

Original article

Cure of undifferentiated small cell carcinoma of the urinary bladder with M-VAC chemotherapy

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Abstract

Small cell carcinoma (SCC) of the urinary bladder is a rare, aggressive malignancy with approximately 135 cases reported in the literature. Treatments have included chemotherapy, radical surgery, radiotherapy, and combinations of these. We present the apparent cure of a 73-year-old man who presented with clinical stage T2 SCC of the urinary bladder. He was treated with three cycles of methotrexate, vinblastine, Adriamycin (doxorubicin), and cisplatin (M-VAC) chemotherapy. Subsequent radical cystoprostatectomy revealed no pathologic evidence of tumor. The patient is alive and well with no evidence of recurrence 3 years post cystectomy. A brief review of the literature is also presented. © 2001 Elsevier Science Inc. All rights reserved.

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1. Introduction

Small cell carcinoma (SCC) of the bladder is an aggressive high-grade tumor whose rarity has precluded large studies of treatment. SCC is most commonly diagnosed in the lung, but has been reported in multiple organs. SCC of the urinary bladder was first reported in 1981 by Cramer et al. [1]. Since then approximately 135 cases have been reported in the literature [2] and it has been estimated to have an incidence of 0.5% [3] to 0.7% [4] of all bladder tumors. We present a case in which a patient was diagnosed with SCC with extensive invasion of muscularis propria by transurethral biopsy. He was successfully treated with neoadjuvant methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC), followed by radical cystoprostatectomy.

2. Case presentation and management

A 73-year-old male retired chemical plant worker presented in March 1997 with painless gross hematuria. The patient's medical history was significant for cigarette smoking and a urinary tract infection at the time of presentation that was treated with trimethoprim-sulfamethoxazole. Phys-

ical examination revealed a muscular thin male with normal genitalia and a 30-g, slightly firm prostate. Laboratory examination, including a liver profile, was unremarkable. Intravenous pyelogram showed a filling defect in the bladder. Contrast computed tomography (CT) of the abdomen and pelvis revealed a filling defect confined to the left posterolateral wall of the bladder with no evidence of adenopathy or metastasis. Cystoscopy revealed a large tumor involving the left hemitrigone. Transurethral resection was performed. The pathology demonstrated a highly cellular, poorly differentiated carcinoma that invaded muscularis propria. The tumor cells showed nuclear molding and lacked nucleoli. Mitotic figures were abundant. The findings were most consistent with a SCC (Fig. 1). CT of the chest and a bone scan showed no evidence of metastasis and were otherwise unremarkable.

The patient received three cycles of M-VAC chemotherapy after which time CT scan demonstrated apparent progression of disease (Fig. 2). Consequently, a radical cystoprostatectomy was performed with an ileal conduit urinary diversion. Histopathologic examination of the bladder specimen found no residual carcinoma. Transmural fibrosis and chronic inflammation were present in the region of prior tumor. No tumor was identified in 10 right and 7 left obturator lymph nodes.

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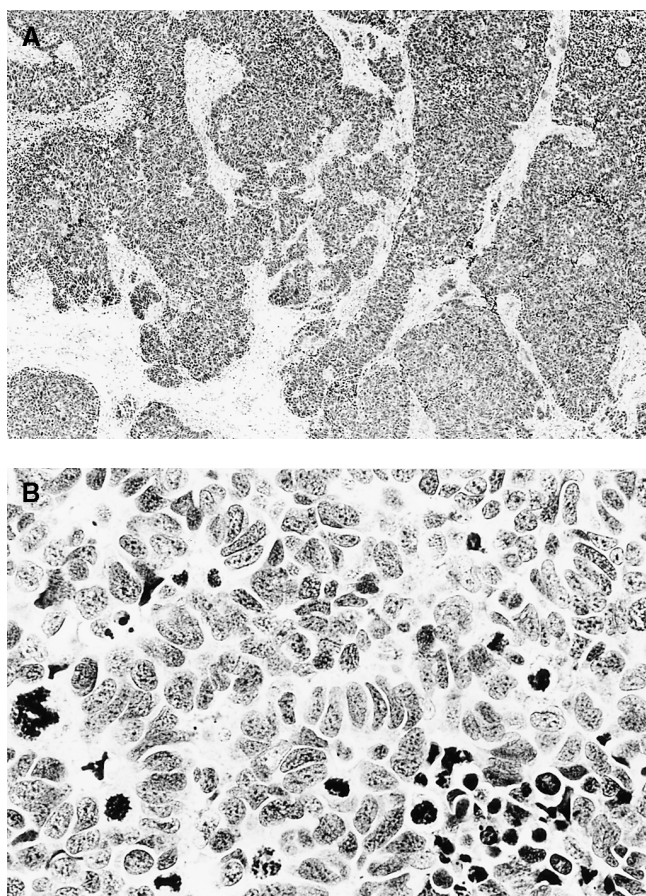


Fig. 1. (A) Photomicrograph of a section through the initial transurethral resection specimen demonstrating a highly cellular, poorly differentiated carcinoma (H&E, reduced from $\times 50$). (B) Tumor cells show nuclear molding and lack nucleoli. Mitotic figures are abundant (H&E, reduced from $\times 500$). These findings are most consistent with a SCC.

The patient had a satisfactory postoperative course and was discharged from the hospital on postoperative day eight. He has had no evidence of tumor recurrence 3 years after surgery on follow-up urine and urethral cytology, chest X ray, and CT scan.

3. Discussion

SCC of the urinary bladder is a rare tumor typically of older men who present with gross hematuria. In the largest review to date, Abbas et al. [2] found that the median age at presentation of 97 males and 27 females studied was 66.1 years. Eighty-seven percent of patients presented with gross hematuria, 18% with bladder irritability, 9% with suprapubic or flank pain, and 3% with obstructive uropathy.

Although there have been no large population studies done of SCC, reviews and smaller studies have described its epidemiologic characteristics. Young and Eble [5] report that of the 50 patients described in the literature between 1981 and 1991, death occurred quickly in 50%, with a mean survival time of 7 months. Only 20% had disease-free sur-



Fig. 2. CT of the pelvis revealing apparent progression of the tumor after three cycles of M-VAC.

vival longer than this at the time of reporting [5]. SCC most often metastasized to local or distant lymph nodes, liver, bone, lung, brain, adrenal gland, spleen, and abdominal cavity, and paraneoplastic syndromes were uncommon [2].

The differential diagnosis of SCC includes small cell metastasis from a site outside of the bladder, a poorly differentiated transitional cell carcinoma (TCC), and primary or secondary lymphomas. It is important to rule out other primary tumors with CT scans of the chest and abdomen.

Grossly, the tumors tend to present as invasive, large sessile or polypoidal, ulcerated, and frequently necrotic bladder lesions. The SCC cells appear as lymphocyte-like single cells with hyperchromatic nuclei and minimal cytoplasm. Intracytoplasmic neurosecretory granules can be found in SCC cells under evaluation with the electron microscope. Immunohistochemically, they react to neuron-specific enolase, which is the most sensitive and frequently used neural marker for SCC, and occasionally to chromogranin and CAM 5.2.

The histogenesis of SCC of the bladder remains unclear. There are three possible explanations for its origin [6]. First, the tumor may arise from a neuroendocrine Kulchitzky-like stem cell that exists in the urothelium of the bladder. The second possibility is that these tumors arise from poorly defined submucosal or muscularis cells of neural crest origin. Finally, SCC may result from a metaplastic transformation of TCC. This would explain the common coexistence of TCC in up to two thirds of patients diagnosed with SCC.

Comparable to results seen with SCC of the lung, distant metastases at presentation are common and cure is unlikely with local therapy alone [7]. In patients with SCC of the bladder, using monotherapy with either radiation (3 patients) [8] or radical cystectomy (10 patients) [9,10], all pa-

tients had either residual disease or succumbed to their metastases. Adjuvant chemotherapy, however, can result in long-term survival. Grignon et al. [8] administered chemotherapy to 5 patients treated with radical surgery, 4 of whom survived at least 10 months (range 10–51 months). In contrast, further local therapy appears to be ineffective, with only 5 of 25 patients achieving long-term remission [4].

There have also been reports of remission attributable to chemotherapy alone. Itoh et al. [11] reported a 67-year-old male with SCC metastatic to the left external iliac lymph nodes. The patient was treated with three cycles of cis-diamine-dichloroplatinum and etoposide and was documented by CT scan to have resolution of the mass. Oesterling et al. [6] reported two cases of SCC, both of which were first treated with radical cystoprostatectomy and adjuvant M-VAC therapy. Neither patient had evidence of recurrence at 1 and 2.5 years post-operatively.

There has only been one reported case that we found in which a patient was apparently cured with M-VAC therapy alone. In 1995, a similar case to ours was reported by Cheng et al. [12]. He was treated with six cycles of M-VAC and radical cystoprostatectomy demonstrated no residual tumor histologically. The patient was reported to be recurrence-free 9 years after his operation.

Platinum-based therapy appears to have significant activity against metastatic SCC. Unfortunately, the limited number of patients with SCC of the bladder treated in this manner make it impossible to determine whether accepted small cell lung regimens such as CAV (cytoxan, adriamycin, vinblastine) or VP-16/cisplatin, or the standard urothelial M-VAC regimen should be used as first-line therapy. Our case, which is similar to that of Cheng et al. [12], suggests that M-VAC

may be considered a valuable treatment option in SCC of the urinary bladder. Further study is warranted to quantify its role in SCC therapy.

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