Hypercalcemia Due to Parathyroid Hormone-Related Protein Induced by Primary Endometrial Clear Cell Adenocarcinoma: Case Report

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Received 27 May 2016; accepted 31 July 2016; published 3 August 2016

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Abstract

Humoral Hypercalcemia of Malignancy (HHM) has been reported in association with a number of malignancies. In gynecologic malignancies, ovarian Clear Cell Carcinoma (CCC) is one of the most common histologic subtypes, whereas HHM caused by endometrial CCC is very rare. We report a case of endometrial CCC with HHM, with a low serum intact PTH level, elevated serum PTH-related Peptide (PTH-rP), and immunohistochemically demonstrated PTH-rP in the neoplasm.

Keywords

Humoral Hypercalcemia of Malignancy, Endometrial Cancer, Clear Cell Adenocarcinoma, Parathyroid Hormone-Related Protein

1. Introduction

Hypercalcemia accompanied by malignancy is a common metabolic complication of malignancies and categorized into two major groups: one is Local Osteolytic Hypercalcemia (LOH), due to local osteolysis induced by the tumor metastasized to bone, while the other is Humoral Hypercalcemia of Malignancy (HHM), due to systemic bone resorption caused by Parathyroid Hormone-related Protein (PTHrP). HHM occurs in up to 10% of patients with solid tumor [1], but is uncommon in patients with gynecological malignancies. HHM caused by endometrial cancer is even rarer and only a few cases of paraneoplastic hypercalcemia associated with endometrial cancer have been reported previously [2]-[5]. We report a case of endometrioid clear cell adenocarcinoma of the uterine corpus associated with HHM prior to the primary surgery and proved immunohistochemically that
endometrial clear cell carcinoma has the potential to produce PTHrP at the primary site.

2. Case Report

An 80-year-old gravid 2, para 2, woman was referred for gynecological examination with occasional purulent vaginal discharge. She also had an eight months’ history of general fatigue and anorexia. Normal menopause occurred at age 50. A pelvic examination confirmed the presence of a remarkably enlarged, immobile, pelvic-abdominal mass. Magnetic Resonance (MR) imaging demonstrated a large mass of mixed signal intensity in the entire uterine wall (Figure 1). Endometrial curetting revealed poorly-differentiated adenocarcinoma of the endometrium, suggesting clear cell adenocarcinoma. The following data were collected before surgery: serum intact PTHrP (15.1 pmol/l; normal < 1.1 pmol/l), intact PTH (8 pg/ml; normal 10 - 60 pg/ml), total calcium (12.2 mg/dl; normal 8.3 - 10.3 mg/dl), ionized calcium (3.08 mEq/l; 2.27 - 2.63 mEq/l), 1.25 dihydroxy vitamin D3 (28.3 pg/ml; 20.0 - 60.0 pg/ml), phosphorus (2.6 mg/dl; normal 2.5 - 4.7 mg/dl), alkaline phosphatase (ALP) (332 IU/l; normal 115 - 359 IU/l), LDH (201 IU/l; normal 119 - 229 IU/l). The patient’s tumor marker profile was as follows: Squamous cell carcinoma antigen (SCC) (1.1 ng/ml, normal < 1.5 ng/ml), CA-199 (8.0 U/ml; normal < 37 U/ml), CEA (1.0 ng/ml; normal < 2.5 ng/ml), CA-125 (13.0 U/ml; normal < 35 U/ml). Alpha-fetoprotein (4.4 ng/ml; normal < 7 ng/ml). Bone metastasis was excluded by bone scintigram findings. All these data were compatible with endometrial adenocarcinoma with HHM.

An exploratory laparotomy with total hysterectomy and bilateral salpingo-oophorectomy was performed. Findings at surgery included markedly enlarged uterus with no evidence of local spread, peritoneal seedings or hepatic metastases. Histology showed the tumor to be a clear cell adenocarcinoma with diffuse positive immunoreactivity for PTHrP (Figure 2). The levels of serum total calcium, ionized calcium and PTHrP rapidly returned to the reference range after surgery. Two years postoperatively, the patient was in good health, with no evidence of recurrence of the malignancy. Plasma PTHrP was undetectable and serum calcium (9.1 mg/dl), was within its reference range.

3. Discussion

We have reported a case of clear cell adenocarcinoma of the endometrium with hypercalcemia and demonstrated the expression of PTHrP in the tumor tissue at cellular level by immunohistochemistry. Clinically, this case exhibited no bone metastasis, and after surgical removal of the uterus, the hypercalcemia was corrected. Suppression of secretion of intact PTH also supports the fact that the hypercalcemia is humorally mediated in this case, due to secretion of PTHrP since the serum level of PTHrP was elevated.
HHM secondary to secretion of PTHrP is frequently seen in squamous cell cancers of the head and neck, esophagus, cervix and lung [6], as well as breast cancer [7], renal clear cell carcinoma [8] and hematological malignancies [9]. Several case reports of gynecologic malignancies with HHM have been only sporadically reported in the literature. Savarin et al. [10] analyzed 34 women with different gynecological malignancies complicated by paraneoplastic hypercalcemia induced by PTHrP production in their review of published cases. Among them, while 22 suffered from ovarian malignancies, 6 suffered from uterine malignancies. They also reported that clear cell carcinoma was the predominant histologic subtype associated with PTHrP expression, accounting for 38% of all cases and 50% of uterine malignancy cases. Regarding endometrial carcinomas, only a few cases have been reported. In the report by Hiller et al. [2], two HHM cases were clear cell adenocarcinoma of uterus, whereas the cause of hypercalcemia was not identified. The case of Buller [3] had a prominent squamous cell component within areas of the adenocarcinoma, which expressed ectopic parathyroid hormone. Furthermore, the case of Sachmechi was serous papillary carcinoma associated with parathyroid hormone-related protein (PTHrP)-induced hypercalcemia [4].

4. Conclusion

Although HHM in endometrial carcinoma is a rare condition, this case illustrates the importance of a thorough evaluation and vigilance of hypercalcemia, especially in cases of advanced endometrial clear cell adenocarcinoma.

Conflict of Interest

The authors have no conflicts of interest in connection with submitted material.

Patient’s Consent

The patient gave her consent for the case report to be published.

References


