Rare but lethal disease of childhood: metastatic, muscle invasive bladder cancer

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Abstract

Bladder cancer is the most common malignancy of urinary tract and the seventh most common cancer in men with the peak incidence in the sixth decade of life. Our knowledge about bladder tumors in pediatric age group mainly relies on case series. The reported cases are mostly low grade and non-muscle invasive. We herein present a case of a 17-year-old male with metastatic high-grade muscle-invasive bladder cancer who was presented with macroscopic hematuria and flank pain.

Introduction

Bladder cancer (BCa) is the most common malignancy of the urinary tract and the seventh most common malignancy of men.[1] Although most of the patients are initially diagnosed as non-muscle invasive bladder cancer (NMIBC), almost 30% of them are eventually progress to muscle invasive bladder cancer (MIBC).[2]

The peak incidence of BCa is in the sixth decade of life,[2] while they are rarely seen in children. Deming was the first to publish a case of BCa in a 10 years old patient, almost 9 years ago.[3] The overall incidence of BCa is 0.1-0.4% in patients under age 20.[4]

When compared to adult patients almost all of the cases are low grade and non-muscle invasive.[4,5]

The patient presented here had a high grade and rapidly progressive disease that eventually resulted in the death of the patient.

Case Report

A 17 years old male was presented to our out patient clinic with macroscopic hematuria of 3 weeks. The history of the patient was unremarkable except for smoking while physical examination revealed only pale skin suggestive of anemia. Patient has smoking history as 10 cigarettes a day for 4 years [(10/20)×3 = 1.5 pack-year]. The hemoglobin level was 6.2 g/dL. The urinary ultrasound demonstrated a 10-cm mass. The contrast-enhanced thoracic-abdominal computerized tomography (CT) was consistent with an intravesical mass with 8 cm diameter and suspicious metastatic lesions in the posterior segment of upper pole (14 mm) and medial part of lower pole (10 mm) of right lung (Figure 1). Although it is not a standard diagnostic tool for BCa, positron-emission tomography (PET) with mCi F-18 fluorodeoxiglucose (FDG) performed for suspicious lung lesions and it revealed the findings of CT scan as lung metastasis with additional hypermetabolic metastatic iliac lymph nodes.

The bimanual examination was compatible with frozen-pelvis. In cystoscopy, the entire bladder wall was occupied with the tumor except for a small area in the dome of the bladder. A subtotal transurethral resection of tumor (TURBT) was performed to confirm the pathological diagnosis, as it was not possible to resect all the tumoral lesions. The pathological specimen was reviewed by two separate adult genitourinary pathologists in two different institutes.

The hematoxylin-eosin sections of the specimen revealed delicate papillas with accompanying fusions. Although the majority of the epithelial cells were arranged regularly, crowded pleomorphic cells in a haphazard alignment with invasion to lamina propria was also noticed. The consensus pathologic diagnosis (Figure 2) of both pathologists blinded to each other was grade 3 transitional cell carcinoma (TCC) based on the 1973 WHO classification (Table 1) and high grade (HG) based on the 2004 WHO classification. However, the staging of the tumor was not accurate because of the lack of muscularis propria in the resected specimen.

A 28-day chemotherapy regimen with gemcitabine (1500 mg) on days 1, 8 and 15 and cisplatin (110 mg) on day 1 was initiated because of the lung metastasis seen on PET. The follow-up CT obtained after the first 2 cycles of chemotherapy revealed progression in the residual bladder tumor and pulmonary lesions. The hemoglobin level of the patient was 4.2 mg/dL because of continuous macroscopic hematuria. Following palliative radiotherapy to control hematuria, paclitaxel (80 mg/k^2) on day 1, 2 and 3 together with adriamycin (50 mg/m^2) on day 1 was started for 4 cycles. Selective angio-embolization was required because of persistent hematuria. Bone scintigraphy with 15mCi 99mm Tc-MDP obtained on July 2014 revealed metastatic lesions at right acetabulum and ischium pubicum. Follow-up CT revealed progression of the pulmonary lesions and increase in number of involved lymph nodes. Despite aggressive treatment, the patient was lost within the first year of diagnosis.

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Discussion

Urothelial carcinoma is rarely seen during the pediatric age group.[6] In a comprehensive review of published BCa series in pediatric age group, Paner *et al.* showed that muscle invasive and high grade tumors was diagnosed in 3.0% and 1.7% of the cases, respectively.[7] As most of the BCa cases diagnosed during childhood are non-muscle invasive and low-grade, the expected outcome is better than that of the older patients.[7]

There are only two cases reported to have high-grade disease in the literature. The first case was published in 2012, in a 5-year old male with gross hematuria.[5] He was treated with partial cystectomy followed by 6-weeks of intravesical bacillus Calmette-Guerin instillations. No recurrence was reported during the 1-year follow-up period. The second case was a 16-year old girl with Hinman syndrome who was diagnosed with invasive transitional cell carcinoma of the bladder. To our knowledge, this is the third case in the literature presenting a high-grade BCa in a patient younger than

Table 1. World Health Organization (WHO) grading of bladder tumor in 1973 and 2004.

WHO 1973	WHO 2004
Urothelial papilloma	Urothelial papilloma
Grade 1: well differentiated	Papillary urothelial neoplasms of low malignant potential
Grade 2: moderately differentiated	Low-grade papillary urothelial carcinoma
Grade 3: poorly differentiated	High-grade papillary urothelial carcinoma

18 years old. In addition to well known environmental risk factors including smoking, occupational exposure to aniline dyes and phenacetin, some genetic conditions are also associated with increased risk of bladder cancer.[8] Although multiple-case families with BCa suggested the presence of a genetic predisposition, it is not clear whether these cases were resulted from a genetic abnormality or common environmental exposure to known carcinogens.[9] In the present case, the patient was smoking for 3 years, but did not report any BCa in the family history. Although absence of muscularis propria in the initial resection specimen is an indication for second TURBT,[10] it was not performed, as the further treatment would not change because of the distant organ metastases. Approximately 30% of the patients with BCa have muscle invasive while 10 to 15% of patients are already metastatic at diagnosis.[11] The median survival of patients with metastatic disease rarely exceeded 6 months before the development of modern platinum-based chemotherapy regimens.[12] Outcome of chemotherapy depends on performance status of the patient and presence or absence of visceral organ metastases.[13] Cisplatin containing combination therapy is recommended as the first line treatment in metastatic patients with up to 49% response rates and prolonged survival up to 14.8 months.[14] However, all these data are collected from adult series and limited evidence exists in the literature for treatment of metastatic disease in children.[15] Because of progression under gemcitabine/cisplatin chemotherapy, paclitaxel/adriamycin treatment was initiated in this case. Moreover, radiotherapy and selective embolization was performed to control macroscopic hematuria but these palliative interventions yielded only transient response. The disease control was not established despite second-line chemotherapy and the patient died soon after diagnosis of bone metastases.

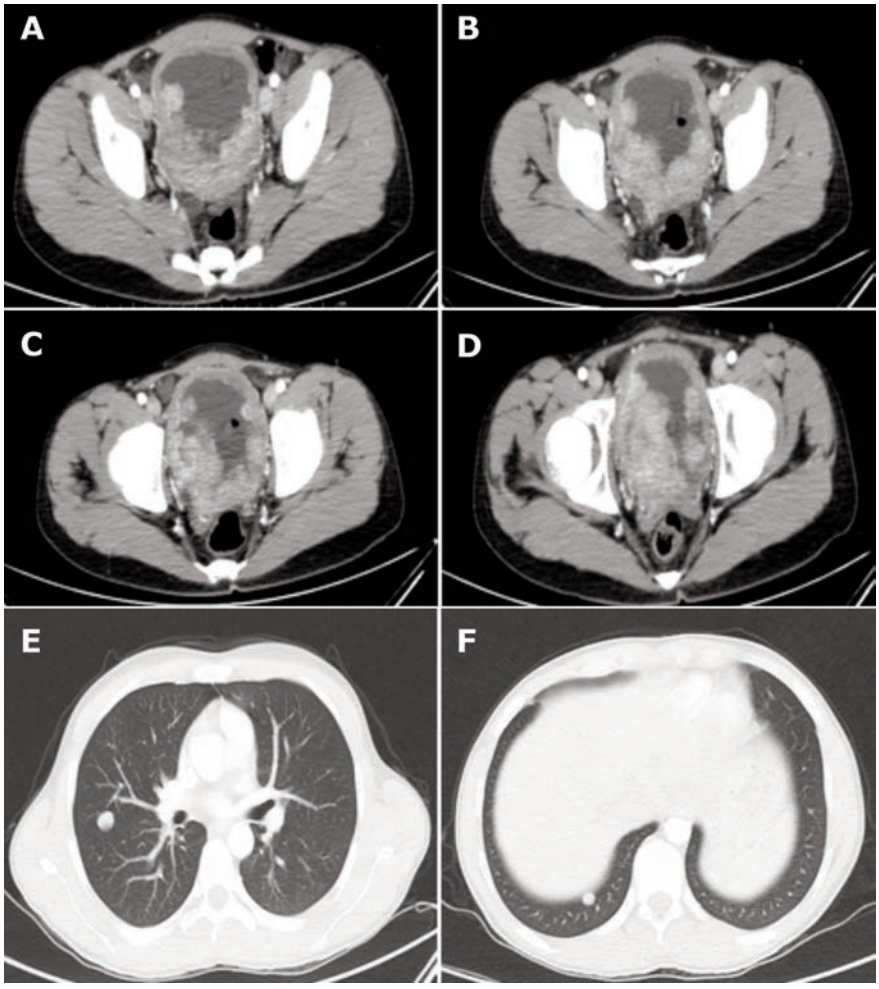

Figure 1. A-D) Preoperative contrast enhanced computerized tomography of the patient. Most of the lateral and posterior walls are occupied with the tumor. E,F) Computerized tomography of the thorax revealed multiple nodular metastatic lesions.

Conclusions

We herein reported a rapidly progressive case of high grade BCa in a young boy. Although uncommon, BCa should always be kept in mind when evaluating macroscopic hematuria in children. In patients with high-grade disease, aggressive resection should be performed and chemotherapy should be considered in the attempt to control the disease and prevent progression and metastases.

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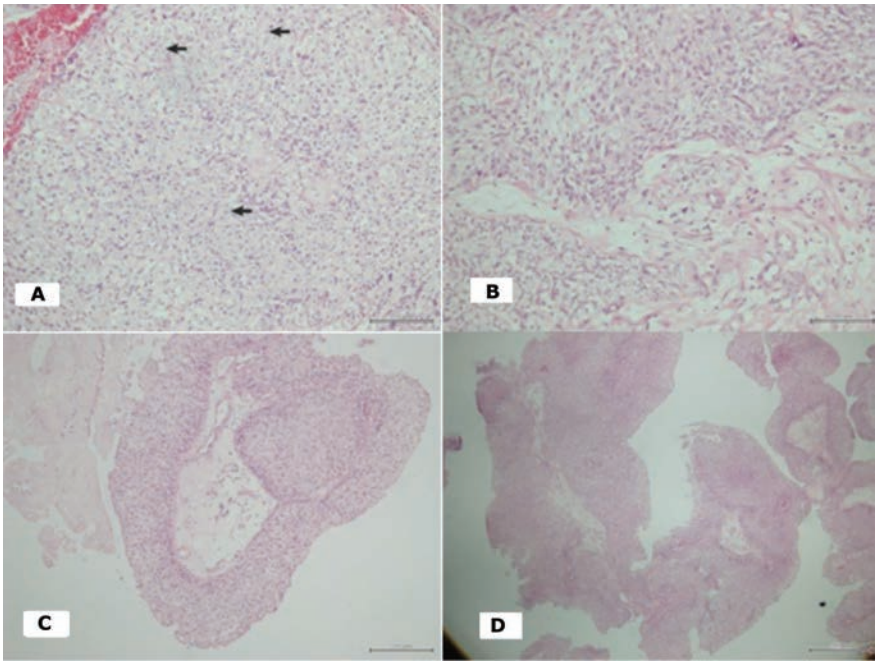

Figure 2. A) High grade urothelial carcinoma with haphazardly arranged cells with significant nuclear pleomorohism and atypical mitosis, Hematoxylin and Eosin 200×. B) High grade urothelial carcinoma with stromal invasion Hematoxylin and Eosin 400×. C) High grade urothelial carcinoma, Hematoxylin and Eosin 100×. D) High grade urothelial carcinoma with papillary fronds, Hematoxylin and Eosin 40×.

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