

# Treatment-resistant Hypercalcemia from Ectopic PTH Hypersecretion Suspected Secondary to Disseminated Ovarian Cancer

Alexander M. Balinski<sup>1,\*</sup>, Neil J. Khatter<sup>1</sup>, Jeffrey M. Gold<sup>2</sup>, Krishna S. Pothugunta<sup>2</sup>, Vamshi K. Garlapaty<sup>2</sup>, Steven M. Rankin<sup>2</sup>, Christopher A. Thorburn<sup>3</sup>, Jamal Abu-khaled<sup>2</sup>

<sup>1</sup>Oakland University William Beaumont School of Medicine, Rochester, MI, 48309 USA

<sup>2</sup>Department of Nephrology, Beaumont Health, Royal Oak, MI, 48073 USA

<sup>3</sup>Department of Anatomic Pathology, Beaumont Health, Royal Oak, MI, 48073 USA

\*Corresponding author: [balinski@oakland.edu](mailto:balinski@oakland.edu)

Received May 13, 2021; Revised June 18, 2021; Accepted June 25, 2021

**Abstract** Hypercalcemia of malignancy (HCM) can present secondary to hypersecretion of parathyroid hormone (PTH)-related protein (PTHrP) from malignant tumors, but rare cases of HCM have also been documented due to inappropriate PTH secretion from ectopic neoplasms. Here, we report an unusual case of HCM due to hypersecretion of PTH suspected secondary to a disseminated mucinous ovarian adenocarcinoma. A 45-year-old female presented with severe hypercalcemia and significant elevations in both PTH and PTHrP two weeks after total abdominal hysterectomy with bilateral salpingo-oophorectomy and suboptimal debulking of a newly discovered left ovarian mucinous adenocarcinoma with numerous metastases. Ectopic PTH secretion was highly suspected after a negative parathyroid ultrasound. Pamidronate, calcitonin, and fluid resuscitation were unable to normalize her serum calcium, resulting in the need for dialysis and subsequent continuous renal replacement therapy. Further intervention with denosumab, etelcalcetide, and cinacalcet was attempted. Serum calcium began to decline, but repeat PTH resulted greater than 2,500 pg/mL. Unfortunately, the patient died just one week into her hospital course from septic shock and multi-organ system failure. While patients with localized PTH-secreting tumors carry a good prognosis, disseminated malignancies can result in significant morbidity and mortality due to severe treatment-resistant hypercalcemia.

**Keywords:** hypercalcemia, malignancy, parathyroid hormone, ovarian adenocarcinoma

**Cite This Article:** Alexander M. Balinski, Neil J. Khatter, Jeffrey M. Gold, Krishna S. Pothugunta, Vamshi K. Garlapaty, Steven M. Rankin, Christopher A. Thorburn, and Jamal Abu-khaled, "Treatment-resistant Hypercalcemia from Ectopic PTH Hypersecretion Suspected Secondary to Disseminated Ovarian Cancer." *American Journal of Medical Case Reports*, vol. 9, no. 10 (2021): 512-515. doi: 10.12691/ajmcr-9-10-9.

## 1. Introduction

Hypercalcemia is a nonspecific clinical condition attributed to an elevation in total serum calcium above normal [1]. Typically, hypercalcemia is a result of primary hyperparathyroidism due to a parathyroid adenoma or parathyroid gland hyperplasia [2]. Other known etiologies of hypercalcemia include chronic kidney disease, hyperthyroidism, chronic immobilization, Paget's disease, sarcoidosis, and malignancy [2]. Hypercalcemia of malignancy (HCM) occurs in up to 40% of cancer patients and is primarily attributed to hypersecretion of parathyroid hormone (PTH)-related protein (PTHrP) from malignant tumors [3]. However, rare cases of HCM have also been documented due to inappropriate PTH secretion from ectopic neoplasms. Here, we report an unusual case of HCM due to ectopic hypersecretion of PTH suspected from a disseminated mucinous ovarian adenocarcinoma.

## 2. Case Presentation

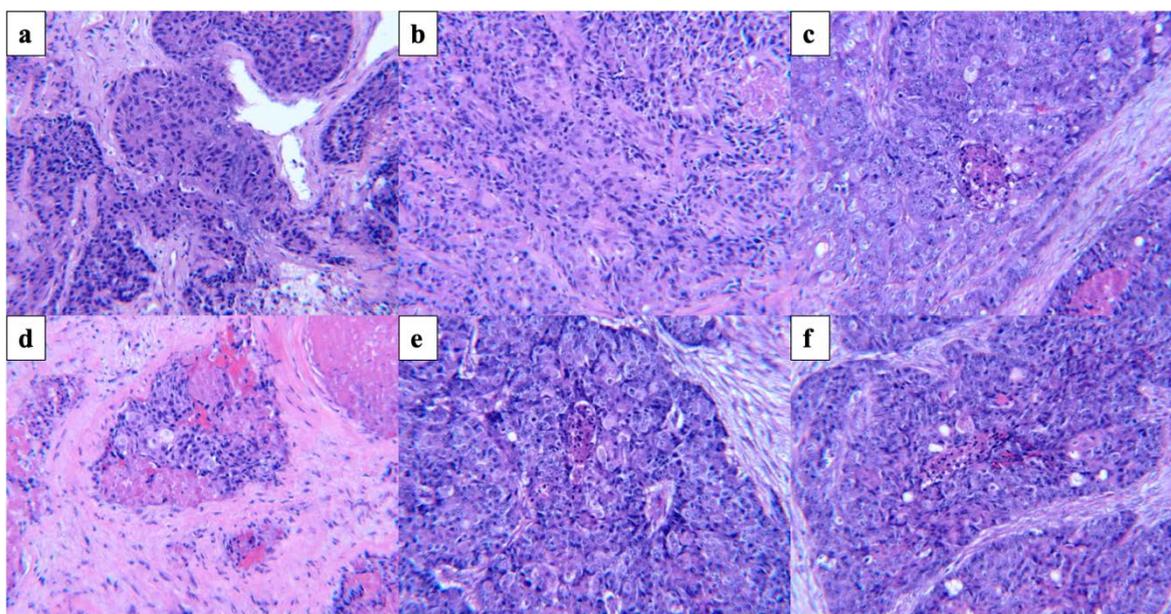
A 45-year-old female presented to the emergency department after her gynecologist discovered a new 7 x 5 x 5 cm left ovarian mass with elevations in cancer antigen 125 (CA-125) (107 U/mL) and inhibin A (61 pg/mL). She subsequently underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy and suboptimal debulking of tumor metastases extending into the bladder, parametrium, vagina, right ovary, and rectosigmoid. Initial tumor pathology favored a poorly differentiated metastatic colorectal adenocarcinoma, but high grade mucinous ovarian adenocarcinoma could not be ruled out (Figure 1). Follow-up computed tomography revealed numerous bilateral pulmonary nodules, hilar adenopathy, liver lesions, and abdominal adenopathy (Figure 2). Once stable, the patient was discharged with plans to follow-up for colonoscopy and chemotherapy. Her colonoscopy was

completed one week later and showed no evidence of primary colorectal malignancy, favoring a new leading diagnosis of disseminated mucinous ovarian adenocarcinoma. Tumor biopsy samples were then sent for a second opinion to confirm her diagnosis.

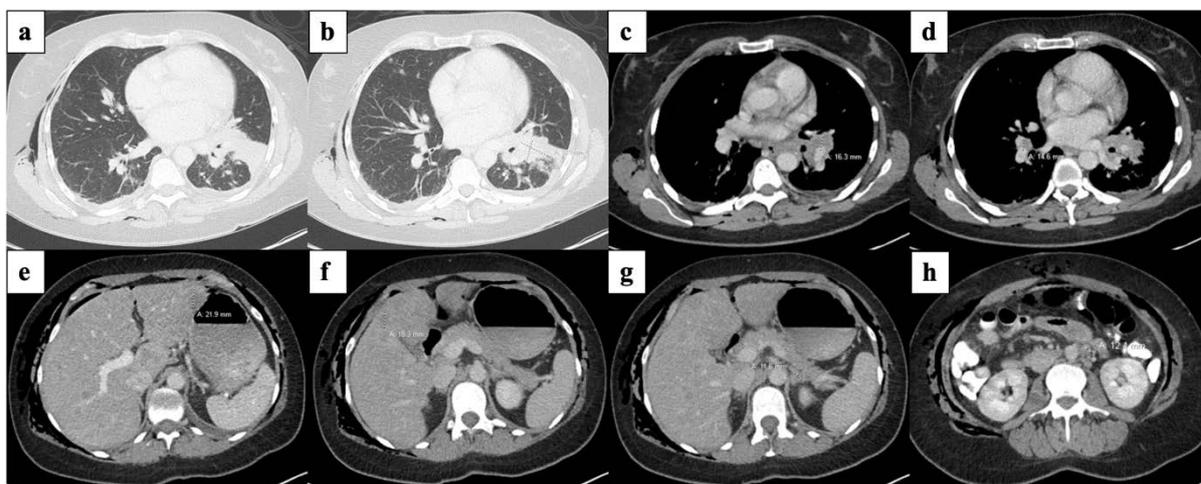
Two weeks after surgery, the patient presented with confusion, constipation, fatigue, and abdominal pain. On exam, she was tachycardic and hypertensive with diaphoresis, dry mucous membranes, respiratory distress, guarded abdominal tenderness, and altered mental status. Her labs were significant for a serum calcium of 21.7 mg/dL, creatinine of 1.93 mg/dL, ferritin of 2,379 ng/mL, leukocyte count of 21.9 bil/L, PTH of 1,061 pg/mL, PTHrP of 29 pmol/L, carcinoembryonic antigen (CEA) of 103.1 ng/mL, and carbohydrate antigen 19-9 (CA 19-9) of 118.9 U/mL (Table 1).

Electrocardiogram noted sinus tachycardia, but was otherwise unremarkable. Suspicion of ectopic PTH secretion from malignancy was increased after parathyroid ultrasound resulted negative for any notable parathyroid masses. Tumor biopsy staining for PTH and total body

sestamibi scan were considered for further classification of disease, but these were not performed due to the rapidly declining status of the patient. Pamidronate (60 mg IV), calcitonin (200 U IM), and fluid resuscitation were unable to normalize her serum calcium, resulting in the need for dialysis and continuous renal replacement therapy (CRRT). Further intervention with denosumab (120 mg SQ), etelcalcetide (5 mg IV), and cinacalcet (60 mg PO) was also attempted due to sustained hypercalcemia. Serum calcium began to decline, but repeat PTH resulted greater than 2,500 pg/mL. Her clinical course continued to decline as she experienced respiratory compromise with the need for intubation. She became progressively unstable with worsening anemia (7.3 g/dL), leukocytosis (31.5 bil/L), and elevations in alkaline phosphatase (ALP) (1,567 U/L), aspartate transaminase (AST) (14,647 U/L), alanine transaminase (ALT) (2,508 U/L), bilirubin (8.6 mg/dL), and lactic acid (12.9 mmol/L) (Table 1). Unfortunately, medical intervention was insufficient and the patient died just one week into her hospital course due to septic shock and multi-organ system failure.



**Figure 1.** Tumor biopsy of the left ovary (a), bladder (b), parametrium (c), vagina (d), right ovary (e), and rectosigmoid (f) showing possible poorly differentiated metastatic colorectal adenocarcinoma versus high grade mucinous ovarian adenocarcinoma



**Figure 2.** Computed tomography chest/abdomen/pelvis with contrast revealing numerous bilateral pulmonary nodules (a,b), hilar adenopathy (c,d), liver lesions (e,f), and abdominal adenopathy (g,h)

**Table 1. Patient lab results on admission and before death**

Test	Patient value on admission	Patient value before death	Reference range
Leukocyte count	21.9	31.5	3.3-10.7 bil/L
Hemoglobin, blood	8.9	7.3	Female: 12.1-15.0 g/dL
Calcium, serum (Ca <sup>2+</sup> )	21.7	10.2	8.4-10.2 mg/dL
Creatinine, serum	1.93	0.84	0.6-1.2 mg/dL
Parathyroid hormone, serum, N-terminal	1080	>2,500	8-72 pg/mL
Parathyroid hormone-related protein (PTHrP)	29	-	< or = 4.2 pmol/L
Ferritin	2,379	-	12-207 ng/mL
Alkaline phosphatase (ALP)	670	1,567	33-120 U/L
Aspartate aminotransferase (AST)	481	14,647	<35 U/L
Alanine aminotransferase (ALT)	120	2,508	8-37 U/L
Bilirubin	2.2	8.6	0.3-1.2 mg/dL
Lactic acid	4.2	12.9	0.5-2.0 mmol/L
Carcinoembryonic antigen (CEA)	103.1	-	0.0-3.0 ng/mL
Carbohydrate antigen 19-9 (CA 19-9)	118.9	-	0.0-37.0 U/mL

### 3. Discussion

Hypercalcemia of malignancy typically arises from tumor secretion of PTHrP, cytokine release from osteolytic metastases, or tumor production of calcitriol [4]. In cases of hypercalcemia due to excess PTH secretion, primary parathyroid etiologies such as a parathyroid adenoma or parathyroid gland hyperplasia are typically considered [2]. Primary parathyroid pathologies are commonly identified using parathyroid ultrasound which boasts an 80% sensitivity [5], but Technetium-99m sestamibi scan can also be utilized to help localize PTH-secreting adenomas [6]. Management of primary parathyroid etiologies of HCM includes exploration of the central neck under general endotracheal anesthesia and parathyroidectomy with resolution of hypercalcemia in 97-99% of cases [7,8].

After ruling out primary parathyroid etiologies, ectopic PTH-secreting tumors should be considered as they are a rare, but known etiology of HCM with documented presentations in the head, neck, thorax, gastrointestinal tract, pelvis, and gynecological sites [9]. Although poorly understood, proposed mechanisms of ectopic PTH production include: regulation of PTH transcription in non-parathyroid cells due to underexpression of calcium-sensing receptors, overproduction of CYP24A1, and noncoding RNA in the PTH 3'-downstream region of ectopic PTH-secreting tumors [9]. In this case, suspicion of ectopic PTH tumor secretion was high due to a negative parathyroid ultrasound and biopsy confirmation of a disseminated malignancy of primary colorectal versus ovarian origin.

Poorly differentiated metastatic colorectal adenocarcinomas and high grade mucinous ovarian adenocarcinomas are histologically similar malignancies and ovarian metastasis occurs in 3-8% of women with primary colon cancers [10]. Colonoscopy is considered the gold standard for diagnosis of colorectal carcinomas and can assist in ruling out primary colon cancers with a diagnostic sensitivity of ~95% [11]. Negative colonoscopy findings in this case suggested a rare diagnosis of PTH-secreting disseminated mucinous ovarian adenocarcinoma. Currently, there are only three cases in the reported literature of ectopic PTH-induced hypercalcemia related to ovarian cancer [12,13,14].

HCM is a common, yet concerning presentation. It offers a poor prognosis with mean survival of 2 to 3 months and in-hospital mortality of ~7% [15]. Currently,

combinations of chemotherapy, pamidronate, calcitonin, and zoledronic acid have demonstrated efficacy in prolonging survival of HCM patients [16], but newer experimental therapies such as denosumab, cinacalcet, and etelcalcetide have also showed some success as second line therapeutics [17,18,19]. Denosumab, cinacalcet, and etelcalcetide were all utilized in this case, but treatment efficacy was difficult to assess due to the patient's rapid deterioration and complicated clinical course.

PTH-secreting ovarian tumors are incredibly rare presentations of severe hypercalcemia and the current literature is limited regarding optimal management of disease. In this case, our patient was unstable throughout the duration of her care which resulted in several limitations in management and further complicated the diagnostic process. First, we were able to rule out primary hyperparathyroidism with ultrasound, but localization of PTH secretion with Technetium-99m sestamibi scan was not possible due to the patient's instability. Second, we did not stain the initial ovarian tumor for PTH production which would have provided early evidence for HCM. Third, the efficacy of denosumab, etelcalcetide, and cinacalcet to aggressively reduce serum calcium remains unclear as the patient was being treated with pamidronate, dialysis, and CRRT in the days prior to their administration.

### 4. Conclusion

PTH-secreting ovarian tumors are incredibly rare presentations of HCM. While patients with localized tumors carry a good prognosis, disseminated malignancies can result in significant morbidity due to severe treatment-resistant hypercalcemia. When clinically indicated, identification of ectopic PTH-secreting tumors through PTH staining of biopsy specimens and total body sestamibi scan may prove useful in early diagnosis and management of disease.

### Acknowledgements

The authors would like to thank the Department of Anatomic Pathology at Beaumont Health for their assistance with this report.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

## Funding

The authors declare no sources of funding.

## References

- [1] Siyam FF, Klachko DM. What is hypercalcemia? The importance of fasting samples. *Cardiorenal Med.* 2013; 3(4): 232-238.
- [2] Turner JJO. Hypercalcaemia - presentation and management. *Clin Med (Lond).* 2017; 17(3): 270-273.
- [3] Batarseh N, Al Sabie F, Evans-Molina C. SAT-494 A Very Rare Case: Hypercalcemia Caused by Ectopic PTH Secretion in Endometrial Cancer. *J Endocr Soc.* 2019; 3(Supplement\_1).
- [4] Seccareccia D. Cancer-related hypercalcemia. *Can Fam Physician.* 2010; 56(3): 244-246.
- [5] Moghadam RN, Amlshahbaz AP, Namiranian N, et al. Comparative diagnostic performance of ultrasonography and <sup>99m</sup>Tc-Sestamibi scintigraphy for parathyroid adenoma in primary hyperparathyroidism; Systematic review and meta-analysis. *Asian Pac J Cancer Prev.* 2017; 18(12): 3195-3200.
- [6] Goldstein RE, Billheimer D, Martin WH, Richards K. Sestamibi Scanning and Minimally Invasive Radioguided Parathyroidectomy Without Intraoperative Parathyroid Hormone Measurement. *Ann Surg.* 2003; 237(5): 722-731.
- [7] Auguste LJ, Attie JN, Schnaap D. Initial failure of surgical exploration in patients with primary hyperparathyroidism. *Am J Surg.* 1990; 160(4): 333-336.
- [8] van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: An institutional perspective. *World J Surg.* 1991; 15(6): 688-692.
- [9] Uchida K, Tanaka Y, Ichikawa H, et al. An Excess of CYP24A1, Lack of CaSR, and a Novel lncRNA Near the PTH Gene Characterize an Ectopic PTH-Producing Tumor. *J Endocr Soc.* 2017; 1(6): 691-711.
- [10] Ongom PA, Odida M, Lukande RL, Jombwe J, Elobu E. Metastatic colorectal carcinoma mimicking primary ovarian carcinoma presenting as “giant” ovarian tumors in an individual with probable Lynch syndrome: A case report. *J Med Case Rep.* 2013; 7(1): 158.
- [11] Pickhardt PJ, Hassan C, Halligan S, Marmo R. Colorectal cancer: CT colonography and colonoscopy for detection-systematic review and meta-analysis. *Radiology.* 2011; 259(2): 393-405.
- [12] Nussbaum SR, Gaz RD, Arnold A. Hypercalcemia and Ectopic Secretion of Parathyroid Hormone by an Ovarian Carcinoma with Rearrangement of the Gene for Parathyroid Hormone. *N Engl J Med.* 1990; 323(19): 1324-1328.
- [13] Chen L, Dinh TA, Haque A. Small cell carcinoma of the ovary with hypercalcemia and ectopic parathyroid hormone production. *Arch Pathol Lab Med.* 2005; 129(4): 531-533.
- [14] Gabriel FGC, Picar RE. A rare case of hypercalcemic encephalopathy from ectopic secretion of parathyroid hormone. *Clin Case Rep.* 2020; 8(3): 423-425.
- [15] Wright JD, Tergas AI, Ananth CV, et al. Quality and Outcomes of Treatment of Hypercalcemia of Malignancy. *Cancer Invest.* 2015; 33(8): 331-339.
- [16] Ramos REO, Perez Mak M, Alves MFS, et al. Malignancy-Related Hypercalcemia in Advanced Solid Tumors: Survival Outcomes. *J Glob Oncol.* 2017; 3(6): 728-733.
- [17] Thosani S, Hu MI. Denosumab: A new agent in the management of hypercalcemia of malignancy. *Futur Oncol.* 2015; 11(21): 2865-2871.
- [18] Asonitis N, Kassi E, Kokkinos M, Giovanopoulos I, Petychaki F, Gogas H. Hypercalcemia of malignancy treated with cinacalcet. *Endocrinol Diabetes Metab Case Rep.* 2017; 2017: 17-0118.
- [19] Friedl C, Zitt E. Role of etelcalcetide in the management of secondary hyperparathyroidism in hemodialysis patients: a review on current data and place in therapy. *Drug Des Devel Ther.* 2018; 12: 1589-1598.



© The Author(s) 2021. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).