Bladder Carcinoma Presenting as Paget's Disease of Vulva: An Uncommon Entity

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Abstract
Paget's disease of the vulva is a rare intraepithelial neoplasm, accounting for <5% of all vulvar lesions. The underlying mechanisms of this disease are still poorly understood, however, diagnosing a Pagetoid lesion early is of prime importance as it may forewarn an underlying systemic malignancy. We discuss the case of an elderly female who was being conservatively treated for infectious lesion of the lower urinary tract and vulva for months. She was subsequently confirmed on histopathology with vulvar Paget's and underlying urothelial carcinoma, with the help of an extensive panel of immunohistochemistry.

Key Words: Paget's disease, urinary bladder carcinoma, vulva

Introduction
Paget's disease was first described by Sir James Paget in 1874 and has been defined by the WHO as an “intraepithelial neoplasm of epithelial origin” expressing apocrine or eccrine gland-like features, characterized by distinctive large cells with prominent cytoplasm.\(^1,2\) While nipple remains the most common site (90%) for this unique expression of an underlying malignancy, extramammary Paget's disease (EMPD) is uncommon and accounts for only about 10% of all Paget cases reported.\(^3\) EMPD was first described by Crocker in 1888, in a male in the penoscrotal region.\(^4\) We describe the case of a postmenopausal female who presented with lower urinary tract symptoms and was eventually diagnosed with vulvar Paget's disease.

Case Report
A 56-year-old female presented with itching in the perineal region and discharge per vaginum for 8 months. She had episodic hematuria for 2 months. Routine urine examination demonstrated pyuria (30 pus cells/hpf) and a few RBCs (2-4/hpf) only. Previously gynecologist had prescribed topical steroids and antibiotics. With no relief of symptoms, she decided to approach our hospital for further workup. Local examination of the perineal and vulvar region showed an erythematous tender area along with patchy areas of depigmentation involving the mucosal surface of bilateral labia minora and the interlabial sulcus [Figure 1]. Cystoscopy was performed and a nodular lesion (0.6 cm × 0.6 cm) was detected, 1 cm lateral to the right ureteric orifice. A biopsy was taken from the bladder nodule as well as from the erythematous vulvar lesion. Sections from vulvar biopsy showed tissue covered by hyperplastic keratinized stratified squamous epithelium with broad and elongated rete pegs. Bases of rete pegs displayed nests of large atypical cells possessing vesicular nuclei and fine granular chromatin with inconspicuous nucleoli housed in copious pale cytoplasm. Such cells also extended laterally as single cells in the prickle cell layer of the epidermis. Subepithelium showed mild lymphocytic inflammatory infiltrate; however, no invasion into subepithelial tissue was noted. On immunohistochemistry (IHC), the tumor cells expressed CK, CK7, CK20, GATA3, BerEP4, and carcinoembryonic antigen while they were negative for mammaglobin, CK5, CDX2, and S-100. Her-2 by IHC was 3+ [Figure 2]. Section from bladder growth displayed epithelial and subepithelial infiltration by small nests and singly scattered pleomorphic cells with eccentric high-grade nuclei residing in moderately eosinophilic cytoplasm. On IHC, the bladder tumor replicated the IHC findings of the vulvar neoplastic population [Figure 3].

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A diagnosis of poorly differentiated urothelial carcinoma with secondary vulvar Paget’s disease was made.

The patient underwent robot-assisted anterior exenteration with extracorporeal ileal conduit with tube in tube ureteric anastomosis, bilateral extended pelvic node dissection, and vulvectomy. On gross examination, no definitive growth was identified in the urinary bladder, however, its wall was thickened ~ 5 mm. Vulva showed thickened circumferential gray-white plaque measuring approximately 3.8 cm × 2.4 cm. Microscopy showed diffuse infiltration of all bladder walls including bladder dome and base by tumor cells having high-grade morphology and collections of signet-ring cells. Foci of urothelial carcinoma in situ (CIS) were also noted. CIS involved bilateral ureters as well; however, the resected margins were free. Sections from urethra margin were free of tumor. Endometrium was atrophic. Myometrium was unremarkable. Sections from the cervix showed infiltration in all quadrants by tumor cells, morphologically similar to bladder growth. Vaginal cuff was free of tumor. Sections from the vulva did not show stromal invasion by tumor cells; however, Paget’s disease was present. Bilateral pelvic nodes were involved by tumor. Subsequent IHC on these resection sections showed tumor cells with positive expression for GATA3, P63, and 34βE12 while they were negative for PAX-8, mammaglobin, and P16. A final diagnosis of urothelial carcinoma with glandular differentiation with metastasis to the cervix and vulvar Paget’s was made.

Discussion

Mammary and extramammary Paget’s diseases are uncommon intraepithelial neoplasms which often mimic an inflammatory and infective etiology as was seen in the present case where the patient had itching and vaginal discharge as primary complaints. Primary EMPD originates in the skin, while the secondary form of EMPD is associated with contiguous extension of tumor cells from underlying adnexa, genitourinary, or gastrointestinal tract. Seldom it has been found that there is no contiguous extension of tumor cells, making it difficult to diagnose the underlying malignancy. It is perplexing as to how a distant malignant tumor can produce localized intraepithelial disease, as was seen in the present case. Various explanations for this phenomenon have been forwarded in this regard including vascular or lymphatic dissemination, seeding, and iatrogenicity.

In the present case, histological examination revealed urothelial carcinoma with glandular differentiation in the form of signet-ring cells collections. The tumor extended posteriorly to involve the cervix in contiguity with the involvement of the cervical stroma and epithelium. However, there was no further contiguous extension to the vagina on serial sectioning. No lymphatic emboli were seen in the vulva. Therefore, it was difficult to comprehend angiolymphatic embolization as a plausible cause of Paget’s vulva in the present case. In the present case, likely explanations of tumor metastasis that could be offered included (a) Pagetoid tumor spread along the basal layers and (b) alteration of tumor microenvironment responsible for disease progression (the seed and soil theory of tumor metastasis).

Pathophysiology of Paget’s has been hypothesized by several authors, while some believe that EMPD has an intraepidermal origin from pluripotent keratinocyte stem cells, others have opined that Paget cells originate from mammary-like glands located in the interlabial sulci. Another theory has been suggested considering origin from precursor Toker cells which may be located in both MPD as well as in EMPD. Kang et al. have even speculated that abnormalities in the PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase,
Catalytic Sub-Unit Alpha) gene and divergent deleted in liver cancer 1 methylation may have significant role in this unusual manifestation. Although the definitive significance of these alterations is yet to be determined; they may act as potential therapeutic targets to prevent disease progression.

Once a Paget’s disease of the vulva is diagnosed on histomorphology, a clinical correlate and immunohistochemical confirmation is mandatory to further classify it according to the Wilkinson classification. In the present case, the authors were fortunate to be able to demonstrate similar immunoprofile of tumor cells in the urinary bladder and vulva. The tumor cells expressed GATA3, P63, and 34βE12 which highlighted urothelial origin while a negative CDX2 expression along with the absence of any radiological lesion ruled out a gastrointestinal primary. Hence, in the present case, a positive immunohistochemical expression of GATA3, P63, CK20, and loss of mammaglobin and CK7 favored a urological secondary in the vulva. Her2 overexpressed in the present case indicating that the patient might benefit from targeted therapy. Plaza et al. in their study on Her2 expressing EMPD found these cases to be more aggressive and showed early relapse when compared with Her2 nonexpressers.

Padhy et al. studied the mean duration for detection of underlying bladder carcinoma in cases of prior vulvar Paget’s which varied from 1 year to 14 years. Wilkinson and Brown reported vulvar Paget’s as a presenting sign of relapse of bladder carcinoma after 6 months of completion of intravesical therapy and postcystectomy.

These findings highlight the fact that itchy, erythematous vulvar lesions should be treated with caution as they may forewarn an underlying bladder malignancy.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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