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Urothelial Cell Carcinoma with Squamous Differentiation of the Bladder in Association with Intermittent Self-Catheterization

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ABSTRACT

Intermittent self-catheterization was introduced as an alternative to reduce the risk of developing cancers of the bladder in patients with indwelling catheters. Since then, case studies have shown that the risk is not entirely mitigated. Squamous cell carcinoma of the bladder and urothelial cell carcinoma with squamous differentiation are rarely reported as consequence of ISC. As such, these diagnoses are not generally considered as risks and alarm symptoms are often disregarded. We report a case of urothelial cell carcinoma with squamous differentiation as a result of decades of ISC.

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INTRODUCTION

Squamous cell carcinoma of the bladder comprises the majority of bladder cancer cases in many regions of the world due to schistosomiasis. In Western countries, SCC makes up less than 5% of bladder cancers and is attributed to chronic irritation from bacterial colonization and indwelling urinary catheters. [1] Intermittent self-catheterization (ISC) was initially presented to decrease the risk of developing SCC from indwelling catheter use but has since been implicated as a risk factor in few isolated case reports. [1] Due to its relative infrequency, especially in cases involving ISC, predisposing risk factors have not been studied sufficiently to establish guidelines for surveillance in high-risk populations. So, patients often present at an advanced stage of disease. This case demonstrates the need to recognize ISC as a risk factor for squamous metaplasia and carcinoma of the urinary bladder as the diagnosis is often made when the disease is clinically apparent and prognosis is poor.

CASEPRESENTATION

A 58 year-old woman with a 60 pack-year history of smoking, depression, and neurogenic bladder due to spina bifida managed with ISC 4-5 times daily for 30 years presented to the emergency department for evaluation of generalized weakness of 4-day duration which was preceded by nausea and vomiting. She reported drinking more water because she attributed her symptoms to dehydration although she noted her cloudy urine and one episode of hematuria during this time. Initial laboratory results showed hyponatremia and acute kidney injury. She was admitted to the intensive care unit where she was administered intravenous crystalloid fluids. Urinalysis showed hematuria, pyuria, and bacteruria. Subsequent urine culture was positive for pan-sensitive *Escherichia coli* for which the patient was treated with appropriate antibiotics. Computed tomography (CT) of the abdomen and pelvis was ordered for lower abdominal pain which revealed severe bilateral hydronephrosis due to obstruction of the distal ureters by a 4.9 x 6.2 cm pelvic mass. (Figure 1) Urology was consulted for placement of ureteral stents. The mass was seen to have invaded the posterior wall of the bladder, suspicious for a cervical carcinoma. So, gynecology was consulted for evaluation. It was decided that urology would perform placement of ureteral stents followed by pelvic exam by gynecology while the patient was under conscious sedation. Cystoscopy revealed bladder wall thickening with extension along the right side and a large mass on the trigone that distorted the anatomy and obscured visibility of the ureteral orifices. The surface of the mass was covered with hyperkeratinized desquamating tissue with adjacent edema of the mucosa. While placing the stents, the urologist noted neoplastic tissue at the trigone of the bladder and sent biopsies to pathology. Pelvic exam did not identify

any structural abnormalities of the reproductive organs but cervical biopsies were obtained for pathology. Once the patient's acute problems had resolved, she was discharged home. Pathology results were available the day after discharge and showed keratinizing squamous cell carcinoma in situ. She was notified by telephone of the biopsy results and instructed to follow-up with gynecology as soon as possible. Obstructive uropathy was managed with regular ureteral stent exchange. The patient returned to the emergency department about a week later complaining of incontinence and was admitted for overactive bladder secondary to ureteral manipulation. During this hospitalization, hematology/oncology was consulted to evaluate the role of the tumor in the patient's current presentation and recommended additional biopsies to confirm the origin of the tumor. Cervical and endocervical biopsies were negative for malignancy and but, tissue from the bladder trigone was consistent with high-grade invasive urothelial carcinoma with squamous differentiation involving the muscularis propria of the detrusor muscle. (Figure 2) The patient decided to forego treatment so no further evaluation was conducted. She was discharged upon improvement of presenting symptoms. The patient continued to decline and eventually expired 4 months after initial diagnosis.

DISCUSSION

Squamous cell carcinoma (SCC) of the bladder comprises the majority of bladder cancer cases in many regions of the world but, is less than 5% in Western countries it. The risk factors for SCC in Western countries, where schistosomiasis is not prevalent, are generally due to chronic irritants such as recurrent urinary tract infections (UTI) and the use of indwelling urinary catheters. [1] Intermittent self-catheterization (ISC) was introduced in the early 1970s as an alternative therapy to indwelling catheters in hopes of mitigating the risk of malignant transformation they incur. Because of its infrequency, little information is available about the risk factors of bladder SCC but, the consequences of urinary catheterization are proposed to have a synergistic effect on its development [1].

Manley and colleagues published a manuscript in 2015 that aimed to uncover the prevalence of various established risk factors for primary SCC of the bladder by assessing 90 cases retrospectively during a ten-year period. Their results substantiated these risk factors for primary SCC including smoking, recurrent UTI, and neurogenic bladder. The study also found a significant association between intermittent self-catheterization (ISC) and the development of SCC, confirming what had previously only been a suggestion of several case reports, the only source of data at the time of publication. [2] Patients are often found to have muscular invasion at the time of diagnosis and present with hematuria and symptoms indicative of advanced disease such as weight loss, back or pelvic pain, and urinary obstruction. Diagnosis is by cystoscopy and in most cases reveals a solitary ulcerating infiltrating tumor associated with keratinizing squamous metaplasia usually at the trigone and lateral walls. [3]

Distinguishing between bladder SCC and other urothelial malignancies with squamous differentiation is important as SCC in situ and urothelial cell carcinoma with squamous differentiation can quickly progress to muscular invasion and tend to have poor prognosis when discovered. [2, Dick] The gold standard for detection and diagnosis of bladder cancer is cystoscopy with biopsy or resection. Several immunohistocehmical staining has been successful in distinguishing cancer types but treatments are typically limited by the time biopsy is sought. [2]

There is no consensus on disease surveillance for those with known risk factors. However, it is common practice to evaluate patients with red flag symptoms like hematuria for malignancy as early diagnosis is associated with improved outcomes. [2] Regardless, some of these signs are masked in most patients performing ISC and may not be reported or may not be attributed to the possibility of malignancy. [1] If these symptoms are present, the disease is likely to be advanced stage which makes the patient less likely to benefit or qualify for surgical resection. For those approximately 25% of cases, radiotherapy or debulking procedures are palliative treatment options. Surgical intervention is currently the only management as there is no evidence showing that chemotherapy or radiation are effective and typically have an unfavorable response when used [2] The invasiveness of the tumor and limited treatments explains how most deaths in primary SCC and urothelial cell carcinoma with squamous differentiation result from uncontrolled locoregional spread. [3, 4] As liquid biopsy technology become more accessible, we may find incentive and justification to identify the role of various biomarkers in the disease process and determine their potential in detecting SCC for non-invasive screening tests. [2, 3]

CONCLUSION

Although rare, bladder cancers with squamous metaplasia including urothelial cell carcinoma with squamous differentiation and squamous cell carcinoma can result from long-term intermittent self-catheterization. Patients with suggested risk factors should be monitored for symptoms indicative of malignancy. Any suspicion should be evaluated promptly as these cancer types are often discovered at a later stage with poor prognosis.

Patient Consent

Written consent for this case report and associated imaging was obtained from the patient.

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FIGURES

Figure 1. Computed tomography (CT) image of the pelvis showing a large mass at the posterior wall of the bladder.

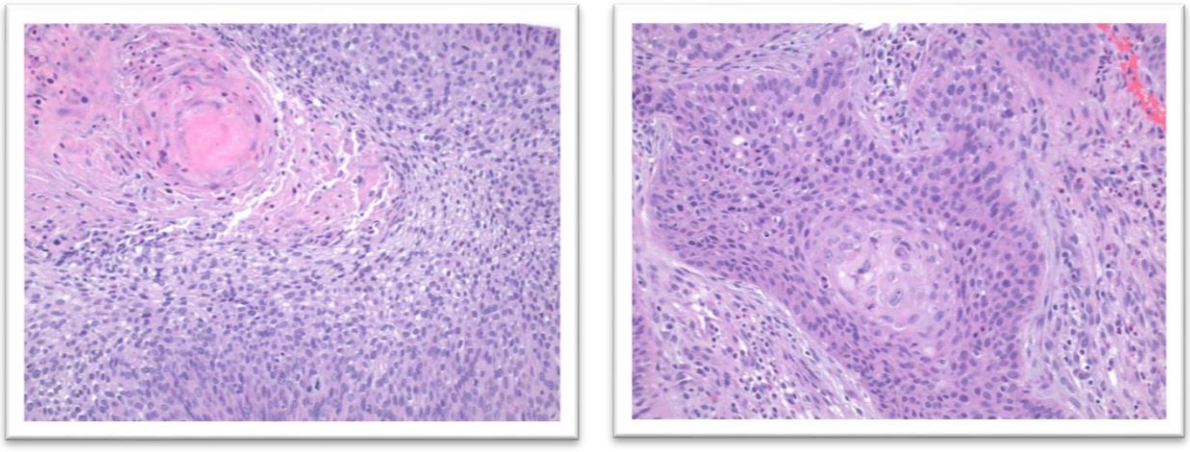

Figure 2. High-power microscopy of bladder tissue samples showing keratin pearl and intracellular bridges.