CASE REPORT

Transitional cell carcinoma of the bladder producing Parathyroid hormone-related protein (PTHrP)

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Hypercalcemia associated with transitional cell carcinoma (TCC) is rarely encountered. We report a case of TCC of bladder with documented production of parathyroid hormone related protein (PTHrP). Our patient had a rapidly progressive course and died 2 months after radical cystectomy. Literature suggests that these patients present with advanced stage and carry a poor prognosis. The histopathologic features, treatment and prognosis associated with this rare paraneoplastic syndrome are reviewed.

Key Words: transitional cell carcinoma, bladder cancer, Parathyroid hormone-related protein, hypercalcemia

Hypercalcemia related to production of parathyroid hormone-related protein (r-PTH) is rarely seen with transitional cell carcinoma (TCC) of the bladder with squamous differentiation. The serological analysis suggested that tumor cells produced parathyroid hormone related protein. We report the clinicopathologic features of this case and review the current available literature.

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Case report

A 47 year old African American female presented with painless gross hematuria of 6 months duration. Cystoscopy with biopsy revealed invasive poorly

differentiated urothelial carcinoma. Abdominal and pelvic computerized tomography showed a 6.9 cm x 3.2 cm bladder mass. Preoperatively the white blood cell count was 8 k/cumm and calcium was 9.8 mg/dl (normal 8.4-10.2 mg/dl). She underwent cystourethrectomy, pelvic lymph node dissection with urinary diversion. Pathological examination showed invasive urothelial carcinoma with squamous differentiation. Tumor invaded the perivesicular fat and four out of 10 lymph nodes were positive for metastatic carcinoma. TNM staging was pT3a, pN2, pM0 bladder cancer. Postoperatively she developed right lower extremity deep venous thrombosis and coumadin was initiated.

One month after the operation she presented with fatigue, malaise, tiredness, back pain and lower extremity weakness. MRI of lumbar spine showed compression deformity of T6 vertebral body with abnormal enhancing tissue within the central canal extending to both neural foramina and paraspinal soft tissue. A CT guided biopsy was consistent with invasive urothelial carcinoma with squamous differentiation. She was started on steroids and radiation therapy was given at 30 Gy/10Fx to the pathologic compression. Laboratory evaluation showed elevated serum calcium levels of 14.0 mg/dl. Serum parathyroid hormone related protein was increased at 16.9 IU/L (normal 0.0-1.5 pmol/l). She was aggressively hydrated and treated with Zoledronic Acid. Her hypercalcemia was successfully treated initially as calcium levels decreased to 9 mg/dl. However, she subsequently developed small bowel ileus, hospital acquired pneumonia, recurrent hypercalcemia, progressive deep venous thrombosis and died 2 months after the operation.

Discussion

Solid tumors account for 80% to 90% of hypercalcemia in cancer. Renal cell carcinoma, breast cancer and squamous cell carcinoma of lung, esophagus and head and neck origin have the highest predilection. In approximately 80% of hypercalcemic patients with malignancy an elevated parathyroid hormone-related peptide (PTHrP) is increased.[1] PTHrP acts like parathroid hormone (PTH) by stimulating osteoclastic bone resorption and enhancing renal tubular calcium resorption.[2] Many cancers express the gene for PTHrP and has been correlated with poor prognosis.[3] Even in patients without humoral hypercalcemia, expression of PTHrP in tumor cells suggest that PTHrP is a local osteolytic factor.[4]

Paraneoplastic syndromes are uncommonly seen with TCC of bladder. While more than 20 reported cases of paraneoplastic hypercalcemia associated with TCC of bladder were reported in the literature, we found only four cases of TCC of bladder with documented elevated levels of PTHrP Table 1. One reported case of hypercalcemia with TCC of bladder was mediated through prostagladin production.[9] Few reported cases also had simultaneous leukocytosis with documented elevated serum levels of granulocyte-colony stimulating factor (GCSF).[5,6] Truong et al recently reported that patients presenting

TABLE 1. **Documented cases of hypercalcemia, elevated PTHrP levels and TCC of bladder**

Author	Age	Sex	Stage	Cell type	Calcium levels mg/dl	PTHrP levels pMol/l	Treatment	Outcome after development of hypercalcemia
Tsuchiya et al[5]	68	F	NR*	TCC	NR*	8.4	cystectomy	died 46 days
Kamai et al[6]	83	M	T2N0M0	TCC	13.8	7.1	cystectomy and post op XRT/chemo	died 1 month
Maeda et al[7]	47	F	T4N2M0	TCC	20.6	29.9	cystectomy	died 7 months
Hirasawa et al[8]	51	M	NR*	TCC/SCC	11.2	2	cisplatin-pirarubicin then cystectomy	alive at 40 months F/U
Chaudhary et al	47	F	T3N2M0	TCC/SCC	13	16.9	cystectomy	died 1 month

*not reported

with hypercalcemia and a wide variety of cancers (including five cases of bladder cancer) with elevated PTHrP levels were associated with higher pretreatment calcium levels and reduced responses to chemotherapy. Furthermore, elevated PTHrP levels were associated with increased mortality in patients younger than 65 years of age.[10]

Patients with elevated PTHrP and hypercalcemia usually present with advanced TCC and appear to have poor prognosis Table 1. In the acute setting aggressive hydration and treatment with bisphosphonates are usually effective in decreasing elevated serum calcium levels. Recently, in randomized clinical trials Zoledronic acid, a third generation bisphosphonate, was found to be superior to Pamidronate in treatment of hypercalcemia of malignancy.[11] However, the overall prognosis appears grim. Similarly our patient died within 2 months after the operation.

In conclusion, patients presenting with humoral hypercalcemia with elevated PTHrP levels in association with TCC of bladder have poor survival. Further, clinical and biologic studies are needed to clarify the role of mediators in hypercalcemia associated with TCC of bladder. □

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