Mixed Serous and Clear Cell Adenocarcinoma of the Ovary Presenting with Symptomatic Hypercalcemia: A Case Report and Clinical Considerations

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INTRODUCTION

Hypercalcemia, defined by a serum calcium level above the upper limit of normal of 10.5 mg/dL, is estimated to occur in 2% of patients with malignancy; however, it is more common in certain tumor types.¹ The most commonly associated tumor types are multiple myeloma, squamous cell, breast, and renal carcinoma.³ Although two-thirds of patients with small ovarian carcinoma of hypercalcemic type present with hypercalcemia, only a few cases in the literature document other ovarian carcinoma histologic types presenting with hypercalcemia.² Three case reports are documented in the literature of clear cell ovarian cancer presenting with hypercalcemia.³⁵ Hypercalcemia can lead to complications, including QT shortening and cardiac arrhythmias, acute kidney injury, and nephrogenic diabetes insipidus presenting as polyuria and polydipsia.⁶ We present a case of mixed serous and clear cell ovarian adenocarcinoma in which hypercalcemia was the presenting sign.

CASE PRESENTATION

Presenting Concerns

A 60-year-old woman with a history of hypertension and hyperlipidemia presented to the outpatient clinic with weakness, nausea, emesis, constipation, and an unintended 9-kg (20-lb) weight loss. Her calcium level was elevated at 15.7 mg/dL (reference range = 8.5-10.3 mg/dL). She was treated for hypercalcemia and subsequently admitted to the hospital 4 times because of recurrence of symptoms. On outpatient workup, she was noted to have an abnormal positron emission tomography scan showing intense activity in the uterus consistent with malignancy. An exploratory laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node staging was performed, and pathologic findings demonstrated high-grade ovarian carcinoma with serous and clear cell features.

Discussion:

Hypercalcemia is a rare but possible primary presenting symptom of ovarian cancer. In these patients, serum calcium measurements could possibly serve as a tumor marker for disease.

Therapeutic Intervention and Treatment

The patient received a potassium supplement, intramuscular administration of calcitonin, and intravenous (IV) fluid hydration, and she was admitted to the hospital for further workup. After treatment with IV fluids, calcitonin, and zoleodronic acid, her calcium level decreased to 11.5 mEq/L. With improvement of her nausea and vomiting, the patient was discharged. It was recommended that...
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Approximately 1 week later, the patient returned to the Emergency Department with similar symptoms and was found to have an elevated calcium level of 15 mEq/L. She was given IV fluids and pamidronate, which improved her symptoms. She was discharged, with further workup to be done on an outpatient basis. This patient presented a total of 4 times to the Emergency Department with similar symptoms of hypercalcemia, as shown in Figure 1.

A bone marrow biopsy was performed, and the specimen demonstrated trilineage hematopoiesis without signs of myeloma. Specifically, it showed reticulin myelofibrosis, erythroid hyperplasia, 1% blasts, and 5% to 10% plasma cells, which appeared polytypic. Flow cytometry found a small plasma cell population of 0.2%. A skeletal survey was negative for lytic lesions. The PTH-related polypeptide level was greatly elevated (218 pg/mL; reference range = 14-27 pg/mL), suggesting paraneoplastic hypercalcemia. A computed tomography scan of her chest, abdomen, and pelvis showed an enlarged and lobulated uterus, likely secondary to underlying uterine fibroids. An outpatient positron emission tomography scan (Figure 2) showed intense activity in the uterus consistent with malignancy.

An exploratory laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node staging was performed. Surgery showed a 10-cm necrotic mass arising from the left adnexa. At the end of the procedure, the tumor was considered optimally debulked, with no gross residual disease. All resected periaortic and pelvic lymph nodes were negative. Initial staging of the 10-cm pelvic mass demonstrated International Federation of Gynecology and Obstetrics (FIGO) stage IIC, grade 3 (T2c, N0, M0). Results of pathologic evaluation demonstrated high-grade ovarian carcinoma with serous and clear cell features. The pathologic findings were confirmed by 3 different pathologists as serous and clear cell, lacking features of small cell carcinoma of hypercalcemic type. Images of the pathologic studies are shown in Figure 3. A genetic cancer panel revealed no germline mutations.

Table 1. Preoperative and postoperative laboratory values

<table>
<thead>
<tr>
<th>Test</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium, mEq/L</td>
<td>8.0</td>
<td>5.8</td>
<td>8.5-10.3</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>3.0</td>
<td>3.9</td>
<td>3.5-5.3</td>
</tr>
<tr>
<td>Urea nitrogen, mg/dL</td>
<td>35</td>
<td>10</td>
<td>7-27</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.91</td>
<td>1.07</td>
<td>≤ 1.11</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.4</td>
<td>NA</td>
<td>3.7-5.7</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>9</td>
<td>8.4</td>
<td>11.5-15.0</td>
</tr>
</tbody>
</table>

NA = not applicable
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**CLINICAL MEDICINE**

**Follow-up and Outcomes**

Laboratory values available both preoperatively and postoperatively are shown in Table 1. Of note, her calcium level decreased from 8.0 mEq/L preoperatively to 5.8 mEq/L postoperatively. Although, after her surgery, the patient’s calcium level transiently dipped, it normalized before discharge and remained normal on follow-up laboratory testing.

Adjuvant dose-dense carboplatin and paclitaxel chemotherapy was given for 6 cycles. Therapy was complicated by grade 3 chemotherapy-induced peripheral neuropathy and pancytopenia. The patient is currently receiving follow-up to monitor for a possible recurrence. No serum CA-125 levels were available for this patient. The patient gave written informed consent for this case report. Figure 4 shows a timeline of the case.

**DISCUSSION**

Ovarian cancer is the fifth leading cause of cancer deaths among women, making it the most deadly gynecologic malignancy.7 Ovarian cancer notoriously presents with an insidious onset of vague symptoms, including fatigue, abdominal distention, postmenopausal bleeding, and/or early satiety.8 Because of the lack of screening methods for ovarian cancer, only 15% of cases are detected at stage I disease, before spread beyond the ovary.9 This case report describes a patient with pathology-confirmed mixed serous and clear cell carcinoma of the ovary who presented with hypercalcemia. Causes of hypercalcemia besides humoral hypercalcemia of malignancy include primary hyperparathyroidism, local osteolysis, ectopic parathyroid hormone in malignancy, granulomatous diseases, thyrotoxicosis, vitamin D intoxication, use of thiazide diuretics, and lithium use.10 There are currently 3 case reports of clear cell carcinoma presenting with hypercalcemia.1-3 However, this is the first known case report to date of mixed clear cell and serous ovarian carcinoma presenting with hypercalcemia.1-3 From this case report, one can infer that two-thirds of patients with this type of small cell carcinoma present with elevated serum calcium levels.2 Three pathologists

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**Figure 4. Timeline of the case.**

CT = computed tomography; ED = Emergency Department; FIGO = International Federation of Gynecology and Obstetrics; IV = intravenous; IVF = intravenous fluids; K+ = potassium; labs = laboratory tests; PET = positron emission tomography; pre-op = preoperative; post-op = postoperative; PTH = parathyroid hormone; PTHrP = parathyroid hormone-related polypeptide; s/p = status post; Vit = vitamin.

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A 60-year-old woman with a history of hypertension and hyperlipidemia presented with weakness, nausea, emesis, constipation, an unintentional 20-lb weight loss, and an outpatient calcium level of 15.7 mg/dL.

ED labs: PTH, < 3 pg/mL [10-65 pg/mL]; phosphate, 3.0 mg/dL [2.7-4.5 mg/dL]; Vit D, 25-OH, 19 ng/mL [20-79 ng/mL]; K+ 3.0 mEq/L [3.5-5.3 mEq/L]

Initial treatments: Potassium supplement, intramuscular calcitonin, IV fluid hydration, zoledronic acid

Calcium level normalized to 11.5 mEq/L [8.5-10.3 mEq/L]; nausea and vomiting improved; patient was discharged

Outpatient labs: PTHrP, 218 pg/mL (normal range, 14-27), suggesting paraneoplastic hypercalcemia

Chest, abdomen, and pelvis CT scan: Enlarged and lobulated uterus
PET scan: Intense activity in the uterus consistent with malignancy, and mild activity in the pancreas and left adrenal gland

Patient re-presented to the ED with abdominal pain, nausea, and vomiting. Her symptoms improved s/p IV fluids, pamidronate, and calcitonin

Pre-op serum calcium, 8.0 mEq/L

Surgery: Exploratory laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node staging; 10-cm pelvic mass demonstrated FIGO stage IIC, grade 3 (T2c, N0, M0).

Post-op serum calcium, 5.8 mEq/L

Calcium normalized and remained within normal limits
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independently confirmed this patient’s tumor type as lacking small cell features. Measurement of the CA-125 antigen is the most commonly used tumor marker for screening and monitoring ovarian cancer. The CA-125 is elevated in 50% of patients with limited disease and in 80% of patients with advanced ovarian cancer. In this patient, the change in calcium over time, as shown in Figure 1, demonstrates a reasonable surrogate tumor marker. Although the patient is doing well in follow-up, we continue to monitor her calcium levels in case of a recurrence. Further studies are warranted to address the question of using calcium measurements in similar patients as a tumor marker to monitor for recurrence of disease.

CONCLUSION
This case demonstrates the successful resolution of paraneoplastic syndrome of hypercalcemia with the surgical treatment of ovarian cancer. This case is intended to provide education about the possibility of ovarian cancer presenting with hypercalcemia and to remind practitioners to keep ovarian cancer in the differential diagnosis of hypercalcemia.

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Author Contributions
Julia Boland participated in acquisition and analysis of the data, and drafting and submission of the final manuscript. Darius Shahbazi; Stephen Wang, MD; and Shahin Shahbazi, MD, participated in analysis of the data and drafting the final manuscript. All authors have given final approval to the manuscript.

How to Cite this Article

References

Disclosure Statement
The author(s) have no conflicts of interest to disclose.