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Case Report

A Rare Presentation of Hypercalcemia in a Patient with Urothelial Adenocarcinoma

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Abstract

Introduction

Hypercalcemia is rare in urothelial cell carcinoma. When it does occur, it is typically through a PTHrP-mediated process although this case was not found to have a definitive etiology.

Material and Methods

A 58-year-old male presented with mental confusion, unsteady gait, and bladder distension due to hypercalcemia. Imaging showed recurrent urothelial carcinoma confirmed by tissue biopsy and immunohistochemical staining.

Result and Discussion

The patient's workup was negative for a PTHrP-mediated process or for osteolytic metastases causing bone destruction. The underlying mechanism of his hypercalcemia was unclear as it did not fit the typical pattern of paraneoplastic hypercalcemia. The patient had good response to supportive therapy but he continued to have acute episodes of hypercalcemia until his demise 5 months later.

Conclusion

Despite an extensive laboratory and radiologic workup, we were unable to show a definite etiology for his hypercalcemia. The most likely cause was through a paraneoplastic process mediated by a PTHrP-like molecule, however the identity and nature of this molecule remains to be discovered. It is important to be aware of this presentation and to suspect it in a patient with supporting clinical symptoms.

KeyWords: Hypercalcemia; Urothelial Cell Adenocarcinoma; Paraneoplastic Hypercalcemia

3. Introduction

Paraneoplastic hypercalcemia is a common syndrome and it is estimated to occur in up to 20-30% of cancer patients [1, 2]. The development of hypercalcemia portends a poor prognosis as it is generally associated with advanced disease with only 30 day median survival after the first episode [3,4]. The most common cancers associated with hypercalcemia are lung, renal cell, breast, and multiple myeloma [5]. Currently the understood mechanisms for paraneoplastic hypercalcemia are PTHrP-related hypercalcemia (80%), osteolytic hypercalcemia (20%), excess extrarenal vitamin D (<1%) and ectopic hyperparathyroidism (<1%) [2].

Paraneoplastic hypercalcemia associated with urothelial carcinoma is rare. One observational study of urogenital malignancies found only 6 instances of hypercalcemia out of 321 cases of bladder cancer (1.9% incidence) [6]. The major causes of paraneoplastic hypercalcemia in urothelial carcinoma are overproduction of PTHrP [7-10] or more rarely osteolytic bone metastases [11] . We report an unusual case of hypercalcemia by unknown mechanism in a patient with relapsed urothelial carcinoma.

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Case Report

The patient is a 58-year-old male with a history of urothelial cell carcinoma invading into muscle, Stage 3 (pT3N0) who was treated with neoadjuvant chemotherapy with cisplatin and gemcitabine. He then underwent radical cystectomy followed by urinary diversion via creation of a neobladder. He was doing well until 13 months later when he presented to the Emergency Department for bladder distension, difficulty self-catheterizing, mental confusion, and unsteady gait. The initial laboratory results show an unexpected elevation of calcium to 16.0 mg/dL (8-10.4 mg/dL), with repeat ionized calcium 9.6 mg/dL (4.5-5.6 mg/dL). Electrocardiogram (EKG) showed tachycardia with shortened QT interval (291ms). On review of symptoms he endorsed unintentional weight loss of 7 kilograms, night sweats, and generalized weakness.

The patient was admitted and further workup showed parathyroid hormone (PTH) 6.0 pg/mL (15-65 pg/mL), PTHrP 1.8 pmol/L (<2.0 pmol/L), 1,25-dihydroxyvitamin D 81.5 pcg/dL (19.9-79.3 pcg/dL), serum and urine protein electrophoresis did not reveal M protein, and angiotensin converting enzyme (ACE) 31 U/L (14-82 U/L). Computer tomography (CT) urogram demonstrated a new 11 x 7 x 10 cm heterogeneous enhancing mass with indistinct margins in the pelvis consistent with recurrent bladder cancer (Figure 1). CT chest/abdomen/pelvis showed interval increase in size of a right upper lobe pulmonary nodule (7 mm) and new 1.2 cm lesion in the left hepatic lobe concerning for metastatic progression. A bone scan did not reveal any acute bony lesions. Biopsy of the pelvic mass and pulmonary nodule revealed poorly differentiated carcinoma with squamous features which was morphologically similar to his initial biopsy. Immunohistochemical profiles supported morphologic findings with positive staining for thrombomodulin, Lu-5 and p63 from the pelvic tissue and positive thrombomodulin and P40 in the lung tissue favoring urothelial origin (Figure 2). Both lung and pelvic tissues were negative for GATA-3 and uroplakin which is unusual but can be negative in up to 33% of cases and usually portends a more aggressive tumor.

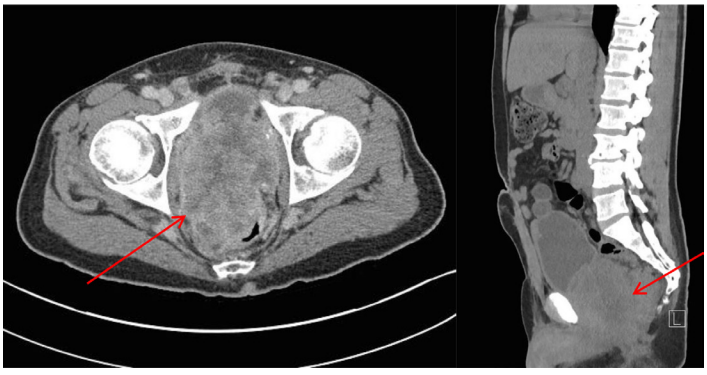

Figure 1. CT urogram demonstrated a large heterogeneous mass in the pelvis measuring 11 x 7 x 10 cm with indistinct borders and mass effect against the rectum

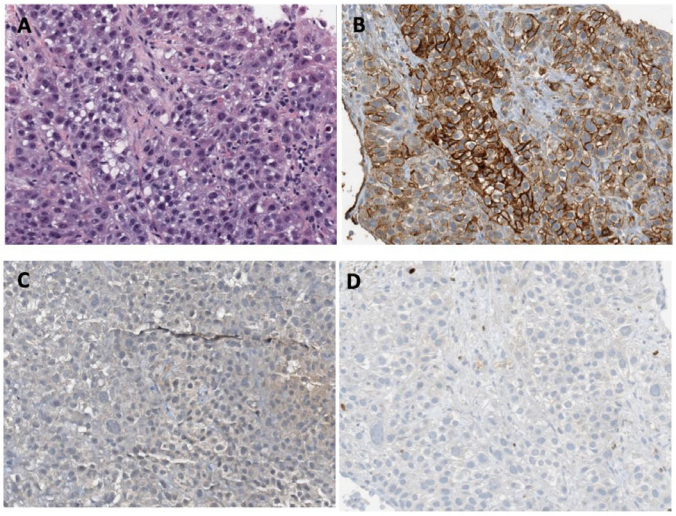

Figure 2. Biopsy of pelvic mass showed: A) Epithelioid malignant cells with enlarged nuclei, prominent nucleoli, moderate to abundant cytoplasm, and squamous differentiation (H&E 20XB.) Tissue immunohistochemical staining was positive for thrombomodulin (B), negative for uroplakin (C), and negative for GATA 3 (D) consistent with patient's prior urothelial cell carcinoma

The patient's hypercalcemia was treated supportively with intravenous fluids, calcitonin 300 IU/ml units and zoledronic acid 4mg with improvement of serum calcium to 9.5 mg/dL (8-10.4 mg/dL). He was started on palliative radiation therapy and immunotherapy with atezolizumab, a monoclonal antibody against programmed cell death-ligand 1 (PD-L1). Unfortunately the patient experienced two additional episodes of acute hypercalcemia prompting inpatient admission for supportive therapy. Five months after diagnosis he passed away at home on hospice care.

Discussion

This patient's presentation was most consistent with a paraneoplastic process as his hypercalcemia did not occur until he had a relapse of his urothelial carcinoma. However the exact mechanism underlying this patient's hypercalcemia could not be elucidated. The most common etiologies for hypercalcemia of malignancy are overproduction of PTHrP or bone destruction from osteolytic metastases. In this case, the patient had a low level of PTHrP 1.8 pmol/L (repeat was 1.6 pmol/L) which does not support PTHrP-mediated hypercalcemia. Furthermore, this patient had no evidence of bony metastases on bone scan that could explain his hypercalcemia. The patient also had decreased levels of PTH suggesting normal physiologic suppression as well as normal levels of 1,25-dihydroxyvitamin D. The workup for other unusual causes for hypercalcemia such as sarcoidosis was negative.

Hypercalcemia is a rare sequela of urothelial carcinoma. In reported literature, the most common mechanism of hypercalcemia in urothelial carcinoma is due to overproduction of PTHrP [7-10] . One hypothesis for this patient's hypercalcemia is that the tumor was producing PTHrP that could not be measured in the plasma but still caused a physiologic response. In a case of relapsed transitional cell carcinoma with PTHrP mediated hypercalcemia reported by Matsuoko et al., PTHrP was detected in the serum and in the tumor tissue by immunohistochemical studies. It is possible that this patient's tumor tissue could have been expressing PTHrP, though it was never formally tested as it is not a standard diagnostic test for hypercalcemia. Another hypothesis for this patient's hypercalcemia is that his malignancy was producing another molecule that induced hypercalcemia that current laboratory technology is unable to measure. PTHrP was not able to be quantitatively measured until 1987, but the idea of a parathyroid hormone like molecule was surmised as early as the 1940s [12]. Currently PTHrP is thought to induce hypercalcemia by binding to PTH receptors in the tissues as well as playing a role as a local factor in the bone environment by regulating endochondral bone development. It is feasible that this patient's tumor cells produced a molecule that mimics PTHrP structurally or functionally but has not yet been identified.

Conclusion

This case illustrates a rare presentation of recurrent metastatic urothelial carcinoma presenting with acute hypercalcemia. The patient was found to have acute hypercalcemia with subsequent workup showing low PTHrP, unremarkable 1,25-dihydroxyvitamin D, negative M protein on serum and urine electrophoresis, and bone scan without osteolytic metastases. CT urogram showed a new pelvic mass and tissue biopsy confirmed recurrent metastatic urothelial carcinoma. Despite exhaustive laboratory and radiologic workup, we were unable to find a definite etiology of his hypercalcemia. The most likely cause of hypercalcemia in this patient is through a paraneoplastic process mediated by a PTHrP-like molecule but the identity and nature of this molecule remains to be elucidated. Although hypercalcemia is rarely associated with urothelial cell carcinoma, it is important to be aware of this presentation and to have a high index of suspicion in a patient with clinical symptoms. The views expressed are those of the authors and do not reflect the official views of the Department of Defense or its Components.

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