Case Report

A Baffled Mind: A Mysterious Presentation of Small-Cell Carcinoma of the Bladder

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Clinical Practice Points

- Small-cell carcinoma of the bladder is a rare cancer that accounts for an estimated 0.35% to 0.75% of all bladder malignancies.
- Hypercalcemia is unusual in small cell carcinoma, and has rarely been described with small-cell carcinoma of the bladder.
- External beam radiotherapy for prostate cancer has led to increases in the incidence of secondary cancers, with bladder cancer being the most common type.
- Early diagnosis and close follow-up are essential to decreasing morbidity and mortality.

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Introduction

Small-cell carcinoma of the bladder is a rare cancer that accounts for an estimated 0.35% to 0.75% of all bladder malignancies.[1] The disease commonly affects elderly white men, particularly those with a history of tobacco use. Most patients present with hematuria, and/or signs of bladder irritation. SCCB is an uncommon malignancy worldwide with few reported cases.[2-4] In this report, we discuss the case of a 72-year-old man who presented with altered mental status secondary to hypercalcemia and was found to have SCCB. One previous report of presentation with hypercalcemia is noted in the English literature.[5]

Case Report

Our patient was a 72-year-old African-American man with a history of schizophrenia, hypertension, hyperlipidemia, diabetes, paroxysmal atrial fibrillation, and prostate cancer status after radiation and hormonal therapy who presented from the psychiatric unit with progressively worsening lethargy over several days. The patient was admitted to the inpatient psychiatry unit 1 month earlier for ongoing hallucinations. He had reported fatigue, weakness, abdominal discomfort and decreased oral intake for several days. The patient was treated for a urinary tract infection with trimethoprim-sulfamethaxole, but continued to have worsening lethargy. He was then transferred to our facility for further workup and management. On initial evaluation, the patient was unable to provide a history and responded to voice with incoherent mumbling. As per his family, he had been less alert from his baseline over the past week and had not had a bowel movement in several days.

Of note, our patient had a history of prostate cancer in 1986 and underwent radiation therapy and androgen deprivation therapy (prostate-specific antigen [PSA], 1.14 ng/mL). Laboratory studies showed hypercalcemia on presentation (serum calcium, 17.7 mg/dL). The patient was not taking any medications that might have contributed to hypercalcemia, such as thiazide diuretics or lithium. He was treated with aggressive hydration with intravenous normal saline, calcitonin, and a dose of zolendronate. By day 7, the patient's hypercalcemia resolved. His mental status improved and he began to speak in full sentences, at times oriented to person and place. Further workup revealed normal parathyroid hormone, parathyroid hormone-related peptide, and 1, 25 hydroxy vitamin D levels.

Serum and urine protein electrophoresis were found to be normal with no significant M spike. Bone scan demonstrated increased uptake throughout the bony structures bilaterally, and a pathological fracture of the left inferior pubic ramus. Because of concern for multiple myeloma, the patient underwent a bone marrow biopsy. Computed tomography scan of the chest/abdomen/pelvis demonstrated right hydronephrosis and hydroureter adjacent to the right kidney, with minimal bladder wall thickening (Figure 1B); multiple

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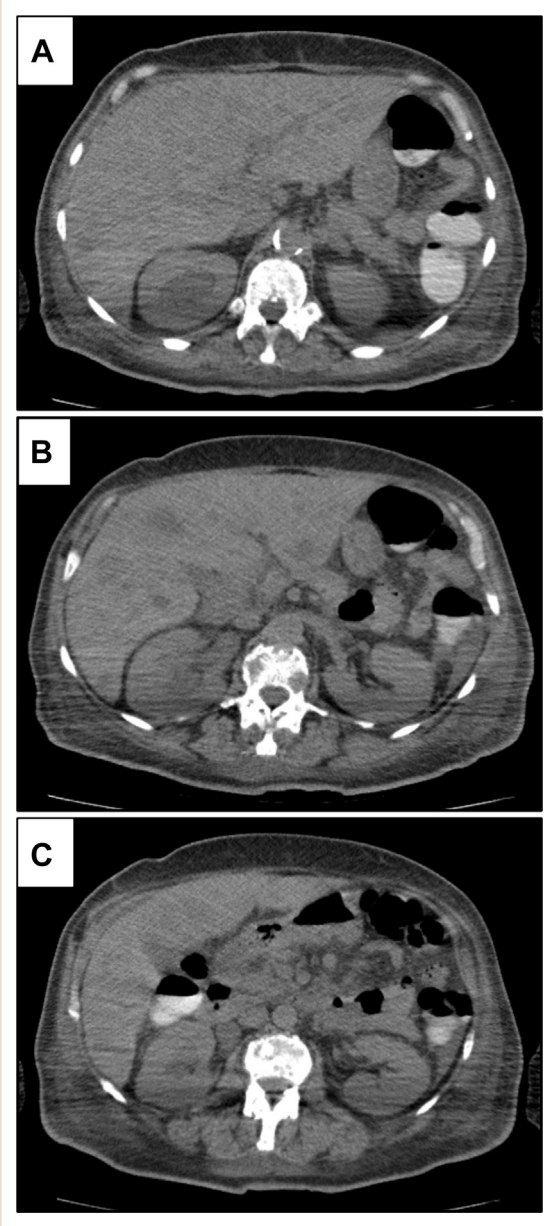
Figure 1 Computed Tomography Scan of the Chest, Abdomen, and Pelvis Demonstrating (A) Hydronephrosis, (B) Heterogenous Lesions in the Liver, and Sclerotic Lesions in the Spine, and (C) Hydroureter Adjacent to the Right Kidney



heterogenous lesions in the liver, a right moderate pleural effusion with no lung lesions, and extensive sclerotic lesions throughout the visualized bony structures (Figure 1). The hydronephrosis was concerning for urinary obstruction, which prompted further workup including urine cytology. Cytological examination of the urine revealed malignant small cells in three separate samples. Bone marrow biopsy showed clusters of atypical small blue cells that were positive for CD56, synaptophysin, and chromogranin, but negative for pan-cytokeratin, cytokeratin-7, thyroid transcription factor-1 and cytokeratin-20, consistent with metastatic small-cell carcinoma (Figure 2). The patient was diagnosed with metastatic SCCB, which was likely a secondary malignancy due to his history of radiation to the pelvis for prostate cancer. Because of his metastatic disease and low performance status, the patient was noted to have a poor prognosis. Per the patient's family, the decision was made for hospice care.

Discussion

Small-cell carcinoma of the bladder is a rare malignancy, more aggressive than transitional-cell carcinoma of the bladder. Although the pathogenesis of SCCB is uncertain, theories such as metaplasia from malignancies, malignant transformation of neuroendocrine cells in the bladder, and derivation from stem cells have been proposed.[1] Gross hematuria is the most common presentation of SCCB. Dysuria, urinary obstruction, abdominal pain, and urinary tract infection have also been reported.[6,7]

Histologically, SCCB is identical to small-cell carcinoma of the lung.[6] The diagnosis is based on the criteria established by the World Health Organization classification system, and workup is similar to that of other bladder cancers.[8] The diagnostic modalities of SCCB include cystoscopy and transurethral resection of the bladder tumor. Immunohistochemical staining is helpful in establishing the diagnosis. Neuron-specific enolase, chromogranin, synaptophysin serotonin, cytokeratin, S-100 protein, epidermal growth factor receptor, C-kit, and thyroid transcription factor-1 are some of the markers implicated.[6] SCCB can occur anywhere in the bladder mucosa, but is most commonly found in the lateral walls.

There is no standardized approach for the treatment of patients with SCCB because of the rarity of the disease, which precludes randomized controlled trials. For localized disease, the treatment involves neoadjuvant chemotherapy followed by radical cystectomy or radiotherapy.[9] Metastatic SCCB is responsive to chemotherapy regimens similar to those that are used for small-cell carcinoma of the lung.[10,11] Metastatic disease is usually managed using chemotherapy with a etoposide-cisplatin regimen.[6] For patients with stage II disease who undergo radical cystectomy, adjuvant treatment is not indicated, but is often considered for patients with stage III or IV disease.[12] Management for SCCB is similar in stages I, II, and III so staging is of little importance. However, because SCCB is highly aggressive and mainly diagnosed at advanced stages, the reported median survival is approximately 12 to 24 months with treatment and about 4 to 5 months without treatment.[1]

Pelvic and retroperitoneal lymph nodes, liver, and bone are among the most frequent sites of metastasis of SCCB.[8,12] In a case series of 44 patients at the Mayo clinic, only 5 patients were noted to have distant metastases at the time of diagnosis.[12] Our patient had multiple heterogenous lesions in the liver, and extensive sclerotic lesions throughout the visualized bony structures on computed tomography scan. Bone scan showed increased tracer uptake in the spine, ribs, pelvis, and femoral heads bilaterally, and a pathological fracture of the lytic lesion of the left inferior pubic ramus was noted. Although the bone lesions could be due to metastatic prostate cancer, it is less likely because of a recent PSA level of 1.14 ng/mL.

Small-cell carcinoma of the bladder commonly affects elderly white men with gross hematuria. However, our patient was an African-American man who presented with lethargy due to hypercalcemia. Hypercalcemia is unusual in small-cell carcinoma in general, and has