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Case report

Docetaxel treatment for widely metastatic invasive vulvar extramammary Paget's disease with multifocal bone metastasis

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1. Introduction

Invasive extramammary Paget's disease (EMPD) of the vulva, first identified in 1901 (Dubreuilh, 1901), tends to occur in Caucasians, ages 50–65 years (St Claire et al., 2019). Approximately 65 % of cases of EMPD occur in the vulva (Lam and Funaro, 2010). Invasive vulvar EMPD represents 1–6 % of vulvar cancers in the United States and has an incidence of 0.36 per 100,000 person years (Kilts et al., 2020). Metastasis to one or more lymph nodes is associated with a significantly worse prognosis (St Claire et al., 2019). In a retrospective cohort study of invasive EMPD patients in Japan, 44 % of patients with metastasis to regional lymph nodes ultimately developed distant metastasis (Ohara et al., 2016). Given the rarity of this disease, there is a paucity of available high quality interventional or outcomes data, and it is unlikely for randomized clinical trials to be feasibly powered to critically investigate therapeutics in this setting (Edey et al., 2019). Treatment for metastatic EMPD is thus guided by retrospective case reports or small case series with varying treatment regimens, including monotherapy with docetaxel, cisplatin, or 5-FU, as well as multi-agent chemotherapy including 5-FU/cisplatin and cisplatin/epirubicin/paclitaxel (Ishizuki and Nakamura, 2021; Fukuda and Funakoshi, 2018; Hashimoto et al., 2021). Furthermore, details regarding specific treatments for invasive EMPD metastatic from a vulvar primary site, and their accompanying efficacy and tolerability profiles, are lacking in the published literature. This report describes treatment utilizing monthly low-dose docetaxel to achieve a highly effective, durable response with minimal toxicity for a case of metastatic invasive vulvar EMPD.

2. Case description

The patient is a 57-year-old, gravida-4 *para*-4, postmenopausal non-Hispanic Black female with past medical history significant for type 2 diabetes mellitus, essential hypertension, peripheral arterial disease, history of cerebrovascular accident (CVA) with residual hemiparesis, and tobacco abuse, who originally received an outside diagnosis of Paget's disease of the vulva after a wide local excision performed in 2009. She presented to the emergency department with one week of postmenopausal spotting and back pain in 2014. Physical exam in the emergency room showed an atrophic vulva with a thick, irregular 2x2 cm left-sided white plaque with a scalloped shape. Work up of the postmenopausal bleeding included a Pap, transvaginal ultrasound, endometrial biopsy, and biopsy of the vulvar lesion. Biopsy of the vulva was consistent with primary vulvar Paget's disease without evidence of stromal invasion. All other workup at this time was benign – pap and endometrial biopsy were negative for dysplasia/hyperplasia/malignancy, and her back pain was deemed to be musculoskeletal in origin without imaging evidence of pathology or metastatic disease. She was referred to gynecologic oncology for further treatment recommendation

Abbreviation: EMPD, extramammary Paget's disease.

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but was lost to follow up.

She presented to clinic 38 months later in 2018, at which time a physical exam demonstrated bilateral vulvar and labial lesions with leukoplakia and a thin rectovaginal septum. A Pap was collected which did demonstrate cytologic evidence of malignant cells not otherwise specified, and HPV negative status. The patient declined a biopsy at this time. CT chest, abdomen and pelvis showed concern for local progression of Paget's disease in the vulva, and there were no findings suggestive of metastatic disease. She declined additional diagnostic workup with biopsies or any treatment at the time.

The patient returned for evaluation one year later and complained of vaginal spotting, pruritus, gray vaginal discharge, and unintentional weight loss. Pelvic exam revealed erythematous, thickened, firm tissue with overlying white plaque replacing the left labium majus. Repeat biopsy of the left vulvar skin at this time resulted with Paget's disease, focally involving a hair follicle. She declined surgical intervention, and thus was prescribed topical imiquimod 5 % cream three times per week for her localized disease. However, compliance with topical treatment was extremely limited due to discomfort and limited mobility. She continued to decline further biopsy, resection, or alternative treatment modalities.

Repeat CT chest, abdomen, and pelvis in February 2020 were delayed due to patient transportation difficulties. Imaging showed progression of locally advanced EMPD involving the vulva and new evidence of widespread metastases with adenopathy in left inguinal, left external and internal iliac, left common iliac nodal regions, and mildly enlarged periaortic and aortocaval lymph nodes. The patient opted to pursue repeat biopsies and imaging 6 months later. Physical examination now revealed a mottled, nodular, and ulcerated left labium majus to the level of the vaginal introitus as well as development of a full-length rectovaginal fistula. Findings were overall concerning for concurrent locally advanced progression with invasion as well as metastasis of disease. A left vulvar biopsy revealed clusters of irregular cells with an infiltrative growth pattern in the vulvar epithelium and stroma, characterized by positive immunohistochemistry staining for cytokeratin 7, CEA, and EMA with negative S100 staining, consistent with a diagnosis of invasive vulvar EMPD (Fig. 1). Repeat imaging the subsequent month displayed significant progressive metastatic disease, with newly enlarged mediastinal lymph nodes and worsening multifocal disease burden in numerous bony sites, retroperitoneum, mediastinum, and retrocrural regions (Fig. 2, left panel).

Her case was discussed at multidisciplinary tumor board among the

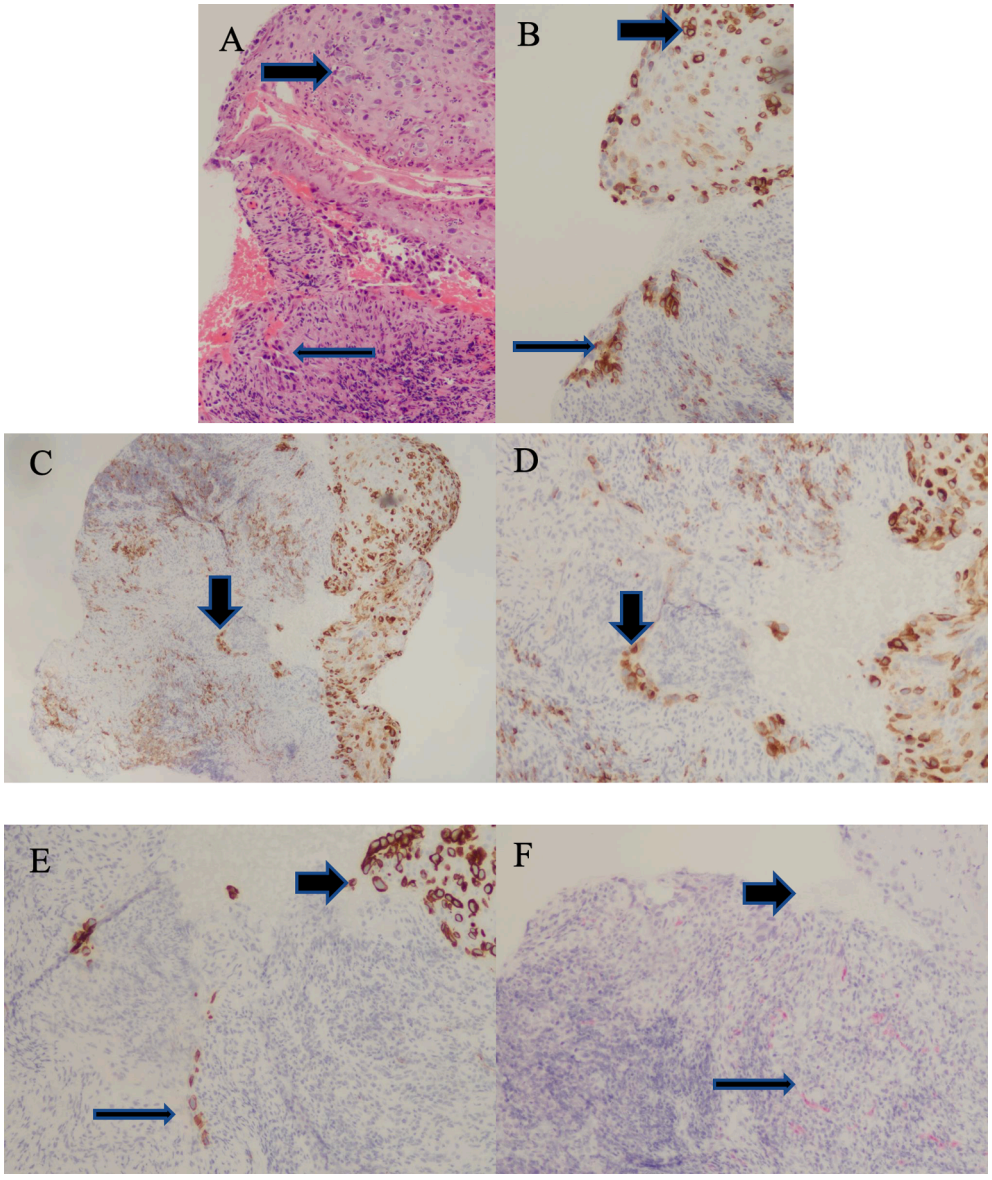

Fig. 1. A) H&E (10x): Broad short arrow showing superficial epithelium with Paget cells. Narrow arrow showing ill defined clusters of invasive Paget cells. B) CEA IH, brown chromogen (10x): Broad short arrow showing membranous positivity in the superficial epithelium with Paget cells. Narrow long arrow showing clusters of invasive Paget cells. C) EMA IHC, brown chromogen (2x): Sections showing membranous positivity in Paget cells within the superficial epidermis and in the invasive component in the dermis (black broad arrow). D) EMA IHC, brown chromogen (20x): Sections showing membranous positivity in Paget cells within the superficial epidermis and in the invasive component in the dermis (black broad arrow). E) CK7 IHC, brown chromogen (10x): Sections showing membranous positivity in the Paget cells within the superficial epithelium (black broad arrow) and in the invasive component in the dermis (narrow long arrow). F) S100 IHC, red chromogen, (10x): Sections are negative in Paget cells within the superficial epithelium (black broad arrow) and in the invasive component in the dermis (narrow long arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

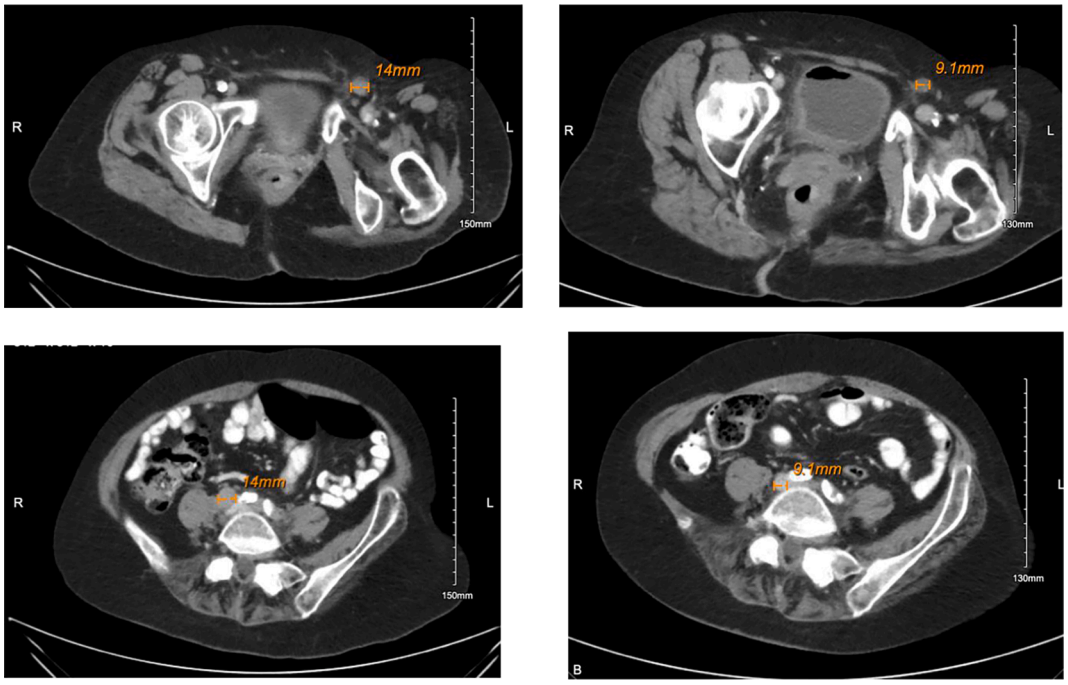

Fig. 2. Treatment response. Left upper panel: left inguinal lymph node on baseline CT scan. Right upper panel: partial response in left inguinal lymph node status post cycle 4 docetaxel. Left lower panel: right common iliac lymph node on baseline CT scan. Right lower panel: partial response in right common iliac lymph node status post cycle 4 docetaxel.

pathology, radiology, genetics, radiation oncology, and gynecologic oncology specialties. A plan for systemic therapy was made based on case series and case reports primarily consisting of male patients with non-vulvar EMPD due to limited clinical evidence and rarity of this disease (Yoshino et al., 2016). The available pathology sample was insufficient for additionally recommended testing (next-generation somatic genetic sequencing analysis, programmed death ligand (PD-L)1 staining, microsatellite instability), and the patient declined repeat tissue sampling. Given the patient's physical limitations, unresectable tumors, and desire to minimize toxicity, she was offered treatment with single agent Docetaxel 60 mg/m^2 on a 28-day cycle. She agreed and proceeded with treatment in September 2020. After completion of cycle 4, surveillance imaging demonstrated a partial response, with significant decrease in multiple retroperitoneal, pulmonary, and pelvic lymph nodes (Fig. 2, right panel). Subsequent MRI after cycle 11 in July 2021 confirmed further impressive treatment response with shrinkage and substantial sclerosis of multifocal iliac and lumbar bone metastases, consistent with continued partial response (Fig. 3). She thus continued active treatment given ongoing favorable response.

CT and MRI surveillance imaging revealed ongoing durable radiographic response, with widespread sclerosis of the bony metastatic lesions, resolution of pulmonary and mediastinal metastasis, and globally significantly decreased adenopathy. Subsequent positron-emission tomography imaging in October 2021 confirmed durable partial response. She completed cycle 21 of docetaxel in July 2022. She has not experienced any treatment-related toxicity or adverse events, and presently remains on treatment.

3. Discussion/Literature Review

Invasive EMPD is a rare disease entity with limited available evidence to guide treatment decisions. Distant disease has a very poor prognosis, with 5-year cancer specific survival of approximately 13 %, compared to nearly 98 % for localized disease (Kilts et al., 2020). Moreover, regional lymph node metastases of 2 or fewer nodes has a 5-year survival rate of 100 % vs 19.1 % in patients with three or more involved lymph nodes (Tsutsui et al., 2020). Unfortunately, recurrence after treatment of invasive EMPD has been reported as 33 % in a case

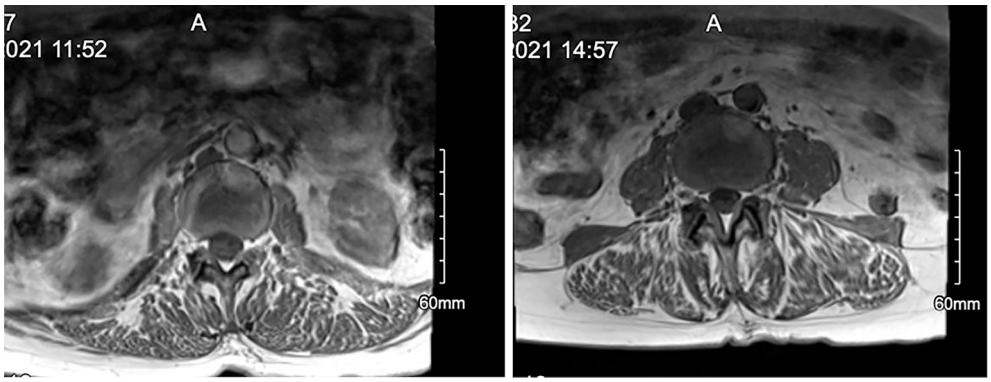

Fig. 3. Partial response in sclerotic lesion of lumbar spine. Left panel: January 2021 MRI status post cycle 4. Right panel: July 2021 MRI status post cycle 11 with continued partial response.

series (Nitecki et al., 2018). No standardized treatment has been established for metastatic invasive EMPD (Edey et al., 2019).

A case series reported use of tri-weekly or monthly Docetaxel at a dose of 60–75 mg/m^2; however, only 2 of 21 patients were females, and they experienced metastasis from an unclear primary site (Hashimoto et al., 2021). Another single-institution retrospective study reported experience with weekly Docetaxel administered at a dose of 25 mg/m^2 in 14 patients, of whom only 2 were female with metastasis to and from unknown sites (Nakamura et al., 2020). Two patients in Japan with "EMPD in the genital region" metastatic to the liver, skin and lymph nodes, were reported to have failed Docetaxel which was administered with radiotherapy or as adjuvant treatment after radiotherapy (Kato et al., 2017). A retrospective study of 13 male patients with metastatic EMPD who received monthly docetaxel showed a disease control rate (partial response or stable disease) in 83 %, with median progression free survival of 7.1 months and an average duration of treatment of 9.1 cycles (Yoshino et al., 2016). Other regimens have been proposed including anti-HER2 antibody for HER2-positive advanced EMPD, low-dose 5-fluoruuracil/cisplatin (FP) therapy, Titanium silicate-1 monotherapy plus docetaxel, FECOM (5-fluorouracil, epirubicin, mitomycin C, vincristine, carboplatin) and PET (cisplatin, epirubicin and paclitaxel) therapy (Edey et al., 2019). Unfortunately, our patient's pathology sample, after initial evaluation, was insufficient for additional genomic profiling testing. She subsequently declined additional sampling and therefore was not a candidate for targeted therapy with, for example, trastuzumab given inability to assess tumoral HER2 status. Furthermore, our patient desired to avoid combination therapy if possible to minimize toxicity and maximize her quality of life. One small, retrospective case series found higher 1-year survival rates with monthly docetaxel than FECOM and FP (Yoshino et al., 2016). A phase II multi-site basket trial utilizing immunotherapy with nivolumab and ipilimumab for treatment of rare malignancies – including invasive EMPD – is ongoing (*NCT02834013*).

Median overall survival in patients with invasive EMPD with distant metastasis is reported to be 1.5 years (Ohara et al., 2016). In this scenario, our female patient has had a tremendous, durable treatment response with indolent minimal disease visualized on PET scan 13 months after initiation of systemic therapy. Furthermore, she has experienced no treatment-related toxicity or adverse events during two years of active treatment after her diagnosis. As with the majority of reported cases of distant metastatic EMPD (Shiomi et al., 2013), our patient had multiple poor prognostic risk factors, including multifocal bone metastases. To our knowledge, this is the first case report of vulvar, metastatic invasive EMPD to exhibit a durable, response to single agent docetaxel. This case of widely metastatic invasive vulvar EMPD, complicated by multifocal bone and lymph node metastases, adds to the small body of available evidence in this rare disease, and supports the usage of monthly docetaxel as an effective, well-tolerated treatment regimen.

Author Contribution

Larissa Aroche-Gutierrez, MD-MPH, wrote the paper with input from all authors. Steven Blaine Holloway, MD, conceived the presented idea and contributed to the final version of the case report. Deepak Donthi, MD, provided pathology expertise and images. Jayanthi S. Lea, MD, contributed to the final version of the case report and provided critical feedback.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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