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CASE REPORT

Parathyroid Hormone Related Peptide Hypercalcemia as a Presentation of Endometrial Clear Cell Carcinoma

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Abstract

Hypercalcemia is a frequent complication of solid tumors and hematologic malignancies yet is only rarely associated with endometrial clear cell carcinoma. Here we report on a 70-year-old female who presented in the context of hip fracture and was incidentally found to have humoral hypercalcemia of malignancy secondary to endometrial clear cell carcinoma. This rare association makes endometrial cancer one of the differential diagnoses to be considered when assessing incidentally found symptomatic or asymptomatic hypercalcemia in the appropriate patient population.

Keywords: Hypercalcemia, Endometrial clear cell carcinoma, PTHrP, HHM, Humoral hypercalcemia of malignancy

1. Introduction

Hypercalcemia is a relatively common complication in patients with solid or hematologic malignancy, occurring in 20−30 percent of cases.[1,2] The pathophysiologic mechanisms of hypercalcemia vary and may involve a combination of local osteolysis, secretion of 1,25 $(OH)_2$ vitamin D, secretion of parathyroid hormone (PTH), or humoral hypercalcemia of malignancy secondary to ectopically produced parathyroid hormone related peptide (PTHrP)[3,4]. While PTH and PTHrP are antigenically, structurally, and functionally similar − they share a nearly-homologous amino terminus and activate the PTH/PTHrP receptor 1 in the kidney and bone[5] − a number of critical differences have been noted.[6] PTHrP, in contrast to PTH, which is secreted exclusively by the parathyroid glands, is secreted by a number of normal and malignant tissues, demonstrates significant C-terminal peptide variability, and divergent functional domains.[6] PTHrP's dysregulated secretion by tumor cells leads to increased bone resorption and reduced renal calcium excretion via the PTH/PTHrP 1 receptor and resultant hypercalcemia.[5]

Gynecologic malignancies are rarely associated with humoral hypercalcemia of malignancy.[7] Here we present a case of humeral hypercalcemia of malignancy secondary to endometrial clear cell carcinoma, a rare malignant uterine tumor.

2. Case presentation

A 70-year-old woman presented to the emergency department after a mechanical fall sustained three days prior with sharp, left-sided hip pain radiating to the groin. Since her fall, she had been unable to bear weight on the affected extremity. On further review of symptoms, she noted that she was post-menopausal, yet had had intermittent vaginal bleeding of one year duration with passage of clots and an associated eighty-pound weight loss. She denied night sweats, lethargy, confusion, weakness, or loss of appetite.

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On presentation to the emergency department, she was hemodynamically stable with mild, low-grade tachycardia (102 beats per minute) and stable oxygen saturation on room air. Physical examination was notable for a mildly obese, but otherwise well-appearing female resting in bed in no distress. Her conjunctivae were noted to be pale. Small ecchymoses were localized to the left hip which demonstrated a limited range of motion, specifically on external rotation, secondary to pain. There was no evidence of limb foreshortening and she remained neurovascularly intact. No tenderness was noted on abdominal examination, nor were any intra-abdominal or pelvic masses or adenopathy appreciated. Vaginal examination demonstrated no evidence of blood; however, a full speculum examination could not be completed secondary to her noted left hip pain. Laboratory diagnostics were notable for mild, neutrophilic-predominant leukocytosis (14.6 k/ul; reference range: 4.0–10.8k/uL) with mild neutrophilia (80.6%, reference range: 43.0%–75.0%), a microcytic anemia with a hemoglobin of 9.3 gm/dL (reference range: 11.0–14.5 gm/dL) and MCV of 73.3 FL (reference range: 81.0–100.0 fL). The remainder of the complete blood count and comprehensive metabolic panel were unremarkable except for an elevated total calcium of 13.7 gm/dL (reference range: 8.7–10.4) and ionized calcium of 1.66 mmol/L (reference range: 1.12–1.32 mmol/L). There was no evidence of a gamma gap. Given the noted hypercalcemia, additional diagnostic workup including Parathyroid Hormone (PTH) and PTH related peptide (PTHrP) were ordered and demonstrated an appropriately suppressed PTH (6.6 pg/mL; reference range 18.4–80.1 pg/ml) and an elevated PTHrP (56.7 pmol/L; reference range 0.0–3.4 pmol/L). The remainder of her workup for hypercalcemia including 1,25-OH Vitamin D was unremarkable. CA-125, sent in the context of her post-menopausal bleeding, was noted to be elevated to 118.6 IU/mL (reference range: 0.0–30.2 IU/mL).

Diagnostic imaging included a Computed Tomography (CT) of the left lower extremity without contrast which demonstrated a left hip fracture involving the intertrochanteric region and greater trochanter and an incidental finding of enlarged uterus (Fig. 1). Transvaginal pelvic ultrasound demonstrated an enlarged uterus, measuring 14.1 × 11.5 × 8.4 cm and the associated finding of a heterogenous, mass-like endometrial lesion measuring 9.5 × 7.0 × 6.9 cm. Given the concern for underlying malignancy, additional diagnostic imaging including a CT of the neck and the chest were performed and revealed metastasis to the left lower lobe of the lung and a right thyroid lobe nodule. Magnetic resonance imaging (MRI) of the brain demonstrated metastases with vasogenic edema without midline shift (Fig. 2). PET/CT scan noted metastases in the chest and in pelvic lymph nodes (Fig. 2).

The patient underwent left hip femoral trochanteric nailing. Urogynecology was also consulted, and the patient underwent radical hysterectomy with bilateral salpingo-oophorectomy. Surgical exploration demonstrated slightly enlarged peri-aortic lymph nodes at the level of the superior mesenteric artery with histological evidence of lymphovascular invasion; pathology demonstrated an endometrial clear cell carcinoma (Fig. 3) arising from within the endometrium and invading into the lower uterine segment, myometrium, cervix, and right ovary. Molecular testing noted an ER-, PR-, MLH1 +, PMS2 +, MSH2 +, MSH6 +, PTEN +, PDL1+, and TMB + status. She was subsequently discharged and underwent outpatient carboplatin-based chemotherapy and stereotactic radiation for brain metastasis. Unfortunately, the patients post-discharge course was complicated by a debilitating ischemic stroke.

3. Discussion

Here, we present a case of humoral hypercalcemia of malignancy associated with endometrial clear cell carcinoma. Although hypercalcemia may manifest as a paraneoplastic syndrome in up to 20–30% of patients with any primary cancer,[1] its occurrence remains rare in gynecological malignancies.[7] A systematic review that included cases from 1984 to 2006 of gynecologic malignancies presenting with humoral hypercalcemia, found only 34 total cases. Only 3 patients in the review had clear cell carcinoma of the endometrium and humoral hypercalcemia of malignancy.[8]

HHM is a common complication of squamous cell cancers of the lungs and the head and neck, breast cancers, urological and renal malignancies; however, it may be associated with any type of cancer.[9] Although initial studies, primarily performed in the 1980s, had suggested humoral hypercalcemia represents up to 75–80% of hypercalcemia occurring in cancer,[3] recent retrospective studies found only 32–38% of those patients had elevated PTHrP levels.[10] In the case of our patient, her PTHrP level was extremely elevated.

Clear cell carcinoma of the endometrium, a rare but aggressive malignancy, represents less than five percent of uterine malignancies.[11] Histologically, the cancerous cells are seen to have clear, hobnail shaped that are eosinophilic; the cells may also have solid, papillary, or tubulocystic architectural patterns. Clear cell carcinomas of the ovary, cervix and

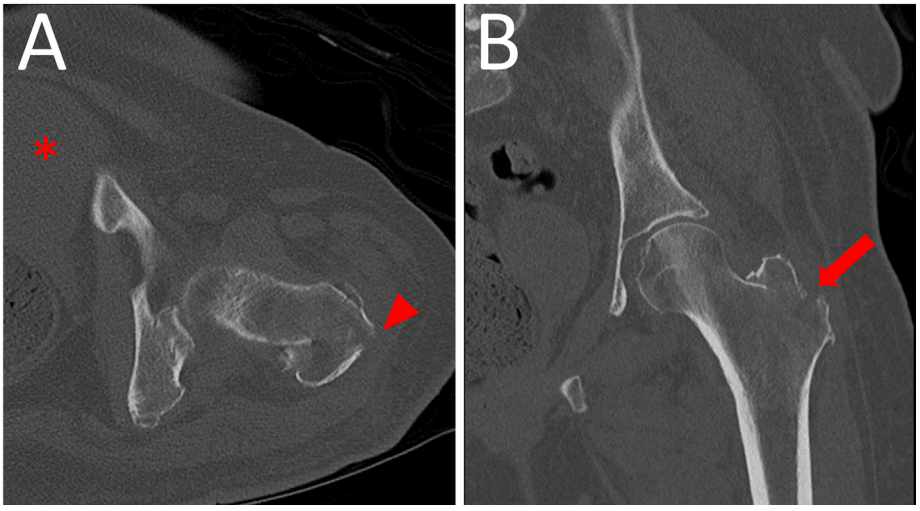

Fig. 1. Computed Tomography of the hip. CT demonstrates the presence of left hip intertrochanteric (arrowhead) and greater trochanter (arrow) fractures. An enlarged uterus is incidentally visualized (asterix).

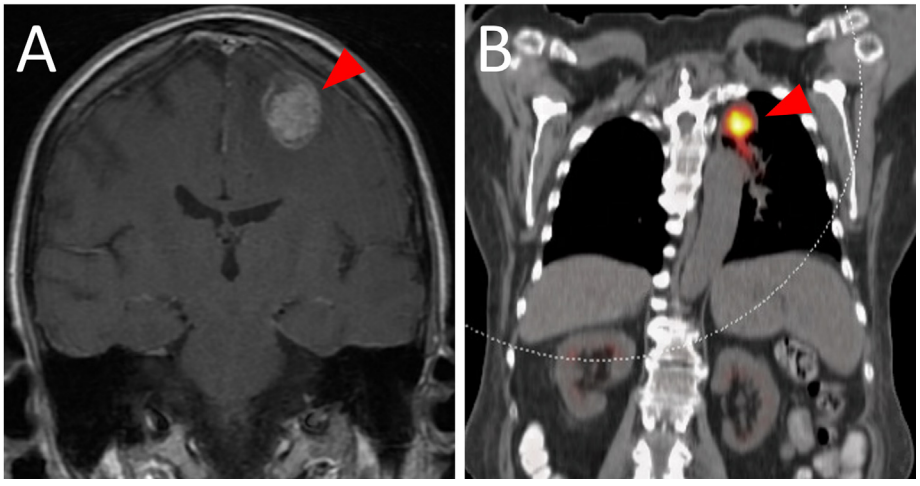

Fig. 2. Magnetic Resonance and Positron Emission Tomography Imaging. MRI (Panel A) demonstrates a heterogeneously enhancing metastatic lesion within the left frontal lobe and associated vasogenic edema (arrowhead), consistent with metastasis. PET-CT (Panel B) demonstrates a hypermetabolic lobulated mass medial left upper lobe that extends contiguously into the left hilum compatible with metastasis.

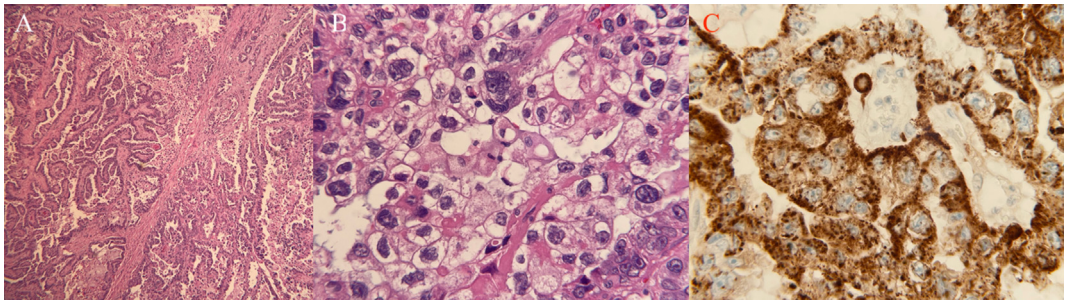

Fig. 3. Histopathology. Hematoxylin & Eosin staining reveals a papillary architecture (characterized by slender, finger-like projections) typical of clear cell carcinoma (Panel A; 4x magnification). Panel B (40x magnification) demonstrates numerous foci of tumor cells with abundant clear cytoplasm, due to the presence of cytoplasmic glycogen, and nuclear atypia, characterized by enlarged nuclei with irregular nuclear membranes. Panel C (40x magnification) reveals strong cytoplasmic Napsin A staining, consistent with Clear cell carcinoma.

vagina exhibit similar histologic features[12] and similar clinical presentations, primarily vaginal bleeding.[13] These tumors are associated with high recurrence and mortality rates; diagnosis usually portends a poor prognosis.[13]

Major molecular alterations including PTEN gene silencing, microsatellite instability, defects in DNA mismatch repair, and mutations in KRAS and/or *β-catenin* genes may be implicated in the pathogenesis of the cancer.[14] In the case of our patient, the molecular profiling (CARIS panel) showed proficient mismatch repair status, stable microsatellite instability, and a high tumor mutational burden of 11 mutations/megabase (≥10 mutations/megabase is considered high tumor mutational burden). She also had pathogenic variant mutations in the PTEN onco-suppressor gene.

The standard surgical treatment for endometrial clear cell cancer comprises of total abdominal hysterectomy (TAH) with bilateral salpingo-oophrectomy (BSO) with comprehensive surgical staging, and subsequent post-operative chemotherapy as well as radiotherapy.[15] With the advent of novel immune check point inhibitors, advanced molecular testing like the CARIS panel can provide information on targeted therapy. Our patient was a candidate for pembrolizumab and levantinib therapy. Indeed, the KEYNOTE-028 trial found a sustained antitumor activity in patients with advanced endometrial cancer that was PD-L1 positive,[16] similar to our patient who had 2+ PD-L1 positivity. The recent phase 3, KEYNOTE-775 study showed significantly improved overall survival and longer progression free survival in patients treated with pembrolizumab and levantinib compared to patients treated with physicians' choice of chemotherapy.[17]

Our patient presented in the context of a mechanical fall complicated by fracture and was incidentally noted to have an enlarged uterus, hypercalcemia, and an elevated PTHrP level, which was later confirmed to be an endometrial clear cell carcinoma. She underwent TAH-BSA with resolution of her calcium levels following surgical intervention, suggesting humoral hypercalcemia of malignancy in the setting of endometrial clear cell carcinoma as the definitive diagnosis.

4. Conclusion

This case highlights the rare, yet clinically relevant association of endometrial clear cell carcinoma and hypercalcemia. It emphasizes the need to consider endometrial cancer as one of the differential diagnoses when assessing symptomatic or asymptomatic humoral hypercalcemia.

Conflict of interest

No conflict of interest.

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