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Case Report

Urethral duct invasion in female urethral melanoma

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ABSTRACT

Primary melanoma of the genitourinary tract represents ≤1% of all melanomas and is a highly aggressive malignancy, usually presenting at an advanced stage. Primary urethral melanomas are often amelanotic, leading to difficulties in early clinical diagnosis and biopsy delays. Herein, we present the clinical follow-up and histopathology of two female patients with microscopic invasion of the urethral ducts, not illustrated by previous reports. This finding, verified by appropriate immunohistochemical markers, can be a useful clue in diagnosing amelanotic melanoma of the genitourinary tract. The pathology reporting for urethral melanoma should include the depth of invasion, mitotic index, the status of resection margins, perineural invasion and lymphatic invasion since they will likely have a bearing on the tumor's biological behavior. Herein, we report two female patients with urethral melanoma exhibiting urethral duct invasion. Moreover, we discuss pertinent histopathological and immunohistochemical features, along with oncogene mutational typing that may aid in confirming the diagnosis and identifying molecular target(s).

1. Introduction

Malignant melanoma of the female urethra remains rare, accounting for approximately 0.2% of primary melanomas [1], with the distal urethra most often involved [2]. The average peak incidence is 65 years [3]. Since the initial description by Reed in 1896 [4], more than 125 cases have been described in the English literature. Symptoms are non-specific but may include the development of a urethral mass, perineal pain, dysuria, increased urinary frequency, urinary incontinence, hematuria or local bleeding [5]. The polypoid nature of these tumors can mimic a urethral polyp, caruncle, or mucosal prolapse. Overall, one fifth of primary urethral melanomas are amelanotic [2], leading to difficulties in early clinical diagnosis and biopsy delays. The presentation of advanced clinical stage in urethral melanomas usually correlates with histologic evidence of vertical growth phase, analogous to nodular sub-type of cutaneous melanoma [6]. Similar to their cutaneous counterpart [7], urethral melanomas tend to metastasize at an early stage via the superficial lymphatics of the vagina and vulva, by the deep lymphatics to the inguinal lymph nodes, and occasionally hematogenously to distal sites [8]. A recent meta-analysis of (73 articles) 112 female patients with primary urethral melanoma showed a median survival of 16 months with a 5-year survival around 10% [3].

In a series of 9 women and 6 men with urethral melanoma, the distal urethra was involved in all men and 8 women [2] with the following histopathology: 1) conspicuous melanin pigment in six cases; 2) polypoid architecture with a mean diameter of 2.6 cm; 3) a vertical growth phase was identified in all and a radial growth phase (intra-mucosal component) in nine tumors; 4) depth of invasion ranged from 2 to 17 mm; and 5) a diverse vertical growth-phase pattern (e.g. diffuse, nested, storiform or mixed). Cytological features include abundant eosinophilic cytoplasm, large nuclei with prominent nucleoli and brisk mitotic activity [2].

1.1. Patient 1

An 89 year-old female presented to UCONN urology department with an amelanotic, hemorrhagic and polypoid urethral mass. A distinct anterior urethral mass measuring 2.1 cm × 1.5 cm was identified with uninvolved vaginal tissue. Patient underwent a partial urethrectomy that included vaginal mucosa, followed by Temodar chemotherapy. The urethrectomy specimen showed an ulcerated squamous mucosa

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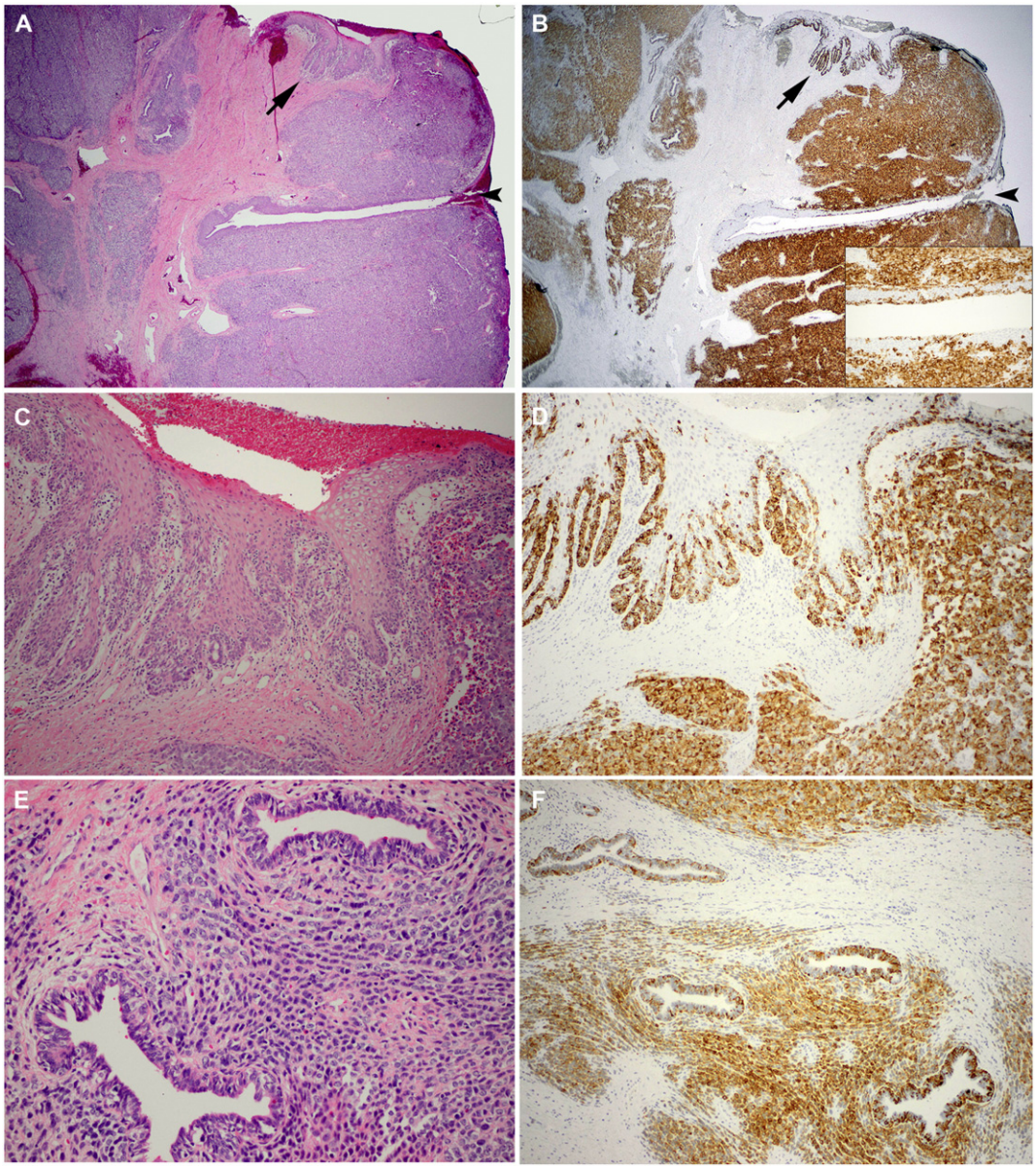

Fig. 1. Ulcerated, amelanotic nodule surrounded the urethral meatus (arrowhead); and melanoma in situ is identified in the adjacent squamous epithelium (arrow, A). Immunohistochemistry for Melan-A highlighted the invasion of melanoma cells in urothelium (arrowhead and inset), squamous epithelium (arrow) and lamina propria (B). Higher magnification of squamous epithelium (area of arrow in A) showed a lack of pagetoid upward scatter but a distinct lentiginous, intra-mucosal component (C), highlighted by Melan-A immunohistochemistry (D). Small, basaloid melanoma cells tightly surrounded and invaded the urethral ducts (E), highlighted by Melan-A immunohistochemistry (F). Original magnification: A and B, 20×; C, D and B inset, 100×; E, 200×; and F, 100×.

overlying expansile, amelanotic nodules in the lamina propria, surrounding and compressing the urethral mucosa (Fig. 1A). The depth of invasion was at least 14.5 mm; tumor cells were extensively transected at the base (deep) resection margin, underestimating the true depth of invasion. The proliferation index was 5 mitoses/mm^2, including atypical mitotic figures. Melan-A immunostaining highlighted a submucosal nodule, urethral (inset) and squamous epithelial invasion by melanoma cells (Fig. 1B–D). The tumor cells tightly condensed around stellate-shaped urethral ducts and invaded them (Fig. 1E), highlighted by Melan-A immunostaining (Fig. 1F). There were areas of lymphovascular invasion, necrosis, hemorrhage and hemosiderin; however, no melanin was identified (not shown). A variety of growth patterns were identified in the specimen: lentiginous, nested, solid sheet and pseudopapillary (not shown). Similar to Melan-A, S100 and HMB-45 immunostaining demonstrated the junctional activity and infiltration of urothelium by melanoma cells (not shown). Immunostaining for both estrogen and progesterone receptors were negative (not shown).

Eight months after the initial excision the patient developed significant and progressive shortness of breath. Positron emission tomography (PET) and computed tomography (CT) scans showed multiple active lesions that had increased in number and size within the bilateral lung parenchyma, thoracic spine vertebral body and posterior segment of the right hepatic lobe. After 11 months, the patient died of metastatic disease.

1.2. Patient 2

An 81-year-old woman presented to the UCONN Gynecology–Oncology department with a prior history of stage IIIB urethral melanoma diagnosed 5 years ago. She initially presented with a small, enlarging pigmented lesion of the distal urethra associated with intermittent bloody vaginal discharge. Initially, the lesion was believed to represent vaginal prolapse. A partial urethrectomy was performed and the specimen revealed fragments with ulcerated, atrophic urethral and