Humoral Hypercalcemia in Uterine Cancers: A Case Report and Literature Review

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Patient: Female, 53
Final Diagnosis: Endometrial stromal sarcoma
Symptoms: Abdominal distension
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare co-existence of disease or pathology
Background: Paraneoplastic hypercalcemia is a well-described complication associated with a variety of malignancies. However, its incidence in gynecological malignancies is low.

Case Report: A 53-year-old woman presented with progressive abdominal distention and irregular vaginal bleeding of several weeks' duration. A contrast CT abdomen and pelvis was significant for a mass in the lower uterine/cervical region, multiple peritoneal and omental masses, enlarged pelvic and paraaortic lymph nodes, and large-volume ascites. A pelvic exam revealed a fungating vaginal mass, with biopsy showing a high-grade tumor with immunohistochemical staining positive for vimentin, CD10, and cyclin D1, consistent with endometrial stromal sarcoma. During her hospitalization, the patient became increasingly lethargic. Workup showed severe hypercalcemia and evidence of acute kidney injury. The patient did not have evidence of bony metastatic disease on imaging studies. Further laboratory evaluation revealed an elevated PTHrP of 301 pg/mL (nl 14–27), a depressed PTH level of 3 pg/mL (nl 15–65), and a depressed 25-OH vitamin D level of 16 ng/mL (nl 30–100), consistent with humoral hypercalcemia of malignancy. The patient was treated with pamidronate, calcitonin, and intravenous fluids. She eventually required temporary hemodialysis and denosumab for refractory hypercalcemia, which improved her electrolyte abnormalities and clinical status.

Conclusions: Uterine malignancies of various histologies are increasingly recognized as a cause of humoral hypercalcemia. They are an important differential diagnosis in a woman with hypercalcemia and abnormal vaginal bleeding or abdominal symptoms.

MeSH Keywords: Paraneoplastic Endocrine Syndromes • Parathyroid Hormone-Related Protein • Uterine Neoplasms

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/900088
**Background**

Paraneoplastic hypercalcemia is a serious and fairly common syndrome associated with a variety of malignancies, including breast cancer, multiple myeloma, squamous cell carcinomas, and lymphomas. Its occurrence in gynecological malignancies is rare. We present a case of paraneoplastic hypercalcemia in a patient with a high-grade uterine malignancy.

**Case Report**

A 53-year-old woman presented to our institution with progressive abdominal distention and irregular vaginal bleeding of several weeks’ duration. A contrast CT abdomen and pelvis revealed an ill-defined, irregular mass in the lower uterine/cervical region (Figure 1). There were multiple peritoneal and omental masses, enlarged pelvic and paraaortic lymph nodes, and large-volume ascites. The initial CBC was significant for hemoglobin of 9.2 g/dL, leukocytosis of 36 790 per microliter, and thrombocytosis of 625 000 per microliter. Serum calcium was elevated at 13.1 mg/dL. BUN and creatinine were within normal limits. Hepatic function was within normal limits. A pelvic exam revealed a fungating vaginal mass. The patient underwent biopsies of the endometrium and the vaginal mass, which revealed a high-grade tumor with predominantly oval-shaped cells. Immunohistochemical staining was positive for vimentin, CD10, and cyclin D1, consistent with a diagnosis of high-grade endometrial stromal sarcoma (Figure 2). The tumor was negative for ER, with rare cells positive for PR. Although immunohistochemical staining for cytokeratins was negative, a biphasic component could not be entirely ruled out given the small size of the biopsy specimen relative to the tumor.

The patient’s Ca125 was markedly elevated at 1624 U/mL (nl ≤34). Contrast CT chest revealed a right-sided pleural effusion but no suspicious nodules or lymphadenopathy. The patient was deemed to have operable disease and was scheduled for debulking surgery. However, preoperative laboratory studies showed that her serum calcium had further increased to 19.2 mg/dL. She had also developed evidence of acute kidney injury, with her BUN rising to 37 mg/dL and creatinine to 1.81 mg/dL. On physical exam, she was noted to be lethargic, with dry mucous membranes. The surgery was cancelled due to the patient’s medical instability.

Further workup revealed an elevated PTHrP of 301 pg/mL (nl 14–27), a depressed PTH level of 3 pg/mL (nl 15–65), and a depressed 25-OH vitamin D level of 16 ng/mL (nl 30–100), consistent with humoral hypercalcemia of malignancy. The patient was treated with pamidronate, calcitonin, and intravenous fluids. She eventually required temporary hemodialysis and denosumab for refractory hypercalcemia.

The patient improved with regard to her electrolyte abnormalities. Given the extent of her disease, she was planned for neoadjuvant chemotherapy followed by surgery if a good response...
was achieved. She was started on a regimen of carboplatin and paclitaxel, which she received for 3 cycles. She also had palliative radiation to the uterus to control bleeding. However, her disease failed to respond significantly to chemotherapy, and she ultimately died from complications of malignancy.

Discussion

Hypercalcemia occurs in about 20–30% of cancer patients and may arise via 3 different mechanisms. Humoral hypercalcemia of malignancy accounts for 80% of cases and is the result of excessive PTHrP secretion by the tumor. Twenty percent of cases...
are attributed to local osteolytic hypercalcemia, in which osteolytic metastases result in osteoclast-mediated resorption of the surrounding bone; breast cancer and multiple myeloma are typical causes. Less than 1% of malignancy-related hypercalcemia is due to tumor production of calcitriol, usually seen in lymphomas. Hypercalcemia typically manifests late in the course of malignancy and portends a poor prognosis [1,2].

The amino terminus of PTHrP shares a similar structure with that of PTH. Both activate the PTH/PTHrP receptor 1, stimulating increased bone resorption and decreasing the renal clearance of calcium. Humoral hypercalcemia of malignancy is commonly associated with squamous cell carcinomas, renal cell carcinomas, genitourinary malignancies, and breast cancers [1–3].

Although hypercalcemia is a fairly common paraneoplastic syndrome, its occurrence in gynecological malignancies is rare. A systematic review of humoral hypercalcemia related to gynecologic malignancies identified 34 cases occurring between 1984 and 2006: 22 ovarian, 6 uterine, 4 vulvar, and 2 cervical malignancies were identified. All of the patients with vulvar and cervical cancer had squamous cell carcinoma. Clear cell carcinoma was the predominant histology in patients with ovarian cancer, occurring in 10 out of 22 patients, and in patients with uterine cancer, occurring in 3 out of 6 patients. The remaining 3 patients with uterine cancer had papillary serous carcinoma, endometrioid adenocarcinoma, and leiomyosarcoma [4]. Since the publication of the aforementioned review, 3 more cases of uterine corpus malignancies associated with humoral hypercalcemia have been reported in the English literature (1 case each of endometrioid carcinoma, carcinosarcoma, and clear cell carcinoma) [5–7].

Endometrial stromal sarcomas are rare mesenchymal malignancies that include low- and high-grade variants [8,9]. Hysterectomy is the treatment of choice for disease limited to the uterus. With more advanced intraabdominal disease, the benefit of cytoreductive surgery is controversial. Systemic therapy with or without radiation is recommended for unresectable disease [10]. To date, there have been no previous reports of paraneoplastic hypercalcemia associated with endometrial stromal sarcoma.

Interestingly, humoral hypercalcemia has also been reported in association with benign uterine conditions, such as leiomyomas and normal and hyperplastic endometrium [11–15]. Mylonas et al. demonstrated the presence of PTHrP in normal, hyperplastic, and malignant endometrial tissue via immunohistochemical staining of PTHrP antibody. The highest expression of PTHrP was observed in adenomatous hyperplasia grade III, a precursor of endometrial cancer. Stromal and myometrial cells were also shown express PTHrP [15].

Conclusions

In summary, we report a rare case of humoral hypercalcemia occurring as a paraneoplastic syndrome in the setting of a high-grade uterine malignancy. Uterine malignancies of various histologies are increasingly being recognized as a cause of humoral hypercalcemia. They are an important differential diagnosis in a woman with hypercalcemia and abnormal vaginal bleeding or abdominal symptoms.

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