



CASE REPORT

Hypercalcemia and Paraproteinemia in Squamous Cell Bladder Cancer

Neil G. Kumar, MS4, Sylvia L. Orozco-Do,
M.D., My Luu, MS4, Rami Mortada, M.D.
University of Kansas School of Medicine-
Wichita

Department of Internal Medicine

Introduction

Squamous cell carcinoma (SCC) comprises about 1.2 - 4.5% of all vesical tumors in the United States.¹ In contrast, it comprises almost 75% of all bladder cancers in areas endemic of *Shistosoma haematobium*. In non-bilharzial regions of the world, SCC involves chronic irritation, such as prolonged indwelling Foley catheters and chronic urinary tract infections, which confers up to 28-fold increased risk for SCC.² There are previous reports of humoral hypercalcemia and paraproteinemia associated with bladder cancers, but not simultaneously.³⁻⁷

We report the first known case of squamous cell carcinoma of the bladder with paraproteinemia and symptomatic hypercalcemia. We also review the literature on humoral hypercalcemia.

Case Report

A 54-year-old African-American female presented with complaints of weakness, urinary retention, and fever of approximately one-week duration. She had a history of multiple sclerosis with a chronic indwelling Foley catheter secondary to a neurogenic bladder. The initial examination in the emergency department showed an obstructed Foley catheter that when replaced, five mL of grossly bloody urine was returned.

The initial labs were significant for a creatinine of 15 mg/dL, BUN of 125 mg/dL, potassium of 5.7 mmol/mL, white blood cell

count of 12900 cells/mm³, and hemoglobin of 8.5 mg/dL. Iron studies were consistent with anemia of chronic disease.

A computed tomography of the pelvis showed bilateral severe hydro-nephrosis with circumferential thickening of the bladder wall. The patient was started on dialysis. Bilateral ureteral tubes failed to relieve the obstruction. Nephrostomy was necessary to drain the kidneys. After initial stabilization, cystoscopy was performed and a bladder tumor was identified. Pathology revealed a moderately differentiated squamous cell carcinoma with focal necrosis and invasion into the muscle wall.

During the hospital course, the patient had multiple electrolyte abnormalities that were corrected. However, she had persistent increased serum protein and symptomatic hypercalcemia of 12.0 mmol/mL that was unresponsive to intravenous hydration and loop diuretic therapy. The hypercalcemia was controlled by pamidronate.

Parathyroid hormone (PTH) and vitamin D were low. Serum and urine immunoelectrophoresis showed a monoclonal peak of 153 mg/dl of immunoglobulin Kappa light chain confirming paraproteinemia and a clinical picture suggestive of multiple myeloma. However, the bone marrow biopsy showed only 1% plasma cells. A skeletal survey and bone scan were negative. The diagnosis of monoclonal gammopathy of undetermined significance (MGUS) was made. Later, lab results for parathyroid

hormone-related peptide (PTH-rP) were found to be elevated, confirming the diagnosis of humoral hypercalcemia secondary to a paraneoplastic syndrome of the bladder tumor.

Ultimately, the patient was stabilized for surgery and underwent cystectomy, hysterectomy with bilateral oophorectomy, and bladder reconstruction. She had severe adhesions in her abdomen and metastatic disease in her peritoneal cavity. Her PTH-rP level dropped to normal after surgery. The patient declined transfer to a skilled nursing home and was discharged home against medical advice.

Discussion

The pathophysiology of hypercalcemia of malignancy is most commonly the result of two mechanisms, osteolytic and humoral.⁸ Osteolytic hypercalcemia occurs by invasion of the tumor into the bone, either by direct invasion or metastatic disease, commonly seen in breast cancer, lymphoma, and multiple myeloma.⁹ Interestingly, myeloma cells activate genes that result in a dysregulation of normal bone homeostasis, resulting in simultaneous stimulation of bone resorption and inhibition of bone formation.¹⁰

Humoral hypercalcemia of malignancy (HHM), first suggested by Albright in 1941,¹¹ is most commonly due to the secretion of parathyroid hormone-related peptide (PTH-rP) and less commonly a result of secretion of the active form of vitamin D, 1,25-dihydroxyvitamin D.³ It is commonly seen in squamous cell carcinoma of the lung, renal cancer, ovarian cancer, and endometrial cancer.⁹ PTH-rP, genetically different than the native variant, is a peptide that binds to the PTH receptor and stimulates osteoclastic bone resorption causing hypercalcemia.

The work-up for metastatic bone disease and multiple myeloma were negative. This

finding is still significant since paraproteinemia, such as MGUS, are associated to solid tumor and are able to bind calcium, causing hypercalcemia.^{7,12} Thus, the patient's hypercalcemia could be due to either HHM, a non-calcium-binding mechanism or paraproteinemia, which can be calcium-binding. The distinction was necessary since therapy is not indicated in the latter.

Hypercalcemia secondary to a calcium-binding paraprotein would be expected to be asymptomatic. The ionized calcium would be expected to be within normal limits. Treatment of hypercalcemia does not affect survival, but is necessary to prevent the complications of hypercalcemia in the interim before surgery.⁹

Our patient had increased ionized calcium along with a finding of PTH-rP, confirming HHM and ruling out a calcium-binding paraproteinemia. Even though one study⁷ suggested that paraproteinemia may be as high as 1.1% in patients with solid tumors, to our knowledge, this is the first report of a patient with HHM with the etiology of the elevated calcium being confounded by paraproteinemia.

Humoral hypercalcemia of malignancy is not uncommon and is well documented in squamous cell carcinomas of the esophagus, cervix, and lung, but is rarely documented in squamous cell carcinoma of the bladder. There have been prior reports of humoral hypercalcemia of malignancy in squamous cell carcinoma of the bladder, but to our knowledge this is the first reported case of hypercalcemia of squamous cell carcinoma of the bladder with an associated paraproteinemia.

References

- 1 Shokeir AA. Squamous cell carcinoma of the bladder: Pathology, diagnosis and treatment. *BJU Int* 2004; 93:216-220.

- ² Cohen SM, Johansson SL. Epidemiology and etiology of bladder cancer. *Urol Clin North Am* 1992; 19:421-428.
- ³ Wolchok JD, Herr HW, Kelly WK. Localized squamous cell carcinoma of the bladder causing hypercalcemia and inhibition of PTH secretion. *Urology* 1998; 51:489-491.
- ⁴ Desai PG, Khan SA, Jayachandran S, Ilardi C. Paraneoplastic syndrome in squamous cell carcinoma of urinary bladder. *Urology* 1987; 30:262-264.
- ⁵ Leobel AS, Walkoff CS. Hypercalcemia in neoplastic disease without bone metastases. *N Y State J Med* 1962; 62:101-104.
- ⁶ Eddeland A, Hedelin H. Bladder cancer associated with hypercalcaemia. A case report. *Scand J Urol Nephrol* 1980; 14:211-213.
- ⁷ Anagnostopoulos A, Galani E, Gika D, Sotou D, Evangelopoulou A, Dimopoulos MA. Monoclonal gammopathy of undetermined significance (MGUS) in patients with solid tumors: Effects of chemotherapy on the monoclonal protein. *Ann Hematol* 2004; 83:658-660.
- ⁸ Mundy GR, Ibbotson KJ, D'Souza SM, Simpson EL, Jacobs JW, Martin TJ. The hypercalcemia of cancer. Clinical implications and pathogenic mechanisms. *N Engl J Med* 1984; 310:1718-1727.
- ⁹ Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med* 2005; 352:373-379.
- ¹⁰ Trimarchi H, Lombi F, Forrester M, et al. Disodium pamidronate for treating severe hypercalcemia in a hemodialysis patient. *Nat Clin Pract Nephrol* 2006; 2:459-463.
- ¹¹ Albright F. Case reports of the Massachusetts General Hospital (Case 27461). *N Engl J Med* 1941; 57:789-791.
- ¹² Side L, Fahie-Wilson MN, Mills MJ. Hypercalcaemia due to calcium binding IgM paraprotein in Waldenström's macroglobulinaemia. *J Clin Pathol* 1995; 48:961-962.

Keywords: hypercalcemia, paraproteinemia, parathyroid hormone-related peptide, squamous cell carcinoma