Invasive low-grade urothelial carcinoma in a bladder biopsy associated with high-stage disease and masquerading as schistosomiasis

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We present an interesting case of a 56-year-old Egyptian woman with high-grade urothelial carcinoma (HGUC) associated with schistosomiasis that appeared initially as low-grade (LGUC) disease on transurethral resection of the bladder tumor (TURBT). Areas of HGUC and tumor invasion were detected only after meticulous microscopic examination of the partial cystectomy specimen. Furthermore, there were no areas of squamous cell metaplasia identified. This case highlights one of the limitations of biopsy for determining cancer grade and stage. It also emphasizes that schistosomiasis may be associated with non-squamous cell forms of bladder cancer, the pathogenesis of which has not been fully elucidated.

Key Words: urothelial carcinoma, low grade, schistosomiasis, invasive

Introduction

Low-grade urothelial carcinoma (LGUC) typically follows a more favorable clinical course than its aggressive high-grade (HGUC) counterpart, and rarely leads to deep muscle-invasive or extravesicle disease.[1] Invasive LGUC has been described under different subtypes such as deceptively benign-appearing, nested, and microcystic transitional-cell carcinoma (TCC).[2] Urothelial carcinoma is also uncommonly associated with schistosomiasis, which has a propensity to develop into squamous cell carcinoma.[3] We describe an unusual case of LGUC with extensive invasion into the perivesical adipose tissue with focal areas of sarcomatoid differentiation. The carcinoma initially appeared as LGUC in urinary bladder biopsy and was masquerading as severe cystitis with *Schistosoma haematobium* infection.

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Case report

A 56-year-old woman, recently immigrated from a small village in Egypt, presented with new onset of gross hematuria and mild dysuria. She had no constitutional symptoms and was generally healthy, except for hypertension. The patient was a nonsmoker and had no previous radiation or occupational exposures. A general physical examination, including the head and neck, chest, and abdomen, was normal. Routine blood and urine studies were also normal, apart from the detection of hematuria.

A cystoscopic study was performed and revealed a small, midline, submucosal mass at the dome of the bladder. Cystoscopic urine showed atypical urothelial cells. On abdominal computed tomography (CT) scan, the lesion appeared as a 16 mm, well-circumscribed, brightly enhancing, soft-tissue nodule arising from the roof of the urinary bladder, without evidence of invasion into adjacent structures, Figure 1. The surgical pathology demonstrated a schistosomial infection and invasive LGUC.

The patient subsequently underwent a transurethral resection of the bladder tumor (TURBT), was treated with a 1-day course of praziquantel for schistosomiasis, and was then scheduled to have quarterly surveillance cystoscopies for LGUC. Five months later however, a repeat cystoscopy and CT scan demonstrated that the tumor size and appearance remained the same, despite the previous treatments. The patient underwent partial cystectomy for the bladder tumor, as it was not possible to fully characterize the tumor on surveillance cystoscopy alone. The surgical pathology demonstrated that the urothelial carcinoma (UC) extended into the perivesical adipose tissue. A complete cystectomy and adjuvant chemotherapy were recommended. The patient however declined further surgery and went on to have surveillance cystoscopies and diagnostic imaging in the form of abdominal CT scan and chest roentography. A follow-up at 12 months did not reveal any recurrence of the disease.

Figure 1. The initial CT scan of the pelvis, showing a 16 mm, well-circumscribed, brightly enhancing, soft-tissue nodule arising from the roof of the urinary bladder (arrow).

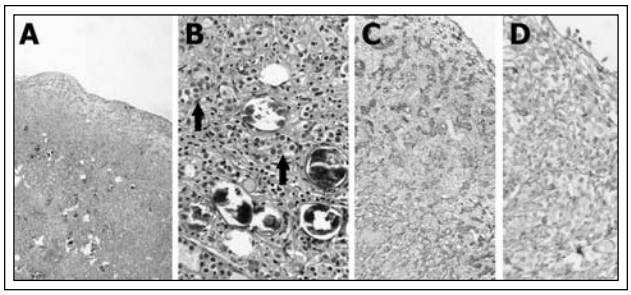

Figure 2. Biopsy showing chronic schistosomiasis cystitis at (A) low magnification (H&E, 4x10); (B) and high magnification, revealing calcified eggs of S. haematobium and closely associated nests of invasive LGUC (H&E, 40x10). Note the mild cytological atypia of UC cells (arrows). (C) Immunostaining for CK7 highlighting the extensive invasive UC (10x10). (D) Immunostaining for CK20 showing negative to weak reactivity (40x10). H&E = hematoxylin-eosin staining.

Pathological examination

The bladder biopsy was superficial and composed only of the sub-mucosa. Microscopic examination revealed severe chronic cystitis associated with *Schistosoma haematobium* measuring approximately 300 microns, Figure 2. The urinary bladder surface was denuded of urothelium except for focal areas displaying mild cytological atypia. A careful microscopic examination

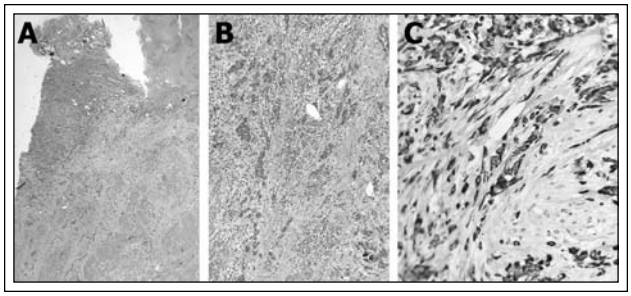

Figure 3. Bladder tumor after partial cystectomy displaying (A) denuded epithelium (H&E, 10x10); (B) LGUC invasion into muscular propria (H&E, 10x10); and (C) immunostaining showing many CK7 positive spindle tumour cells) (40x10). H&E = hematoxylin-eosin staining.

revealed small nests of mildly atypical cells extensively involving all biopsy chips. The cell nests were irregular in shape and contained occasional lumina. Immunostaining revealed strong reactivity in nests of atypical urothelial cells in the stroma for cytokeratin 7 (CK7) which also stained the surface urothelium. The atypical urothelial cells showed negative to weak reactivity for cytokeratin 20 (CK20) and positive reactivity for p53 and proliferative antigen MIB1 in 5% and 15% of atypical cells respectively. There was no HGUC or squamous cell metaplasia identified.

The partial urinary bladder resection, as in the biopsy showed chronic schistosomiasis cystitis, Figure 3. In the lamina propria there was LGUC with stromal invasion associated with urothelial dysplasia. In the muscularis propria, the invasive tumor cells became more atypical with marked hyperchromasia and some increase in tumor cell size. Mitotic figures were frequently seen. In focal areas the tumor showed sarcomatoid changes with spindle cells displaying reactivity for CK7 but there was no squamous differentiation. Surgical margins were clear of tumor and there was no lymph node metastasis detected. The final pathological stage of the bladder tumor was T3bN0M0.

Discussion

LGUC is part of the 1998 WHO/ISUP classification of bladder neoplasms, and is characterized by minimal cytologic atypia, a low rate of local recurrence, and focal stromal invasion.[1,4] However, several cases have described LGUC with extensive invasive disease, in which the initial diagnosis on TURBT was more benign in appearance.[2] In the presented case, the initial pathology showed only LGUC and schistosomiasis. Due to the severe inflammatory and fibrotic reaction, the nests of invasive LGUC were only detected by a meticulous examination and immunostaining for CK7, Figure 2. Furthermore, high-grade areas of UC showing sarcomatoid differentiation were only detected in the microscopic evaluation of the complete tumor after partial cystectomy, Figure 3. TURBT may therefore be limited in identifying HGUC, which occurred in the deeper portion of the invasive component. The HGUC likely represented dedifferentiation of the superficial LGUC in this case.

Another interesting aspect of this case is the presence of schistosomiasis leading to UC. The causal link between genitourinary schistosomiasis and bladder cancer has been well established.[3] It was first described by Ferguson in 1911, and is thought to arise mainly from chronic irritation and inflammation of the bladder.[6] In addition, various host and environmental factors have been described, involving: genetic changes in oncogenes and tumor suppressor genes, secondary infections, exposures to urinary tract carcinogens, and diet.[3,7] The major histopathological subtype associated with schistosomiasis is squamous cell carcinoma. It is the most common malignant neoplasm in Egypt, and occurs with high incidence in parts of the Middle East and Africa.[6] In contrast, transitional cell carcinoma is the most prevalent type of non-bilharzial bladder cancer in North America.[6] Further studies, applying both host and environmental factors, important in the pathogenesis of the various subtypes of bladder cancer associated with schistosomiasis will be necessary to better elucidate the causal relationship.

Conclusion

LGUC may show focal areas of high-grade cancer not detected by biopsy and these may be associated with extensive invasion. In addition, schistosomiasis may be associated with non-squamous cell forms of bladder cancer; the causal relationships of which are not yet well characterized. Further research of the pathogenesis into both of these phenomena may impact the future management of bladder tumors. □

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