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Oncology

Progression of Intravesical Condyloma Acuminata to Locally Advanced Poorly Differentiated Squamous Cell Carcinoma

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ABSTRACT

Condyloma acuminata (CA) is a common sexually transmitted disease caused by Human Papilloma Virus (HPV) infection. CA of the bladder, however, is an exceedingly rare lesion. We present a rare case of poorly differentiated locally invasive squamous cell carcinoma (SCC) arising from recurrent CA of the bladder in an immunocompetent patient and discuss pathophysiology and management of this unusual condition.

Introduction

The role of HPV in inducing neoplasia is well studied. HPV has been implicated in cervical, vulvar, penile, oropharyngeal and possibly esophageal cancer.[1] Condyloma acuminatum is a predominantly benign epithelial proliferative tumor attributed to HPV. It is the most common sexually transmitted infection in North America and usually involves the external genitalia, perianal and perineal regions respectively. CA of the bladder, however, is an extremely rare lesion, with less than 15 reported cases in the literature. We report here a rare case of poorly differentiated locally invasive advanced squamous cell carcinoma (SCC) from recurrent CA of the bladder.

Case presentation

A 45-year old African American woman presented with abdominal pain, dysuria, frequency and nocturia. She had been previously managed for painful bladder syndrome. Her medical history was significant for smoking and genital CA. She denied any exposure to radiation or bladder carcinogens. Urinalysis revealed 4-10 RBCs, >100 WBCs and urine culture was negative. A CT of the abdomen and pelvis showed diffuse, irregular, mural thickening of the bladder along with a polypoid lesion along the right lateral wall (Fig. 1). On cystoscopy, there was diffuse involvement of the bladder with sessile and papillary lesions involving the trigone, bladder neck, right lateral and posterior walls respectively. Bimanual and pelvic exam revealed a mobile bladder and a normal appearing cervix. A transurethral resection was performed, and pathology revealed verrucous hyperplasia with prominent koilocytic changes (Fig. 2A) consistent with condyloma and no evidence of dysplasia or malignancy. Immunostains revealed a high Ki-67 proliferative index, but was negative for p53 and p16. Post-operatively, the patient experienced significant improvement in her symptoms. She was managed with surveillance cystoscopies, and underwent repeat transurethral resections upon worsening of her symptoms or regrowth of her condyloma. Three doses of Gardasil vaccination was administered as an immunomodulator. Over a 5-year period, she underwent a total of 10 resections at approximately 6 month intervals. The pathology remained consistent with CA with occasional focal mild or moderate squamous dysplasia characterized by the presence of significant cytological atypia in the lower and middle layers. However, her final transurethral specimen revealed SCC invading into the lamina propria (Fig. 2B) with areas of necrosis arising in the background of CA. Immunohistochemical stains for GATA-3 and p16 were negative.

The patient underwent radical cystectomy with creation of an Indiana pouch as definitive management. Final pathology showed moderately to poorly differentiated SCC of the bladder invading the perivesical fat (pT3) arising in the background of CA (Fig. 2C and D). No lymphovascular invasion was identified. All surgical margins

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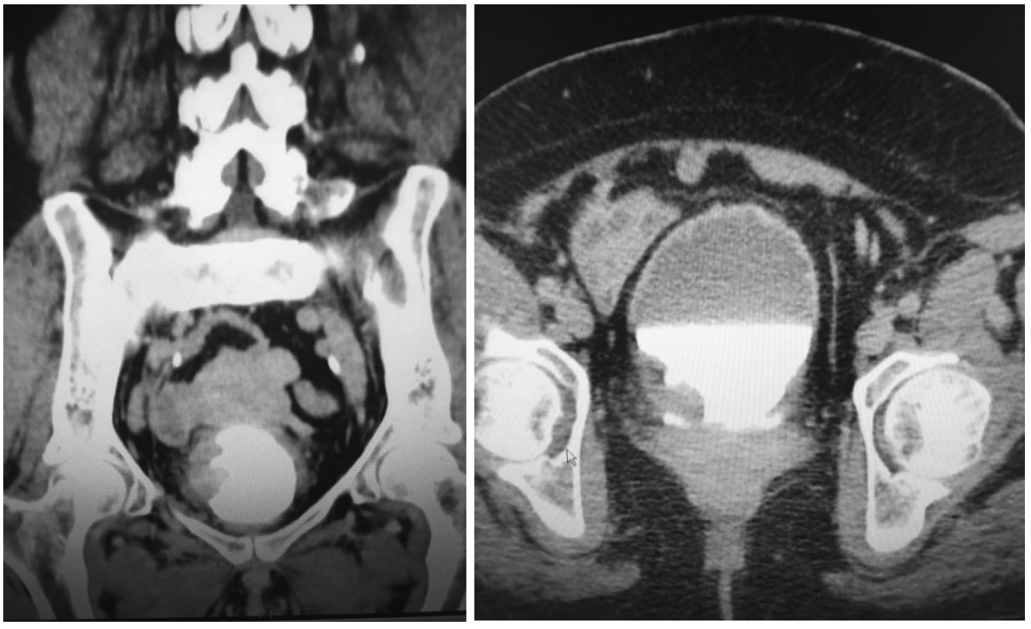

Figure 1. Representative coronal and axial images showing diffuse mural thickening of the bladder with a polypoid lesion involving the right lateral and posterior walls.

were negative, and there was no evidence of lymph node metastasis. There is no evidence of recurrence at 6 months.

Discussion

CA is a benign epithelial proliferation associated with HPV. Presenting symptoms may include hematuria, storage bladder symptoms and recurrent UTIs. On cystoscopy, CA may present as a pale and discrete, focal lesion, or have a more extensive, erythemetous 'carpet' like appearance.

The role of HPV in SCC of cervical and anogenital malignancies is well described.[1] Based on its oncogenic capacity, HPV can be grouped in to low risk (genotypes 6 and 11) and high risk categories (genotypes 16 and 18). However, the association of HPV with

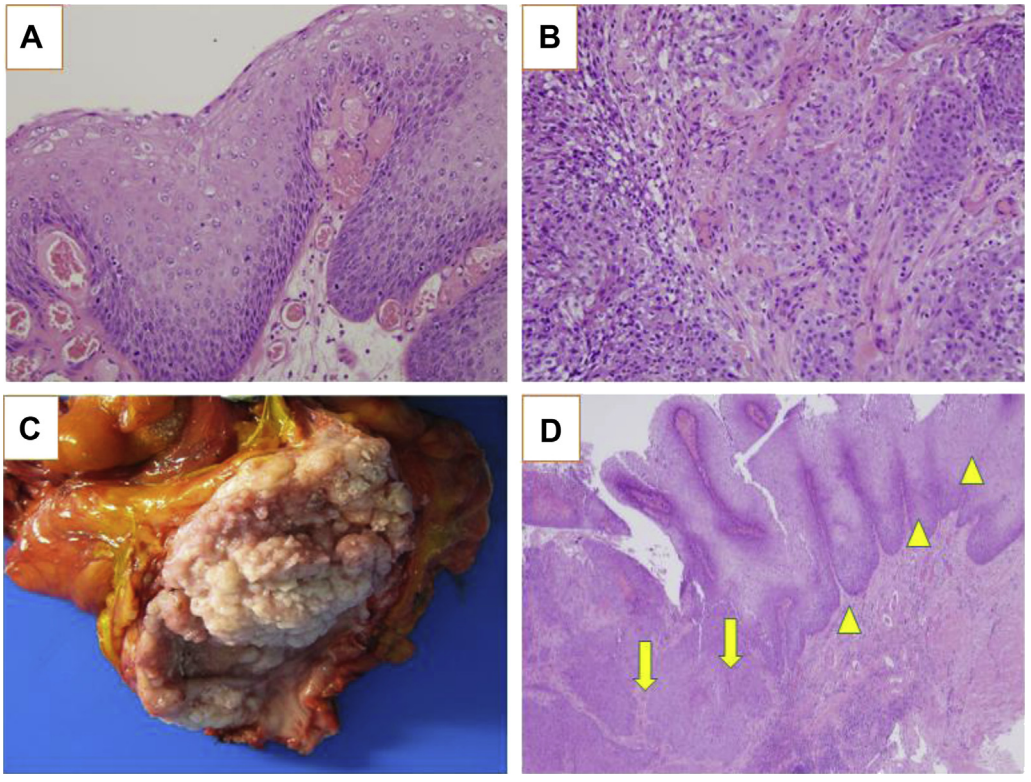

Figure 2. Invasive squamous cell carcinoma arising in condyloma acuminata. A) Condyloma characterized by the presence of kiolocytes, present in the initial TUR specimen in 2011. B) Squamous cell carcinoma invading the lamina propria, identified in the final TUR in 2015. C) Gross appearance of the bladder tumor in cystectomy specimen is a bulky tumor involving the major portion of the bladder. D) Presence of both invasive squamous cell carcinoma (right, arrows) and associated condyloma (left arrow heads) in the cystectomy specimen.

bladder carcinogenesis is debatable. Pure SCC of the bladder is rare, accounting for up to 5% of cases in the Western world.[2] Pathogenesis includes chronic irritation of the urothelium caused by factors such as long term catheterization, recurrent urinary tract infections, and bladder calculi. Kerley et al described the first case of intravesical keratinizing SCC associated with HPV infection.[3] Nevertheless, more recent series have failed to demonstrate the prevalence of HPV infection in urothelial or SCC of the bladder.[4]

Although HPV can induce SCC, the malignant transformation of CA only occurs in a very small percentage of cases. Typically, CA may progress to squamous dysplasia, a premalignant lesion, followed by carcinoma *in situ*, and finally invasive SCC.

There have been few reports on the association between CA of the bladder and warty or verrucous carcinoma.[5] These heavily keratinized lesions are typically well-differentiated with an indolent course and either no or very low metastatic potential. Only one case of invasive SCC in the background of CA has been reported; however, clinical and pathological details were not described.[2] We report a very unusual case of poorly differentiated SCC arising from CA that rapidly progressed to locally advanced disease. Our patient had extensive, recurrent CA of the bladder causing long term storage symptoms. The chronic inflammation caused by CA may have also played a role in the development of SCC in addition to the malignant transformation of the lesion itself.

Given rarity of intravesical CA, there is no standard treatment. Due to the presumed benign nature of CA, conservative, bladder sparing strategy has been suggested in most cases for symptomatic relief. This has included anticholinergics, intravesical fluorouracil, transurethral resection, electrocoagulation and radiation. Cystectomy was performed in one case due to obstructive nephropathy secondary to intravesical proliferation of CA.[5] Our patient experienced significant improvement in her symptoms with TUR alone each time. However, she progressed from CA of the bladder to locally advanced, poorly differentiated invasive SCC within 6 months. Hence, patients should be counseled on the risk of malignancy associated with intravesical CA. Surveillance cystoscopy and biopsy are very important, especially with recurrence of lesions with dysplasia because of its potential of malignant transformation into invasive SCC. In symptomatic patients with high volume, recurrent CA that is refractory to multiple TURs, early cystectomy should also be discussed as a management option, since these patients may be at a higher risk for development of SC.

Conclusion

CA of the bladder is a rare entity that can transform into SCC, especially in patients with recurrent symptomatic disease. Periodic surveillance cystoscopy and biopsy should be considered in these patients.

Conflict of interest

The authors have no conflict of interest.

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