Metastatic Vulvar Adenocarcinoma with Extramammary Paget’s Disease: A Case Report and Systematic Literature Review

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Abstract—

Background: Extramammary Paget’s disease of the vulva (EMPDV) is a rare and unusual entity that can be associated with an underlying primary vulvar adenocarcinoma.

Case: We report a case of EMPDV initially treated surgically; however, the patient ultimately developed an adenocarcinoma with hepatic metastases. She had an excellent initial response after systemic chemotherapy with carboplatin and paclitaxel as demonstrated by positron emission tomography–computed tomography. However, she went on to develop additional biopsy-proven hepatic metastatic lesions while undergoing treatment.

Conclusion: Adenocarcinoma of the vulva associated with EMPDV is an aggressive malignancy that can spread distantly in a relatively short period of time. This case highlights the importance of close surveillance with frequent exams by experienced practitioners in patients with EMPDV to detect persistent or recurrent disease. Systemic chemotherapy with a platinum and taxane regimen is an option for treating local and metastatic disease.

Keywords — Paget’s Disease, Vulvar Adenocarcinoma

INTRODUCTION

Paget’s disease of the vulva can masquerade as several other benign or non-invasive entities and typically presents with pruritus and tenderness. Diagnosis is based on histology showing large cells with abundant clear cytoplasm and enlarged nuclei.1 We report a case of EMPDV initially treated surgically that progressed to adenocarcinoma with hepatic metastasis.

CASE

Patient NN is a 60-year-old Vietnamese gravida I, para I who originally presented to her internist with vulvar pruritus. Topical antifungal agents and oral antibiotics resulted in no improvement, prompting a vulvar biopsy demonstrating EMPDV (Figure 1A). She was subsequently lost to follow-up, but re-presented 10 months later with persistent symptoms. Her perineum now showed markedly erythematous bilateral labia with overlying white plaques (6x3 cm, left, and 4x2 cm, right) extending to the left clitoral edge and anterior anus. The anal canal was uninvolved.

Six-weeks later, she underwent a simple vulvectomy with a split thickness skin graft harvested from her thigh. No invasive carcinoma was identified; however, the anal verge and left vaginal margin contained focal Paget’s cells. She was asymptomatic and commenced surveillance. Pelvic exams in the clinic consistently showed no gross lesions; however, exams were limited by a narrow vaginal introitus and multiple examiners. One year later, the patient reported recurrent vulvar pruritus. A pelvic exam now showed a 3x1 cm excoriation just inferior to the clitoral hood and a 3x3 mm erythematous, fleshy lesion on the left distal vaginal wall. Biopsies of these lesions showed Paget’s disease of the infracloital lesion, and Paget’s disease and adenocarcinoma with 2 mm of invasion of the left vaginal wall. (Figure 1B). Paget’s cells were positive for CK7 and negative for CK20. (Figure 1C) Imaging with 18-fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET/CT) showed FDG-avid bilateral inguinal and external iliac nodes with no visceral metastases (Figure 2A).

Additional biopsies under anesthesia and a bilateral inguinal lymph node dissection revealed adenocarcinoma involving the urethra, clitoris and bilateral inguinal lymph nodes. Restaging PET/CT revealed more prominent FDG-avid adenopathy now involving the bilateral pelvic and para-aortic nodal basins. Additionally, the PET/CT showed new multifocal solid hepatic lesions consistent with metastatic disease, including a new 2.4 cm FDG-avid right hepatic lobe mass (Figure 2B).

Treatment was initiated with systemic carboplatin (AUC 5) and paclitaxel (175 mg/m2) dosed every 21 days with radiographic improvement of her previously FDG-avid hepatic mass and left external iliac lymph node (Figure 2C) and complete clinical resolution of the previously appreciated infracloital nodularity after just 3 cycles. She went on to complete an additional 4 cycles of carboplatin and paclitaxel for a total of 7 cycles. A post-treatment PET/CT after her last cycle demonstrated a new hypermetabolic left hepatic lobe lesion, but no other concerning lesions were identified (Figure 2D). Given that these finding suggested a mixed response, an
ultrasound guided core needle biopsy of the left hepatic lesion was obtained. The biopsy findings were consistent adenocarcinoma (Figure 3). The patient was then started on weekly paclitaxel.

**DISCUSSION**

Paget’s disease of the breast was first reported in 1874, with the primary vulvar iteration of the disease 27 years later by Dubreuilh. Wilkinson and Brown proposed a useful system of categorizing EMPDV into three subtypes: (1) EMPDV, (2) invasive EMPDV, and (3) EMPDV with concomitant invasive adenocarcinoma. The current case offers a unique albeit unfortunate opportunity to histologically and radiographically follow the natural history of non-invasive EMPDV that progressed to metastatic adenocarcinoma. Due to the profound scarcity of EMPDV associated with an adenocarcinoma in the literature, whether this case represents progressive EMPDV or synchronous Paget’s disease and adenocarcinoma is uncertain. Fanning reported a 4% prevalence of an underlying adenocarcinoma in a case series of 100 Caucasian patients with EMPDV. Cai reported a 7% prevalence of an underlying adenocarcinoma among a case series of 43 Chinese patients. Rarer still is metastatic disease originating from the underlying adenocarcinoma. We conducted a review of the literature to identify EMPDV cases associated with an underlying primary vulvar adenocarcinoma with disease extending beyond the vulva. A PubMed search of English language articles (January 1, 1970 - April 1, 2014) using the terms “vulva,” “Paget’s,” and “adenocarcinoma” produced 248 abstracts and 18 cases of metastatic EMPDV associated with an underlying vulvar adenocarcinoma (Table 1).

Inguinal lymph nodes represent the most common site for primary vulvar adenocarcinoma arising from EMPDV to spread. The most common sites of distant metastasis are the bones and liver. Metastatic spread of Paget’s disease without an underlying adenocarcinoma is rare. Up to 20% of EMPDV cases are associated with entirely separate malignancies, such as cancer of the breast, colon and bladder. The tumorigenic or metastatic relationship between these malignancies and EMPDV is not well understood, but may derive clinical utility from future molecular characterization of these tumors and targeted treatment options.

**CONCLUSIONS**

Herein, we describe an uncommon case of an adenocarcinoma arising from EMPDV with distant metastases. Historical series describe variable success treating nodal metastases with either radiotherapy or systemic chemotherapy. This patient had an impressive initial response to carboplatin and paclitaxel, but went on to develop additional metastatic hepatic lesions while undergoing treatment.

This case contains two important clinical lessons about a rare malignancy. First, it demonstrates the rapidity that EMPDV can progress despite an extensive excisional procedure. Secondly, the case also highlights the diagnostic challenge of adequate and thorough clinic pelvic exams as a consequence of anatomic distortions after extensive and repeated perineal excisional procedures. This patient developed a stenosis of the vaginal introitus that resulted in sub-optimal pelvic exams and possibly delayed the diagnosis of her recurrent disease. Exam with conscious sedation or in the operating room should be strongly considered for patients being monitored for EMPDV recurrence that have limited office exams. Similarly, surveillance exams should be done by experienced practitioners and there should be a low threshold to obtain imaging.

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Figure 1: Histologic timeline of Paget’s disease. (A) Initial vulvar biopsy showed groups or nests of Paget’s cells. Paget’s cells (arrows) show characteristics of large round cells with ample pale cytoplasm situated in the basal layer with focal migration to the upper epidermic layer. (B) Vaginal wall biopsy 2 years later now shows nests of tumor cells infiltrating the stroma. These cells form vague glandular architecture. Lymphovascular space invasion is present (white arrows). (C) Immunostains demonstrate cytokeratin 7 (CK7) is positive in the tumor cells.

Figure 2. (A) PET/CT imaging at initial diagnosis of adenocarcinoma shows no hepatic lesions and a hypermetabolic left external iliac lymph node (B) Re-staging PET/CT 2-months later now shows a 2.4cm FDG-avid right hepatic lobe mass with maximum standardized uptake value (SUV) of 9.2, consistent with metastatic disease. The left external iliac node is unchanged. (C) PET/CT imaging following three cycles of carboplatin and paclitaxel shows radiographic improvement of the right liver lesion and right internal iliac node. (D) After 7 cycles of carboplatin and paclitaxel there is a new left hepatic lobe lesion; the left external iliac node remains minimally FDG-avid.
REFERENCES


Figure 3. High-power magnification of core needle biopsy of left hepatic lesion features cells with a high nuclear-cytoplasmic ratio and prominent nucleoli, supporting the diagnosis of adenocarcinoma.