Plasmacytoid Variant Urothelial Carcinoma: Diagnostic and Grossing Challenges

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Abstract

Plasmacytoid variant urothelial carcinoma (PUC) is a rare variant form of urothelial carcinoma that typically presents with macroscopic hematuria, and tends to present late, with metastasis, and is associated with a poorer prognosis compared to nonvariant urothelial carcinoma. Presented here is a case of PUC, outlining the diagnostic and grossing challenges associated with this rare bladder neoplasm. The gross appearance of the tumor can mimic the classic wall thickening seen in cystectomies treated with neoadjuvant therapy, leading to oversampling. The tumor cells themselves have abundant cytoplasm, with an eccentric nucleus, closely resembling plasma cells. Due to the variable presentation of the tumor, the differential diagnosis can be wide. Immunohistochemistry plays a crucial role in diagnosis, specifically to rule out plasma cell derived tumors and demonstrating the presence of an epithelial component. This case is a well-rounded example of many facets of pathology working together to make an accurate diagnosis, ultimately providing the best patient care. It is important for everyone at the grossing bench to be aware of rare, variant types of tumors because it has potential to lead to more efficient grossing and submission.
Patient History

A 62 year-old male presented to his primary care physician with dysuria and a burning discomfort during urination, with increased frequency and urgency, specifically during the night. He was advised to alter his nighttime fluid intake, and was treated for overactive bladder symptoms; however, the treatment was discontinued due a lack of improvement and unpleasant side effects. After two months of worsening symptoms, he underwent an abdominal ultrasound, revealing mild left hydronephrosis with irregular thickening of the bladder wall. The patient is a nonsmoker with no known industrial exposure to carcinogenic agents.

Diagnosis
Following failed therapeutic attempts to alleviate the patient’s symptoms, and an abnormal ultrasound, a cystoscopy was performed, with transurethral resection of the bladder tumor. The biopsy slides were sent to our institution for consultation, and a diagnosis of a T2, poorly differentiated urothelial carcinoma, plasmacytoid variant, was made. The following immunostains were positive, supporting this diagnosis: pankeratin, CK7, CK20, monoclonal CEA, and MOC-31. The patient completed 4 cycles of neoadjuvant chemotherapy and was scheduled for a cystoprostatectomy.

Upon receipt, the specimen consisted of an intact cystoprostatectomy specimen. The bilateral ureter margins were submitted for frozen section diagnosis and were negative for tumor. The specimen was inked and opened along the anterior aspect to reveal a 5.0 x 4.5 cm pink-red, flattened, and slightly ulcerated area involving the anterior and left lateral bladder walls (Figure 1). This area did not appear to involve the ureteral orifices
or distal urethral margin. The bladder wall was diffusely thickened, particularly at the anterior and left lateral wall, corresponding to the lesion (Figure 1). The prostate was unremarkable.

This case presented a specific grossing challenge, in that the lesion was ill-defined and the patient had a history of neoadjuvant chemotherapy. At our institution, treated nonvariant urothelial carcinomas are generally submitted entirely. Because this lesion presented as a slight ulceration with associated diffuse bladder thickening, I was advised to submit the lesional area entirely, along with additional sections of each bladder wall. The routine sections of right and left ureteral orifices, prostatic urethra, and prostate were also submitted.

Microscopic examination revealed mitotically active tumor cells exhibiting a large amount of eosinophilic cytoplasm with an eccentrically located nucleus (Figure 2), similar in appearance to plasma cells. The tumor cells display both a nesting and cord-like dispersal pattern into and through the smooth muscle of the bladder wall (Figure 3). Figure 4 displays the classic appearance of the tumor in a background of fibrofatty soft tissue, representing tumor extension into the perivesicular soft tissue. The case was signed out as T3 high-grade invasive urothelial carcinoma, plasmacytoid variant with extension into the perivesicular fat. Tumor was identified diffusely throughout the bladder, present at the right lateral, left lateral, anterior, and posterior walls, dome, and right and left ureteral orifices. The final margins were negative for tumor, and metastasis was present in 4 of 20 lymph nodes. No recurrence has been reported in the six months following the surgery.
Discussion

Plasmacytoid variant urothelial carcinoma (PUC) was first described by Zuckerbe et al. in 1991, as a tumor either presenting with a marked lymphoid infiltrate, obscuring the invasive nature of the bladder cancer, or as a diffuse pattern of lymphoid-like cells with a histologic similarity to malignant lymphoma or plasmacytoma. The case presented here demonstrates the latter, posing one of the specific challenges in diagnosing PUC. Because the tumor cells so closely resemble plasma cells, the differential diagnosis for PUC can be wide, especially in small biopsy cases, or in cases with abnormal presentation. It is of utmost importance to be aware of variant types of urothelial carcinoma, to avoid an initial misdiagnosis. Sahin et al. discussed a case of PUC initially misdiagnosed as multiple myeloma due to presentation with multiple lytic bone lesions of the skull and ribs, displaying cells with a distinct plasmacytoid appearance. The differential diagnosis in cases like these, and the one presented here, ranges from benign diagnoses such as cystitis with plasma cell infiltration, to plasma cell derived neoplasms including plasmacytoid-type lymphoma, multiple myeloma, and large B-cell lymphoma. The overall clinical picture, including the patient's initial presenting symptoms, is helpful in narrowing the differential diagnosis.

PUC generally cannot be diagnosed from histology alone. CD138, an immunohistochemical marker for plasma cells, can be initially employed if the differential diagnosis is wide, to rule out a plasma cell derived lesion. CD138 is positive in both plasmacytoma and PUC, with κ and λ light chain markers differentiating the two. PUC is positive for CD138, but negative for light chains. Once a primary plasma cell tumor can
be ruled out, the identification of an epithelial component via immunohistochemistry solidifies the diagnosis of PUC\textsuperscript{3,4}. CK and CK7 will confirm the epithelial origin of transitional cells\textsuperscript{3}. In this case, both the bladder biopsy and tumor from the cystoprostatectomy specimen stained positive for CK7. This demonstrates the valuable role that immunohistochemistry plays, in conjunction with histology, to diagnose PUC.

Because the tumor cells tend to form nests, with cords of malignant cells extending deep into the musculature of the bladder wall\textsuperscript{3}, the appearance of the tumor can make grossing more challenging. Several of the case reports in the literature document an ill-defined, diffuse lesion, affecting multiple areas of the bladder, with associated rigidity of the bladder wall\textsuperscript{3,5,6}. In cases like this, and the one presented here, it is difficult to approximate the overall size of the lesion. We followed the same grossing guidelines that we use for nonvariant urothelial cancers, and submitted the grossly obvious lesional area entirely, but this arguably may have been over submission. At sign-out, tumor cells were identified throughout the bladder, within the described area of ulceration, but also in the areas of what appeared to be associated edema. Because neoadjuvant therapy can lead to morphology changes of the bladder itself, such as fibrosis of the bladder wall\textsuperscript{7}, treatment effect may look strikingly similar to the tumor itself. We are no longer hunting for residual tumor in a bladder wall thickened by treatment effect. Armed with the understanding that PUC presents as a diffuse, infiltrative tumor, representative sections of each area of the bladder may be a more prudent approach than attempting to block out a single solitary lesion.
PUC is commonly diagnosed at an advanced stage and is associated with a poorer prognosis than that of other urothelial neoplasms. The most common presenting symptom is hematuria, commonly with accompanying urgency and frequent micturition, as seen in this case. An associated tendency for peritoneal recurrence is also a factor in the overall survivability of this neoplasm. A retrospective look into the Indiana University Bladder Cancer Database, at all patients undergoing curative cystectomy revealed that 80% of the 30 patients with PUC on TURBT were upstaged at cystectomy to ≥pT3, and 60% had lymph node involvement, as seen in this case. The standard treatment for muscle-invasive PUC is cystectomy with lymph node dissection. In the case presented here, the patient underwent 4 rounds of neoadjuvant therapy prior to the cystoprostatectomy. While individual cases of complete response of PUC to neoadjuvant chemotherapy exist in the literature, broader studies suggest that PUC may show an initial response to neoadjuvant therapy, but long-term survival is limited to a few patients.

This case is noteworthy on two levels. Not only is PUC an interesting, rare variant of bladder cancer, it can pose a challenge at the grossing bench, and histologically. Upon first look at the bladder mucosa, it may resemble inflammation, rather than a discrete, readily identifiable mass. Under the microscope, the tumor cells may be misidentified as plasma cells, thus leading to misdiagnosis of a benign inflammatory process or plasma cell derived neoplasm. Understanding the gross presentation of a case diagnosed as PUC on biopsy will help guide sectioning and submitting decisions. Further study into the effect of neoadjuvant therapy on PUC is necessary to solidify a specific grossing protocol for PUC. This is an excellent example of a complex case requiring multiple levels of analysis in the grossing room and beyond. A complete clinical history, a
pathologists’ assistant with a keen eye and understanding of the urothelial carcinoma variants, in combination with the appropriate immunohistochemical stains will lead to accurate diagnosis and ultimately the best level of patient care.

References:


