated that 80% of patients with lymphadenopathy had regional metastases compared to only 15% of patients without clinical lymphadenopathy. The presence of invasive disease also has been shown to correspond with lymph node metastases.[40] Ogata et al[40] showed that 0% of cases with in situ EMPD had a positive sentinel lymph node biopsy (SLNB) compared to 4% and 43% in cases that showed evidence of microinvasion and dermal invasion, respectively. Lymph node metastases are associated with poor prognosis, with increasingly worse prognosis when there are multiple lymph nodes affected.[41] In our case series, patient 1 had lymphadenopathy and both patients had invasive EMPD; they both later developed metastases and died.

Lymphadenopathy should be further investigated with imaging and biopsy or fine-needle aspiration.[42] Recent expert consensus guidelines recommended this method of investigation over routine use of SLNB, as there is no evidence that a positive SLNB affects treatment that changes disease-specific survival.[2]

Treatment of EMPD—Surgical excision of the primary lesion is the first-line treatment of EMPD,[1,2] which can be performed by wide local excision; however, studies have demonstrated higher recurrence-free survival with margin-controlled surgery (complete circumferential peripheral and deep margin assessment) or Mohs

micrographic surgery (MMS), especially with CK7 immunostaining.[2,37,43] The literature on MMS of invasive EMPD is sparse, accounting for 57 patients.[25,37,44] Other reports describe management with surgical excision, wide local excision, regional resection, or vulvectomy, in addition to lymph node dissection, radiation therapy (RT), and/or chemotherapy.[1-36,39,43-46] Despite the improved outcomes with MMS, the predominance of other surgical approaches in our search suggests that MMS may be currently underutilized for the treatment of invasive or locally advanced EMPD.

Among patients with unresectable disease or distant metastases, management includes RT with curative intent, chemotherapy, or a combination of both.[1,2] In our review, 267 cases were treated using RT and 77 with chemotherapy. Radiation therapy is an effective therapeutic option with a reported response rate of 62% to 100% and can be employed as either primary or adjuvant treatment.[3] For patients with lymph node metastasis the combination of RT and lymph node dissection has been shown to have improved outcomes compared to lymph node dissection alone, with 1 study showing a 5-year survival of 75% for patients who received adjuvant RT compared to 0% for lymph node dissection alone.[45]

There are currently no consensus guidelines on the best chemotherapeutic regimen for metastatic EMPD. Several regimens have been reported, including docetaxel monotherapy; low-dose 5-fluorouracil and cisplatin; combination chemotherapy FECOM (5-fluorouracil, epirubicin, carboplatin, vincristine, mitomycin); or combination therapy with cisplatin, epirubicin, and paclitaxel.[1]

Prognosis of Metastatic EMPD—Because invasive and metastatic EMPD is rare, its natural history is hard to predict. Poor prognosis is associated with nodule formation, tumor thickness, perianal or vaginal involvement, lymphovascular invasion, nodal metastasis, and distant metastasis. The 5-year survival for metastatic EMPD has been reported to be less than 10%.[46] Our cases underscore the poor prognostic risk associated with metastatic EMPD.

For all cases of EMPD, close follow-up is warranted. Guidelines recommend physical examination with lymph node assessment every 3 to 6 months for 3 years and every 6 to 12 months for the subsequent 5 years.[2] Specific recommendations for follow-up in invasive disease have not yet been described, though the 20% probability of developing an internal malignancy within 5 years after diagnosis and poor prognostic outcomes associated with invasive and metastatic disease support the need for close monitoring.[2]

Conclusion

Although in situ EMPD often is a slow-growing tumor with good prognosis, invasive disease has high potential to behave aggressively with high morbidity and mortality. Increased awareness and prompt identification of invasive EMPD, expedited comprehensive workup, and early multidisciplinary management might impact patient outcomes.

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