Bladder squamous cell carcinoma in situ in the background of condyloma acuminatum in a kidney transplant recipient

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Condyloma acuminatum with synchronous squamous cell carcinoma in situ (CIS) rarely occurs in the bladder. In developed countries, bladder squamous cell carcinoma (SCC) is uncommon. Among the various noninvasive squamous bladder lesions, there is significant morphological overlap, which further complicates accurate diagnosis. Immunosuppression and human papilloma virus increase the risk of bladder condyloma acuminatum, which has a strong association with bladder SCC. Herein, we describe a case of a 79-year-old man with a history of end-stage renal disease with kidney transplantation and anal SCC who presented with bladder squamous cell CIS arising in the background of condyloma acuminatum.

Key Words: bladder, squamous cell carcinoma in situ, condyloma acuminatum, immunosuppression

Introduction

Squamous cell carcinoma (SCC), both invasive and in situ, accounts for less than 5% of bladder cancers in developed countries.[1] In regions where Schistosoma hematobium infection is endemic, such as the Middle East and Egypt, SCC constitutes the predominant histological type. Smoking is the major risk factor for all types of bladder cancers. Risk factors for non-schistosomiasis-associated SCC include chronic bladder irritation secondary to indwelling catheter use, chronic urinary tract infection, an immunosuppressed state, and bladder stones, among others.[1] Studies have explored a possible relationship between human papilloma virus (HPV) infection and condyloma acuminatum in the evolution of bladder SCC (either

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in situ or invasive) with variable conclusions.[2-6] Here, we report a rare and diagnostically challenging case of bladder squamous cell carcinoma in situ (CIS) with concurrent condyloma acuminatum in an elderly renal transplant recipient.

Case report

A 79-year-old man on chronic immunosuppression presented with gross hematuria. He had a history of end stage renal disease with living donor kidney transplant about 20 years prior, anal SCC (T1N0M0) that was successfully treated with chemoradiation about 10 years prior, and type 2 diabetes mellitus. His immunosuppressive regimen was tacrolimus and prednisone. He smoked half a pack of cigarettes per day for 30 years.

The patient was well-appearing with no revealing physical examination findings. His creatinine level was at baseline. Urine culture and polymerase chain reaction were negative for bacterial and fungal infection. Urine cytology revealed atypical urethral cells, which prompted further work up. CT of the abdomen and pelvis without contrast was unremarkable. Retrograde pyelography of his native kidneys and ureters was also unremarkable. Washings of the native ureters were negative for malignant cells. Cystoscopy revealed a 1 cm lesion overlying the neo-ureteral orifice of the transplanted kidney at the bladder dome, which was biopsied. Several attempts were made to access the transplanted ureter without success due to its heterotopic position.

Bladder washing cytology revealed rare cells with cytologic features of polyomavirus effect. Histopathologic examination of the biopsied specimen showed an initial diagnosis of high-grade papillary urothelial carcinoma with squamous differentiation and no lamina propria involvement. Given this initial diagnosis, the patient underwent a 6-week course of Bacillus Calmette-Guerin intravesical immunotherapy. However, follow up cystoscopy 3 months later revealed a persistent 1 cm lesion on the ureteral orifice of the transplanted kidney.

Given the patient's normal creatinine level, he was re-evaluated with a CT scan with contrast, which demonstrated moderate circumferential urinary bladder wall thickening with heterogeneity, Figure 1. Transurethral resection of the bladder tumor was performed. To protect the neo-ureteral orifice, a percutaneous nephroureteral catheter was placed preoperatively. Anterograde pyelography of the transplanted kidney and ureter demonstrated a normal collecting system without filling defects. With the catheter visualized exiting the neo-ureteral orifice, the tumor adjacent to the neo-ureteral orifice was biopsied, cauterized, and destroyed.

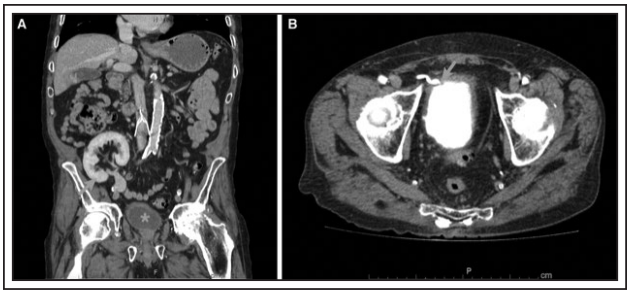

Figure 1. (a) Coronal view of the computed tomography of the abdomen and pelvis with contrast showing the transplanted kidney **(arrow)** and thickened bladder wall **(star)**. **(b)** Axial view of the computed tomography of the abdomen and pelvis with contrast showing the transplanted ureter entering the dome of the bladder with bladder wall thickening at the ureterovesical junction **(arrow)**.

Biopsy revealed nonkeratinizing, hyperplastic papillary fronds of squamous epithelium with koilocytic change, viral atypia, and no lamina propria involvement, Figure 2. The tumor was positive for GATA3, p16, and p40 and negative for

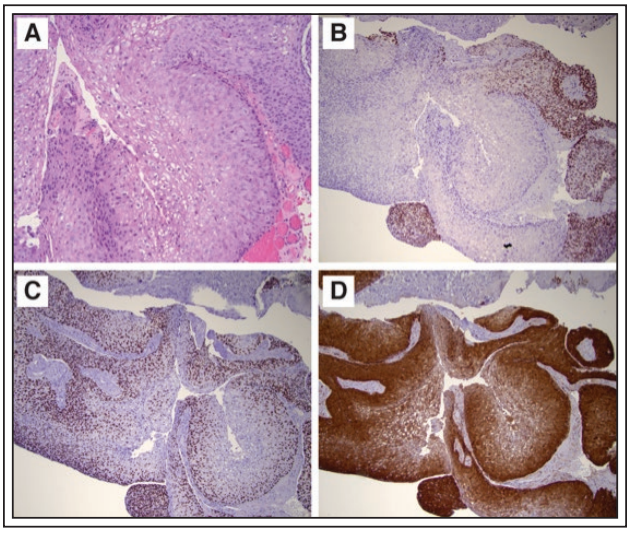

Figure 2. (a) Hematoxylin and eosin (H&E) stain showing nonkeratinizing, hyperplastic papillary fronds of squamous epithelium with koilocytic change. Positive immunohistochemistry staining for **(b)** GATA3, **(c)** P40, and **(d)** P16.

CK20 on immunohistochemistry, Figure 2. A high proliferative index was determined by Ki67 staining. BK polyomavirus and high-risk and low-risk HPV were negative on in-situ hybridization. Urine cytology revealed persistent atypia with polyomavirus effect. These observations established the final diagnosis of squamous cell CIS arising in the background of condyloma acuminatum.

The treatment plan was changed to active surveillance. Radical cystectomy or chemoradiation were not performed given the patient's advanced age, comorbidities, and prior pelvic chemoradiation. He has had follow up cystoscopies every 3 months, which have been unremarkable for 15 months. Urine cytology continues to show atypia with polyomavirus effect. He has had no signs of recurrence on CT imaging at 1 year follow up as well.

Discussion

Our patient presented a diagnostic challenge given the rarity of urinary bladder SCC in the United States. Urothelial carcinoma constitutes over 90% of bladder cancers in Western countries, and it is the most common type in renal transplant recipients. SCC accounts for less than 5% of bladder cancers.[1] There is also significant morphological overlap between the various noninvasive squamous lesions of the bladder, such as verrucous squamous hyperplasia, condyloma acuminatum, squamous papilloma, and squamous cell CIS, making accurate diagnosis a challenge.[2,3] Limited reports describe urinary bladder squamous cell CIS arising in the background of condyloma acuminatum.

Our patient had several risk factors that supported the diagnosis of a non-schistosomiasis-associated urinary bladder SCC, including a lengthy smoking history, prior pelvic radiation exposure, and renal transplantation. In a large population-based study by Guan et al, radiation was reported to be associated with an increased risk of developing secondary bladder cancer in rectal cancer patients.[7] Renal transplant recipients have a 665-fold higher risk of developing bladder SCC compared to the general population.[8] Immunosuppressive medications used to prevent transplant rejection interfere with host immunity and increase the risk of malignancies.[9] In addition, immunodeficiency is a major risk factor for developing condyloma acuminatum secondary to HPV infection.[10] Growing evidence supports the association between condyloma acuminatum of the bladder and SCC (either invasive or in situ).[3] However, HPV infection itself does not appear to have a direct or salient role in bladder SCC oncogenesis.[5,6] In a case series that included 19 patients with bladder condyloma acuminatum and associated SCC, 9 (47.4%) of patients had negative HPV in situ hybridization.[3] Lastly, our patient's history of anal SCC and the highly characteristic features on histology further support concurrent urinary bladder condyloma acuminatum.

There is a paucity of prospective studies pertaining to bladder SCC treatment options, particularly for non-schistosomiasis-associated SCC. Small observational studies support radical cystectomy with or without chemotherapy as the preferred treatment for localized bladder SCC.[5,11] Clinical trials evaluating the efficacy of immune checkpoint blockade for bladder SCC, such as PD-1 and CTLA-4 blockade, have shown early promise.[12,13] Radical surgical management and chemotherapy were deferred for our patient given his advanced age, comorbidities, and history of pelvic chemoradiation. Rather, a transurethral resection of the bladder tumor was performed, and the patient is under active surveillance.

Unfortunately, malignancies in renal transplant recipients tend to be more aggressive with high mortality. In addition, pure non-urothelial carcinoma bladder cancers have worse prognosis than pure urothelial carcinomas.[11] Routine cancer screening for transplant recipients has been recommended by American and European professional organizations but is far from standardized. Moreover, most recommendations are extrapolated based on data from the general population given the lack of studies in the renal transplant population. Our patient has had follow up cystoscopies every 3 months, which have been unremarkable for 15 months. At 1-year post-diagnosis, he has had no signs of recurrence on CT imaging as well.

Conclusion

In summary, this case raises awareness for the rare diagnosis of squamous cell CIS arising in the background of condyloma acuminatum, especially in immunosuppressed patients. It is very important to distinguish it from urothelial bladder cancer with partial squamous differentiation for carrying out the optimal treatment plan. Immunosuppression increases the risk of bladder condyloma acuminatum, which has a strong association with bladder SCC. Urologists must be cognizant of these risk factors so that they may make a timely and accurate diagnosis of this rare entity. □

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