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

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ABSTRACT

Introduction: Hypercalcemia is a common phenomenon in patients with cancer but is more common among certain cancer types. Hypercalcemia in ovarian cancer is the common presenting sign in small cell carcinoma of the ovary, hypercalcemic type; however, there are no known documented cases of hypercalcemia as the presenting sign for mixed serous and clear cell adenocarcinoma. This case report describes symptomatic hypercalcemia as the presenting sign of mixed serous and clear cell carcinoma of the ovary.

Case Presentation: A 60-year-old woman with a medical 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.

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.[1] 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.[3-5] 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 with weakness, nausea, emesis, constipation, and an unintended 9-kg (20-lb) weight loss. Her outpatient calcium level was elevated at 15.7 mg/dL (reference range = 8.5-10.3 mg/dL). The change in calcium levels over time is plotted in Figure 1. She had no family history of cancer. She was subsequently referred to the Emergency Department for workup of the hypercalcemia and found to have acute kidney injury and hypokalemia. Her potassium and other abnormal preoperative laboratory values are shown in Table 1.

Her serum level of parathyroid hormone (PTH) intact was below 3 pg/mL (reference range = 10-65 pg/mL); the phosphorus level result was normal at 3.0 mg/dL (reference range = 2.7-4.5 mg/dL); and the 25-hydroxyvitamin D level was 19 ng/mL (reference range = 20-79 ng/mL), which excluded diagnoses of primary hyperparathyroidism or hypervitaminosis D. The patient denied taking vitamin D, vitamin A, or calcium supplements. She reported drinking little milk.

A serum protein electrophoresis study was obtained and was remarkable only for a low total protein level of 5.6 g/dL (6.0-7.7 g/dL) and a low albumin level of 3.06 g/dL (reference range = 4.0-5.0 g/dL). The β2-microglobulin level was elevated at 3592 μg/L (reference range = 900-2300 μg/L). Kappa/λ light chains measured 1.80 mg/L (reference range = 0.26-1.65 mg/L). Kappa free light chains were elevated at 35.20 mg/L (reference range = 3.30-19.40 mg/L). There also was a protein spike of monoclonal IgG λ type. A 24-hour urine protein concentration was elevated at 221 mg (reference range = 0-150 mg/total volume). A urine protein electrophoresis result was negative for a monoclonal protein. Thus, monoclonal gammopathy of undetermined significance was diagnosed. Her low hemoglobin level (9 g/dL) was likely secondary to chronic inflammation.

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 zoledronic 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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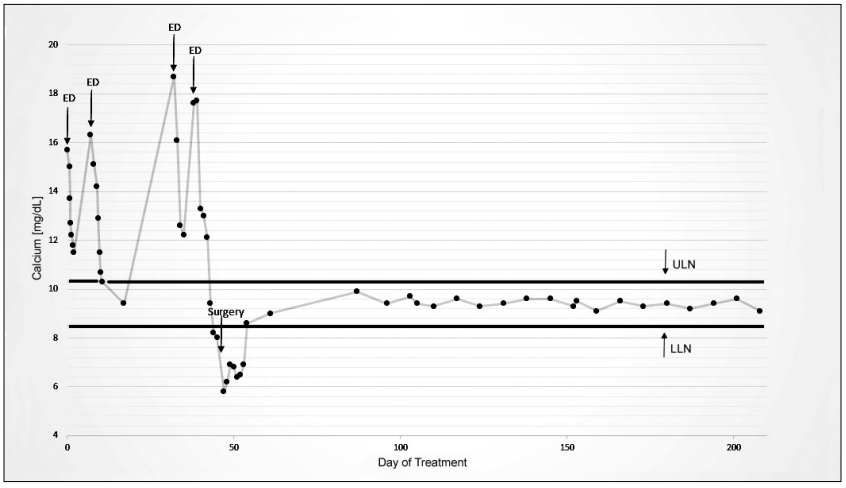

Figure 1. Change in serum calcium levels over time. Time 0 was defined as the day of the patient's first Emergency Department (ED) visit. Her 4 ED visits are noted, along with the day of surgery. Upper limit of normal (ULN) and lower limit of normal (LLN) for serum calcium level at our institution (8.5-10.3 mg/dL) are displayed.

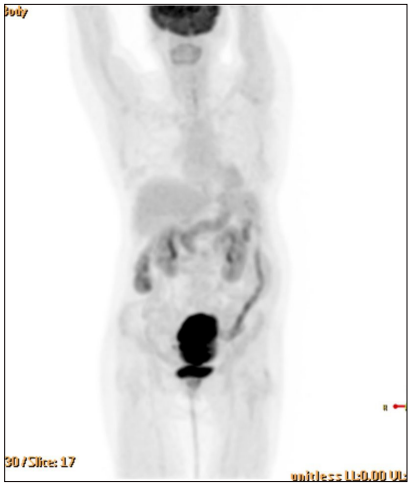

Figure 2. Positron emission tomography scan demonstrating intense activity in the uterus consistent with malignancy.

she follow-up with an oncologist as an outpatient.

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 and mild activity in the pancreas and left adrenal gland.

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.

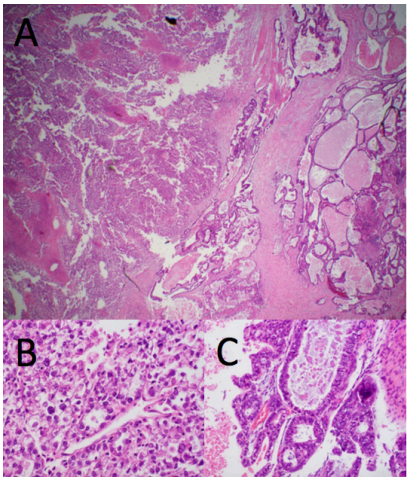

Figure 3. Histopathologic findings. A. Mixed clear cell and serous carcinoma of the ovary (4× magnification). B. Clear cell histologic features of pleomorphic high-grade nuclei and clear cytoplasm (20× magnification). C. Serous carcinoma of the ovary demonstrating pleomorphic high-grade nuclei, coarse chromatin, and prominent nucleoli (20× magnification, hematoxylin-eosin stain).

Table 1. Preoperative and postoperative laboratory values

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

NA = not applicable

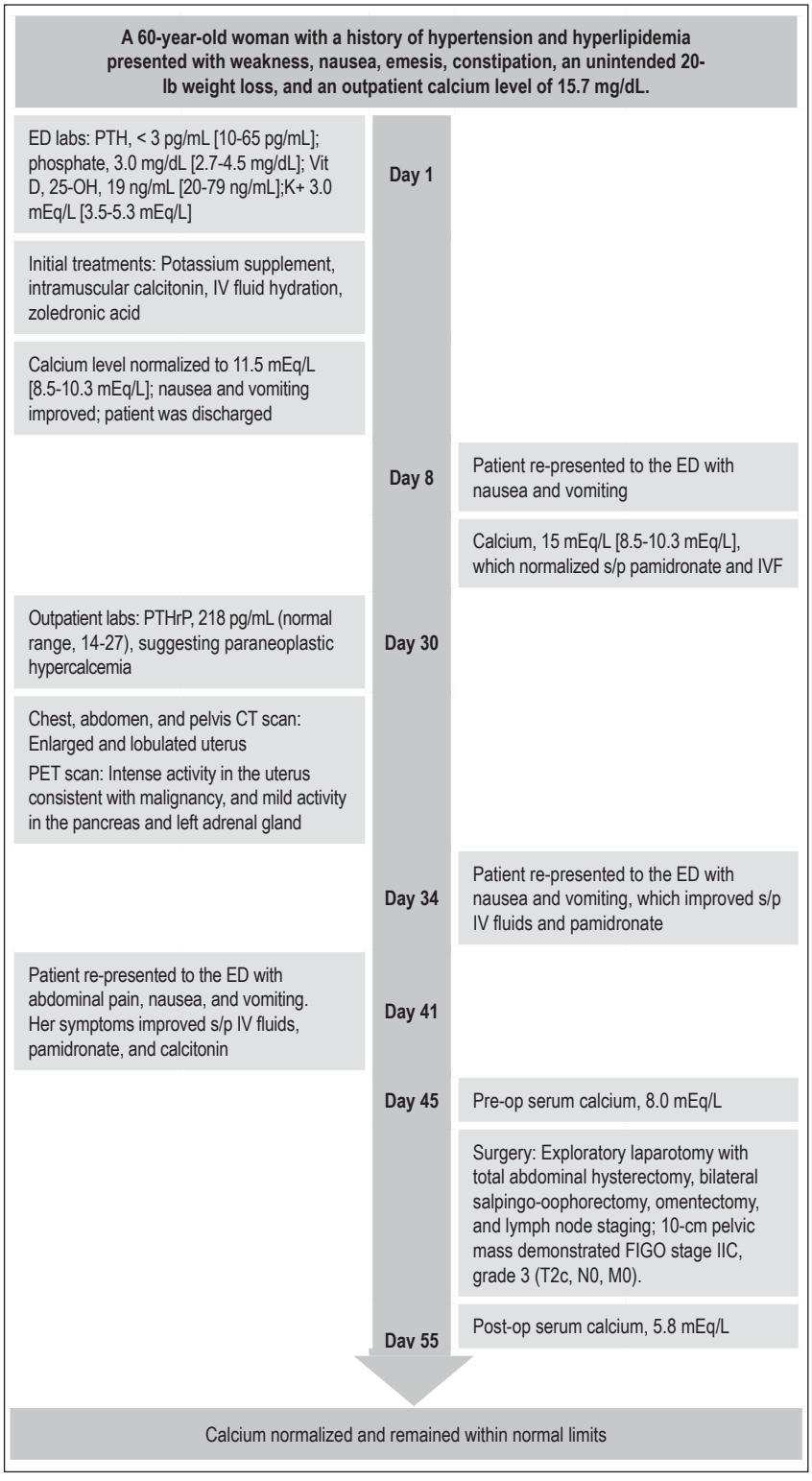

Figure 4. Timeline of the case.

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.

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.[3-5] However, this is the first known case report to date of mixed clear cell and serous ovarian carcinoma presenting as such. Numerous case reports document small cell carcinoma of the ovary, hypercalcemic type presenting with hypercalcemia, because two-thirds of patients with this type of small cell carcinoma present with elevated serum calcium levels.[2] Three pathologists

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.[11] The CA-125 is elevated in 50% of patients with limited disease and in 80% of patients with advanced ovarian cancer.[11] 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. ❖

Disclosure Statement

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

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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.

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