

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

Kyousuke Takeuchi, Akari Shirakuni, Ai Yoshida, Akiko Takeda, Makoto Sugimoto

Department of Obstetrics and Gynecology, National Hospital Organization, Kobe Medical Center, Kobe, Japan
Email: kyousuket@dolphin.ocn.ne.jp

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

Copyright © 2016 by authors and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

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

How to cite this paper: Takeuchi, K., Shirakuni, A., Yoshida, A., Takeda, A. and Sugimoto, M. (2016) Hypercalcemia Due to Parathyroid Hormone-Related Protein Induced by Primary Endometrial Clear Cell Adenocarcinoma: Case Report. *Open Journal of Obstetrics and Gynecology*, 6, 521-524. <http://dx.doi.org/10.4236/ojog.2016.69066>

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 PTH-rP 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.

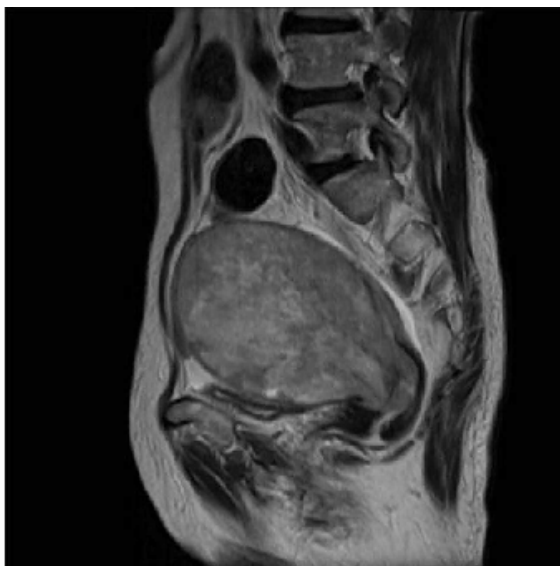


Figure 1. MR imaging showing a large mass of mixed signal intensity in the entire uterine wall.

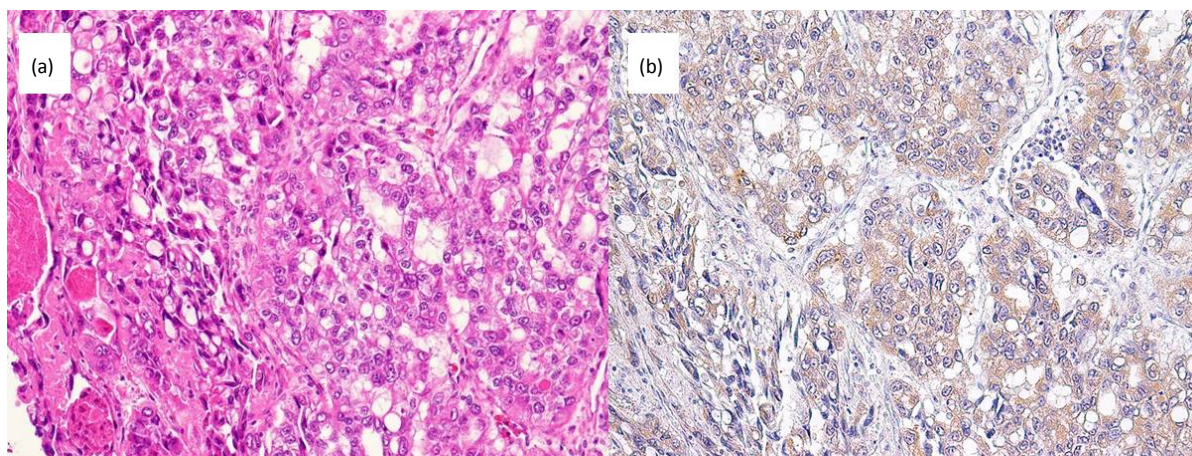


Figure 2. Microscopic finding of H & E staining (a) and immunochemical staining with PTHrP (b). Clear cell adenocarcinoma of the endometrium shows cells with clear cytoplasm and pleomorphic high-grade nuclei and the cytoplasm of tumor cells is strongly immunopositive for PTHrP (A, B $\times 400$).

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 case 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

- [1] Mundy, G.R. and Martin, T.J. (1982) The Hypercalcemia of Malignancy: Pathogenesis and Management. *Metabolism*, **31**, 1247-1277. [http://dx.doi.org/10.1016/0026-0495\(82\)90012-9](http://dx.doi.org/10.1016/0026-0495(82)90012-9)
- [2] Hiller, N., Sonnenblick, M. and Hershko, C. (1989) Paraneoplastic Hypercalcemia in Endometrial Carcinoma. *Oncology*, **46**, 45-48. <http://dx.doi.org/10.1159/000226679>
- [3] Buller, R., Taylor, K., Burg, A.C., Berman, M.L. and Disaia, P.J. (1991) Paraneoplastic Hypercalcemia Associated with Adenosquamous Carcinoma of the Endometrium. *Gynecologic Oncology*, **40**, 95-98. [http://dx.doi.org/10.1016/0090-8258\(91\)90095-M](http://dx.doi.org/10.1016/0090-8258(91)90095-M)

- [4] Sachmechi, I., Kalra, J., Molho, L. and Chawla, K. (1995) Paraneoplastic Hypercalcemia Associated with Uterine Papillary Serous Carcinoma. *Gynecologic Oncology*, **58**, 378-382. <http://dx.doi.org/10.1006/gyno.1995.1246>
- [5] Kinugasa, Y. (2006) Parathyroid Hormone-Related Protein-Secreting Uterine Endometrioid Adenocarcinoma. *Japanese Journal of Clinical Oncology*, **36**, 113-115. <http://dx.doi.org/10.1093/jjco/hyi215>
- [6] Stewart, A.F. (2005) Clinical Practice. Hypercalcemia Associated with Cancer. *New England Journal of Medicine*, **352**, 373-379. <http://dx.doi.org/10.1056/NEJMcp042806>
- [7] Burtis, W.J., Brady, T.G., Orloff, J.J., Ersbak, J.B., Warrell Jr., R.P., Olson, B.R., Wu, T.L., *et al.* (1990) Immunohistochemical Characterization of Circulating Parathyroid Hormone-Related Protein in Patients with Humoral Hypercalcemia of Cancer. *New England Journal of Medicine*, **322**, 1106-1112. <http://dx.doi.org/10.1056/NEJM199004193221603>
- [8] Strewler, G.J., Stern, P.H., Jacobs, J.W., Eveloff, J., Klein, R.F., Leung, S.C., Rosenblatt, M., *et al.* (1987) Parathyroid Hormonelike Protein from Human Renal Carcinoma Cells. Structural and Functional Homology with Parathyroid Hormone. *Journal of Clinical Investigation*, **80**, 1803-1807. <http://dx.doi.org/10.1172/JCI113275>
- [9] Clines, G.A. and Guise, T.A. (2005) Hypercalcaemia of Malignancy and Basic Research on Mechanisms Responsible for Osteolytic and Osteoblastic Metastasis to Bone. *Endocrine-Related Cancer*, **12**, 549-583. <http://dx.doi.org/10.1677/erc.1.00543>
- [10] Savvari, P., Peitsidis, P., Alevizaki, M., Dimopoulos, M.A., Antsaklis, A. and Papadimitriou, C.A. (2009) Paraneoplastic Humorally Mediated Hypercalcemia Induced by Parathyroid-Related Protein in Gynecologic Malignancies: A Systematic View. *Onkologie*, **32**, 517-523.



Scientific Research Publishing

Submit or recommend next manuscript to SCIRP and we will provide best service for you:

Accepting pre-submission inquiries through Email, Facebook, LinkedIn, Twitter, etc.

A wide selection of journals (inclusive of 9 subjects, more than 200 journals)

Providing 24-hour high-quality service

User-friendly online submission system

Fair and swift peer-review system

Efficient typesetting and proofreading procedure

Display of the result of downloads and visits, as well as the number of cited articles

Maximum dissemination of your research work

Submit your manuscript at: <http://papersubmission.scirp.org/>