CASE REPORT

Malignant pheochromocytoma of the urinary bladder

Daniel Zwahlen, MD, Paula N. Fishman, MD, John Honey, MD, Michael Milosevic, MD, Ian Tannock, MD

Radiation Medicine Program and Department of Medical Oncology and Hematology, Princess Margaret Hospital, Department of Urology, St. Michael's Hospital and the Departments of Radiation Oncology, Medicine and Urology, University of Toronto, Toronto, Ontario, Canada

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This report describes an illustrative case of malignant pheochromocytoma of the urinary bladder in a 28-year old man. A combined-modality treatment plan with partial cystectomy and post-operative radiotherapy and concurrent chemotherapy with single agent cisplatin weekly was performed. Three weeks after completing concurrent chemoradiation the first of four planned cycles of cisplatin 25 mg/m^2 and etoposide 100 mg/m^2 was administered daily over 3 days. Although there are no controlled series offering proof of benefit, postoperative concurrent chemoradiation followed by chemotherapy alone are reasonable options for patients with residual disease or at high risk for locoregional relapse.

Key Words: bladder, malignant pheochromocytoma, chemoradiation, chemotherapy

Introduction

The neuroendocrine tumor, malignant pheochromocytoma of the bladder, is a rare neoplasm with a reported incidence of < 1% of all bladder tumors and < 1% of all pheochromocytomas. Here we describe a case of malignant pheochromocytoma of the bladder in a 28-year old man.

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The first two authors contributed equally to the development of this manuscript.

Address correspondence to Dr. P. Fishman, Princess Margaret Hospital/University Health Network, 610 University Avenue, Toronto Ontario M5G 2M9 Canada

Case description

An otherwise healthy 28 year-old Vietnamese man living in Canada presented with a 2-year history of intermittent gross hematuria. Pelvic CT scan and MRI showed a mass measuring 7.4 cm in greatest dimension involving the bladder dome as shown in Figure 1, and a 1.4 cm left external iliac lymph node that was felt to be inflammatory. Cystoscopy confirmed the bladder mass and biopsies were consistent with pheochromocytoma.

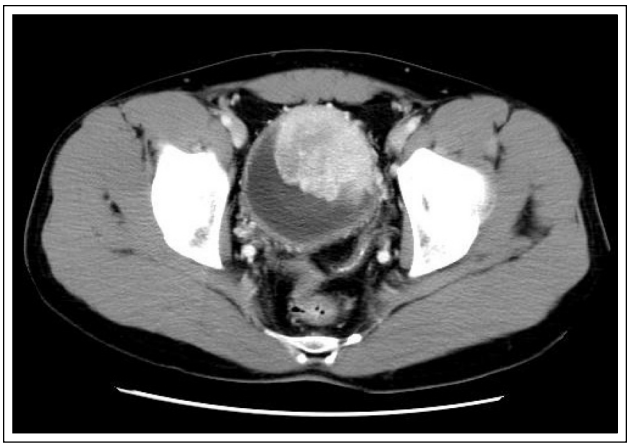

Figure 1. Axial CT image of enhancing bladder pheochromocytoma antero-laterally at the dome.

At the time of diagnosis, blood pressure was normal and there was no history of palpitation, headache or abnormal sweating. Blood cell counts, serum creatinine, electrolytes and liver function tests were normal. A 24-h urine collection showed elevated catecholamines, including vanillomandelic acid (VMA) of 54.7 mmol (normal 6-35), metanephrines of 11.9 mmol (normal < 5.5), norepinephrine of 2841 nmol (normal < 600) and epinephrine of 83.7 nmol (normal < 60). The patient was treated with alpha and beta adrenergic blockers, and 2 weeks later underwent partial cystectomy and perivesicle lymph node dissection. No attempt was made to resect the left iliac lymph node.

Histological examination showed a 4.5 cm malignant pheochromocytoma of the bladder with invasion through the muscularis propria into the perivesicle fat, and lymphvascular space invasion. Metastatic disease was identified in all four perivesicle lymph nodes. The resection margins were negative for malignancy. Urinary catecholamines were normal post-operatively. A whole body meta-iodobenzylguanidine (MIBG) scan showed no active uptake in the residual bladder or in other areas of the body, including the enlarged pelvic lymph node. CT scans of his chest and abdomen were normal. A bone scan showed a small focus of increased uptake in the sacrum of uncertain clinical significance. Bladder function was excellent. Genetic testing for causes of pheochromocytoma was completed including VHL screen which was negative. RET gene screen for MEN II syndrome is not available in Ontario, but the patient had no features of this syndrome and his family history was negative.

A combined-modality post-operative treatment plan with radiotherapy and chemotherapy was recommended. He received radiotherapy consisting of 50 Gy in 25 daily fractions over 5 weeks using a four-field technique to encompass the bladder and pelvic lymph nodes, followed by a boost of 10 Gy in five fractions to the residual bladder. Chemotherapy with single-agent cisplatin 40 mg/m^2 was delivered weekly during radiotherapy for six doses. Three weeks after completing radiotherapy he received the first of four planned cycles of cisplatin 25 mg/m^2 and etoposide 100 mg/m^2 administered daily over 3 days. A treatment delay of 2 weeks occurred after the second cycle because of neutropenia and mild azotemia. Carboplatin with an AUC of 5 was substituted for cisplatin during cycles three and four.

Six months after completing treatment, the patient had fully recovered and was asymptomatic. Urinary catecholamine levels were normal apart from epinephrine, which was minimally elevated at 87 nmol. CT scans of the abdomen and pelvis showed a stable left iliac lymph node but no new abnormalities.

Discussion

The diagnosis of malignant pheochromocytoma of the bladder is difficult. Hematuria and signs of ureteric or bladder outflow obstruction are common. Hypertension, palpitation, headache and sweating are characteristic of catecholamine-secreting tumors. However, 17% of pheochromocytomas are hormonally inactive. The diagnosis of malignancy is based on histologic evidence of chromaffin tissue in regional lymph nodes or at distant sites. In one series, up to 40% of extra-adrenal pheochromocytomas were reported to be malignant, which was higher than for adrenal pheochromocytomas, and more likely to recur after treatment.[1] In contrast, in another series of 104 cases, pheochromcytomas arising at adrenal and extra-adrenal sites were similar with respect to the rate of malignancy and patient outcome.[2] The reported 5-year survival rates for malignant pheochromocytomas are between 36% and 60%.[3]

Malignant pheochromocytoma of the bladder is rare and optimal management is controversial. Biopsy should be obtained at cystoscopy and complete or partial cystectomy with regional lymph node dissection is a rational approach.[4] Partial cystectomy was undertaken in this patient because of his young age and the desire to preserve normal bladder anatomy and function, and was facilitated by the location of the tumor at the dome. Patients should be treated with alpha and beta adrenergic blockade prior to cystectomy to minimize the risk of symptomatic chatecholamine excess from surgical manipulation of the tumor.

Although there are no controlled series offering proof of benefit, postoperative radiotherapy and chemotherapy are reasonable options for patients with residual disease or at high risk for locoregional relapse. Radiotherapy is known to be effective for adrenocortical carcinomas and extra-abdominal non-chromaffin paragangliomas.[5] Published case reports have suggested that malignant pheochromocytomas may be relatively radio-resistant, and that external beam radiotherapy might have limited efficacy in comparison to ^{131}I-MIBG.[6] There is evidence from randomized clinical trials that radiotherapy and concurrent cisplatin improve local control and survival for other tumors, including squamous cell cancers of the cervix and head and neck, transitional cell cancer of the bladder, and neuroendocrine tumors such as small cell lung cancer.[7-10] Advances in radiotherapy, including CT-based treatment planning, 3D-conformal radiation techniques and image guidance may also allow better target coverage and higher doses with tolerable side effects relative to older series.[11]

Combination chemotherapy with cyclophosphamide, vincristine, and decarbazine (CVD) produces response rates of approximately 80% in children with metastatic neuroblastoma,[12] which shares clinical and biologic characteristics with pheochromocytoma. The CVD regimen yielded a response rate of 57% in 14 patients with malignant pheochromocytoma, and reductions in serum markers in 79% of patients.[12] In another series of 45 patients with metastatic neuroendocrine carcinomas who received cisplatin and etoposide, only two partial responses were seen among 27 patients with well-differentiated carcinoid or islet cell carcinomas. However, 12 of 18 patients with anaplastic neuroendocrine tumors responded.[13] Other series have used cisplatin and etoposide as second or third line treatment in patients with poorly differentiated or rapidly progressing neuroendocrine tumors, and have reported response rates of about 50% with a median response duration of about 9 months.[14]

Malignant pheochromocytoma with distant metastases is not curable but there are long-term survivors. Metastases have appeared up to 15 to 41 years after initial treatment,[15] and lifelong follow-up is therefore mandatory. Patients should be followed by imaging to detect local and distant recurrence and by monitoring of 24-h urine collections for catecholamines and their derivatives. It is too early to make conclusions about the effectiveness of the tri-modality approach used in the patient described here. Further surgery with removal of the left external iliac lymph node remains an option if it is persistent or progressive. □

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