กรณีศึกษาภาวะแคลเซียมในเลือดสูงรุนแรงในผู้ป่วยมะเร็งรังไข่ชนิดเคลียร์เซลล์

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บทคัดย่อ

บทนำ ภาวะแคลเซียมในเลือดสูงเป็นภาวะแทรกซ้อนทางอายุรศาสตร์ที่พบได้บ่อยที่สุดในผู้ป่วยโรคมะเร็ง การค้นหาสาเหตุและให้การรักษาที่เหมาะสมจึงเป็นสิ่งจำเป็นในเวชปฏิบัติ

วัตถุประสงค์ เพื่อรายงานกรณีศึกษาการเกิดภาวะแคลเซียมในเลือดสูงรุนแรงในผู้ป่วยมะเร็งรังไข่ชนิดเคลียร์เซลล์ ขั้นตอนการตรวจวินิจฉัย ผลการรักษาและการรักษาผู้ป่วย

วิธีการศึกษา ศึกษาข้อมูลย้อนหลัง ประวัติ การดำเนินโรค อาการ อาการแสดงของผู้ป่วยจากการซักประวัติ ตรวจร่างกาย ภาพถ่ายอาการแสดงของผู้ป่วย ผลการตรวจทางห้องปฏิบัติการและการติดตามการดำเนินโรคจากเวชระเบียนผู้ป่วย

ผลการศึกษา กรณีศึกษาผู้ป่วยแคลเซียมในเลือดสูงรุนแรงหนึ่งราย พบสาเหตุจากสารเพปไทด์คล้ายฮอร์โมนพาราไทรอยด์ ซึ่งเป็นภาวะที่พบได้ไม่บ่อยนักในผู้ป่วยโรคมะเร็งรังไข่ รวมถึงได้อภิปรายแนวทางการวินิจฉัยแยกโรค และการรักษาภาวะแคลเซียมสูงรุนแรงในผู้ป่วยรายนี้

สรุป สารเพปไทด์คล้ายฮอร์โมนพาราไทรอยด์ใช้บ่งชี้ความรุนแรงของโรคมะเร็งรวมถึงการกลับเป็นซ้ำของตัวโรค การตรวจพบสารนี้ร่วมกับภาวะแคลเซียมในเลือดสูงจึงมีความสำคัญต่อกระบวนการรักษาโรค

คำสำคัญ แคลเซียมสูง มะเร็งรังไข่ สารเพปไทด์คล้ายฮอร์โมนพาราไทรอยด์

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A case report of Humoral Hypercalcemia of Malignancy in a patient with clear cell ovarian cancer

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Abstract

Introduction: Hypercalcemia is the most common medical complication in cancer patients. Finding the cause and providing the appropriate treatment is essential in medical practice.

Objective: We're reporting on a case study of severe hypercalcemia in a patient with clear-cell ovarian cancer, from the clinical presentation, diagnosis, investigations, and treatment.

Study Methods: A retrospective study that presents the patient's history, physical examinations, laboratory investigations, imaging, clinical course, and treatment. The data used has been derived from the patient's hospital medical records.

Results: A 62-year-old female patient was presented to the outpatient clinic with fatigue and constipation. The patient had a history of clear cell adenocarcinoma. An initial diagnosis of severe hypercalcemia was made, and an elevated level of parathyroid hormone related peptide (PTH-rP) was later to be found. Parathyroid hormone related peptide is an uncommon association with ovarian cancer. Differential diagnoses and treatment of this patient is discussed in this case report.

Conclusion: Parathyroid hormone related peptide (PTH-rP) was used to predict the severity of malignancy and recurrence in this patient. The detection of hypercalcemia with a high level of PTH-rP was necessary for a proper management plan.

Keyword: Hypercalcemia, ovarian cancer, parathyroid hormone related peptide

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Received: June 26, 2023 Revised: September 8, 2023 Accepted: September 11, 2023

การอ้างอิง

ระวีวรรณ วิฑูรย์ อวฤทธิ์ โภคาธิกรณ์ และ อโนชา วนิชชานนท์. กรณีศึกษาภาวะแคลเซียมในเลือดสูงรุนแรงในผู้ป่วยมะเร็งรังไข่ชนิดเคลียร์เซลล์. บูรพาเวชสาร. 2566; 10(2): 77-88.

Citation

Witoon R, Pocathikorn A and Wanitchanont A. A case report of Humoral Hypercalcemia of Malignancy in a patient with clear cell ovarian cancer. Bu J Med. 2023; 10(2): 77-88.

Introduction

Hypercalcemia is a common problem encountered by many physicians -- found in up to 20 to 30% of patients with cancer [1] and can be a challenging problem to fully evaluate and treat, due to its non-specific presentation of symptoms, such as fatigue, bone pain and constipation.

There are various etiologies of hypercalcemia, one of those being from malignancy. Hypercalcemia of malignancy is associated with a high mortality rate of 50% within 1 month of diagnosis, despite available treatments[2]. The pathophysiology of how cancer is related to hypercalcemia is proposed through four different mechanisms. Humoral hypercalcemia of malignancy (HHM), which is mediated through parathyroid hormone related peptide or PTH-rP, can be found in up to 80% of cases. Other mechanisms of hypercalcemia include local osteolysis, calcitriol mediated and ectopic authentic PTH production[1,3].

Common malignancies associated with PTH-rP mediated hypercalcemia are typically cancers of squamous cell origin such as lung, head, neck, esophagus, skin, cervix, adenocarcinomas of the breast, prostate and ovary[3,4]. However, it is an uncommon manifestation in ovarian cancer, with a limited number of cases reported and is suggestive of poor prognosis. This paper is intended to report a case regarding ovarian cancer with hypercalcemia associated with PTH-rP.

Background

A 62-year-old Thai female with a history of previously treated clear cell ovarian cancer (stage IIIB) was presented with 7 days of constipation, as well as fatigue with nausea and vomiting.

Her clear cell ovarian cancer was staged IIIB due to involvement of the serosa of the uterus (Figure 1) with peritoneal metastasis < 2 cm. The patient underwent an operation of surgical staging and a total abdominal hysterectomy with bilateral salpingectomy, just five months prior to this admission. She received a total of 6 cycles of chemotherapy consisting of a regimen of paclitaxel and carboplatin, completed 2 months prior to this admission. Her initial CA-125, as of the first and last cycles of chemotherapy, was 163.50 and 25.38, respectively. Imaging studies (including the tumor marker levels after treatment) showed a remission stage of malignancy (Figure 2).

Sections of the right ovary reveal a solid cystic tumor, with the cystic lesion lined by malignant cuboidal-to-columnar cells, as well as large round-to-polygonal cells with enlarged hyperchromatic nuclei. We observed solid areas consisting of large polygonal cells with enlarged pleomorphic nuclei and large amounts of clear cytoplasm. We noted tubulopapillary growth structures formed by tumor cells, as well as the focal necrosis of the tumor cells. We also noted lymphovascular invasion by the tumor cells – as well as capsular invasion by the tumor cells with ovarian surface involvement. The section of tissue labeled “left ovary” reveals pieces of clear cell carcinoma. No ovarian parenchyma is seen.

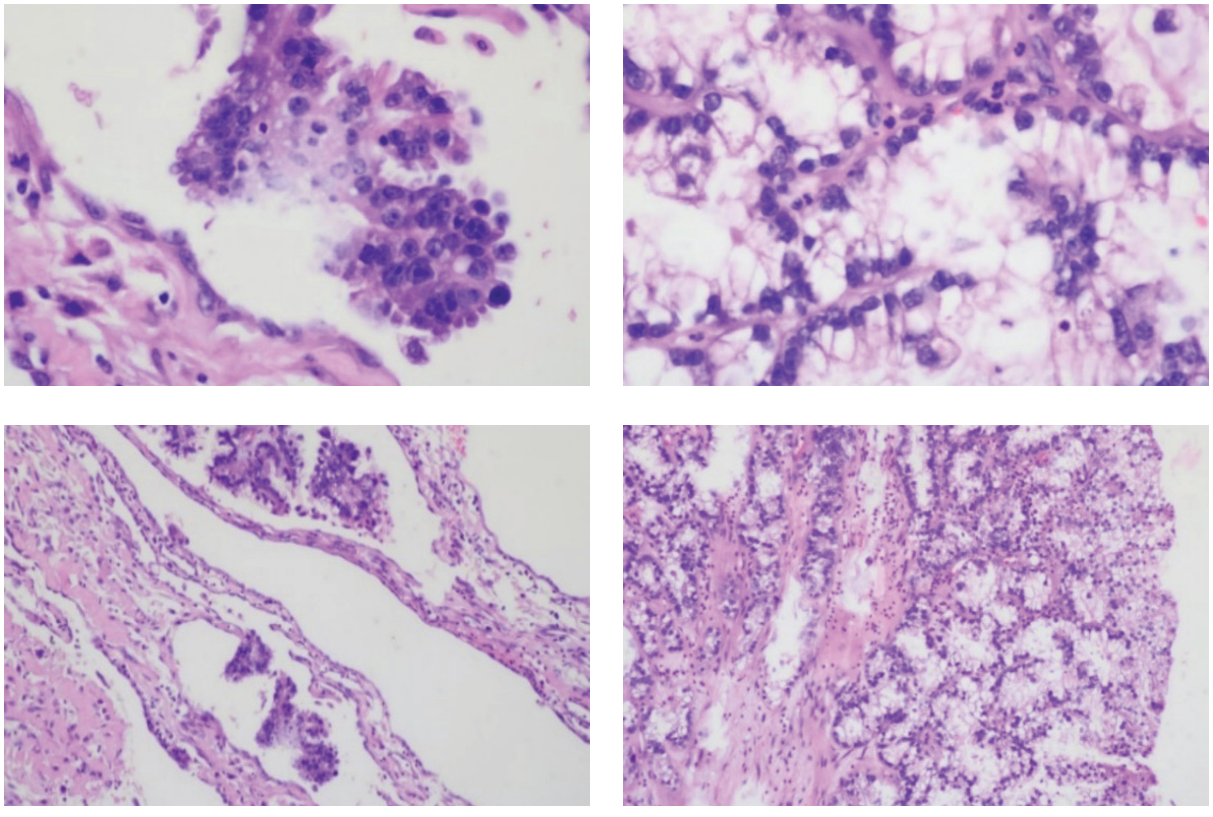

Figure 1: Histopathology sections from the ovarian tumor tissue

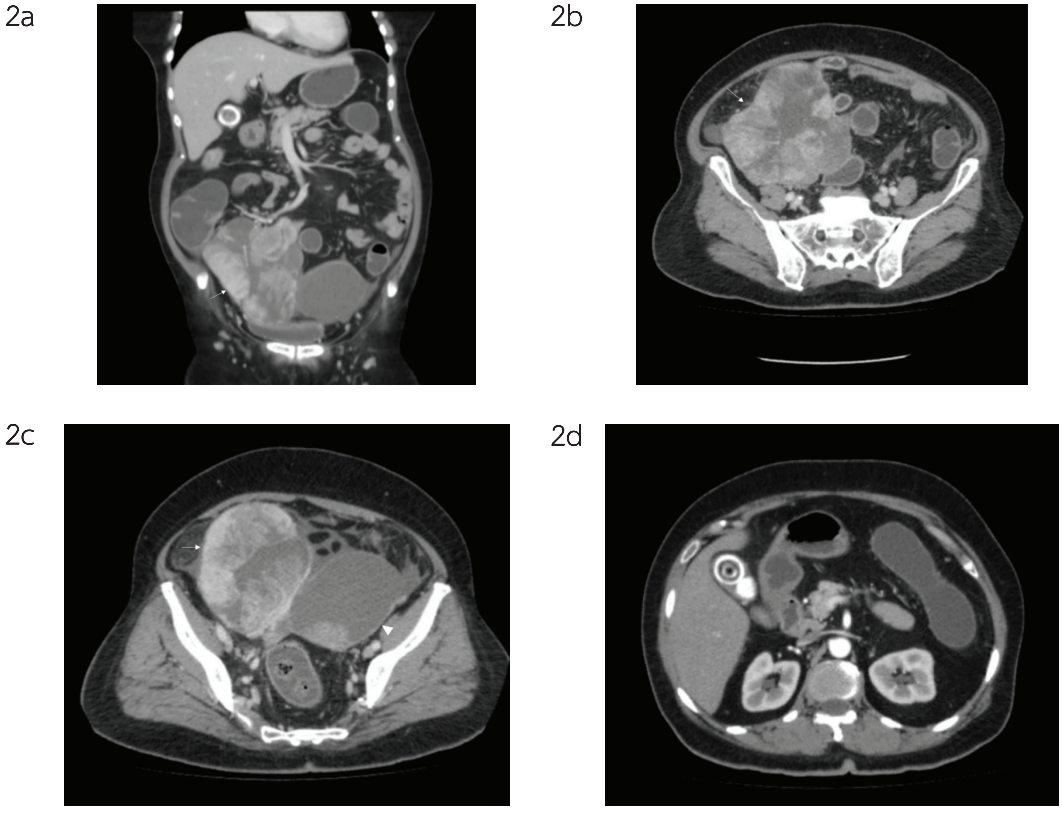

Figure 2: Computed Tomography of the Whole Abdomen with Contrast Media, 5 June 2022

The computed tomography shows a 10.0x13.2x12.0 cm heterogenous enhancing solid mass at the right side of the adnexa (2a, 2b), with abutting right uterine fundus; mild central cystic/necrosis, with no calcification. Minimal ascites is seen. A 7.0x10.7x7.5 cm cystic mass at the left adnexa, showing an eccentric enhancing mural soft tissue, with rim coarse calcifications (2c, 2d).

A complete review of the patient's medical history was made, along with a physical exam. She was shown to have had generalized abdominal discomfort for 7 days, accompanied by bloating with fatigue and constipation. The patient denied any previous use of laxatives, herbs, or other over-the-counter medicine for her condition. Pertinent physical examination findings showed a distended abdomen with generalized tenderness, but without guarding upon palpation. Other than a mildly pale conjunctiva, the patient's physical was an unremarkable exam. She was provisionally diagnosed with a partial gut obstruction suspected from the mass effect of ovarian cancer recurrence. Surgery was consulted to rule out partial gut obstruction.

Investigations and Treatment Course

An initial work-up of laboratory investigations was done. A plain radiograph of the acute abdomen series was done, though no gut obstruction was found. The blood chemistry showed a blood urea nitrogen measurement of 72.30 mg/dL, serum creatinine levels were 4.26 mg/dL (The baseline creatinine from 2 months prior was 0.91 mg/dL), serum calcium levels were 17.40 mg/dL (The corrected calcium level was 18.00 mg/dL), serum phosphate levels were 3.80 mg/dL, serum magnesium was 1.80 mg/dL and serum albumin levels were 3.20 g/dL. Due to high calcium levels, the physician added further laboratory tests for parathyroid hormone levels and vitamin D, which was measured at 11.10 pg/mL (Normal value: 15-65 pg/mL) and 31.50 ng/mL (Normal value: ≥30 ng/mL) respectively. PTH-rP was also taken but was not reported at first due to a pending laboratory schedule. A 12-lead ECG was done and showed a normal ECG without any shortening of the QT interval.

The laboratory investigation revealed severe hypercalcemia, and the patient was treated with aggressive hydration – an initial loading of a 1000 mL isotonic saline solution during the first hour, followed by a continuous infusion of 150 mL per hour. The patient's urine output was closely monitored to be at least 2 mL per kilogram per hour. A subcutaneous calcitonin of 300 IU was administered every 6 hours. After two days of aggressive hydration and 2 doses of subcutaneous calcitonin, the patient's blood chemistry showed decreased levels of calcium (Serum calcium was 14.10 mg/dL, with corrected calcium at 15.20 mg/dL) and creatinine (Serum creatinine was 3.75 mg/dL, eGFR 12.24). Both aggressive hydration and calcitonin were continued, while 4 mg of zoledronic acid was administered intravenously.

For diagnostic purposes, an abdominal paracentesis was performed, alongside a series of additional laboratory tests. On the 21st of December 2022, the ascites profile and additional laboratory Investigations were done, including a gram stain – yellow and cloudy, with no bacteria found. The ascitic WBC count was 1505 cells/mm^3 (40% PMN, 40% mononuclear). The ascitic RBC count was 10000 cell/mm^3 with 15% mesothelial cells. Ascitic protein level was 4.40 g/dL, and ascitic albumin was 2.10 g/dL, however cytology and culture results were still pending. The serum ascites albumin gradient was calculated to be 1.10.

The ascites fluid profile was shown to be suggestive of a peritoneal disease or infection. Empirical antibiotics were initiated, and an abdominal paracentesis was planned to evaluate the patient's response.

The Gynecology department was also consulted to evaluate the patient's recurrence of ovarian cancer (Figure 3). Blood was taken for CA125 and CA 19-9 levels, which were found to be elevated – with levels of 290.40 U/mL (Normal value: 0.00-35.00 U/mL) and 19.70 respectively (Normal value: 0.00-37.00). Additionally, a bone scan was requested but could not be conducted due to limited resources. Computed tomography of the whole abdomen with contrast media was recommended but was not done due to the patient's ongoing acute kidney injury.

Laboratory investigations showed that the patient had abnormal liver function tests, a reversed albumin to globulin ratio (Serum albumin: 3.20; Serum globulin: 4.20) and mildly increased alkaline phosphatase level of 120 (Normal values 35-104 U/L). To further determine the etiology of hypercalcemia, additional investigations were performed. Serum protein electrophoresis, urine protein electrophoresis, immunoelectrophoresis, urine Bence-jones protein and serum free light chain were taken to identify multiple myeloma, due to the presence of hypercalcemia, acute kidney injury, anemia, and bone pain, all of which are common presentations of the hematologic disease but demonstrated polyclonal immunoglobulin with a kappa/lambda ratio of 1.60. No rouleaux formation or plasma cells were seen in the peripheral blood smear, which precluded an etiology of multiple myeloma. A long bone survey was done due to a mildly elevated level of alkaline phosphatase, showing normal results with no osteolytic or osteoblastic lesions.

After 72 hours, subcutaneous calcitonin was discontinued. The patient's volume status was reassessed to be slightly hypervolemic, and intravenous furosemide was added. The patient's serum calcium levels decreased to normal ranges as shown in table 1.

Table 1 Laboratory investigations of serum calcium, serum creatinine and BUN in this admission

Date	Serum Calcium (Corrected Calcium) mg/dL	Serum Creatinine mg/dL	BUN mg/dL
20/12/22	17.40 (18.00)	4.26	72.30
21/12/22	14.10 (15.20)	3.75	63.10
22/12/22	13.20 (14.30)	3.18	52.10
23/12/22	11.30 (12.40)	2.91	41.30
24/12/22	10.50 (11.60)	2.87	37.20
25/12/22	10.20 (11.70)	2.72	33.50
26/12/22	10.30 (11.80)	2.51	32.50
27/12/22	10.40 (11.90)	2.52	33.60
28/12/22	10.10 (11.40)	2.31	34.70
31/12/22	9.60 (10.90)	2.42	45.20
4/1/23	10.10 (11.70)	1.54	48.80
7/1/23	10.40 (12.40)	1.40	52.90

Normal serum calcium levels (Normal 8.6-10.0 mg/dL)

PTH-rP levels were elevated with a value of 26.30 pmol/L (Normal value 0.00-1.10 pmol/L) and were identified as the cause of hypercalcemia in this patient.

Ascites fluid cultures were negative; however, cytology revealed malignant cells, indicating a recurrence of ovarian cancer. Further plans for treatment of malignancy were proposed, including outpatient visits.

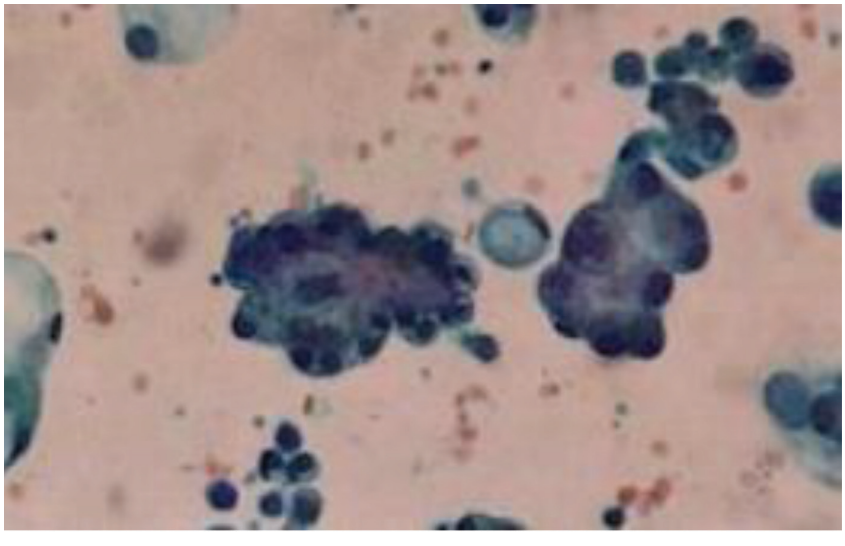

Figure 3: Ascites Cytology of 21 December 2022

Positive for malignant cells – suspected of metastatic carcinoma: The cytology smears show moderate cellularity consisting of clusters and groups of atypical epithelial cells, having pleomorphic nuclei and intracytoplasmic vacuoles.

The patient was not discharged due to persistent high white blood count levels, suspected as a leukemoid reaction to ascitic infection. A follow up ascites fluid profile was taken on the 7th day of admission with decreased levels of white blood cells. Histological examination showed moderate cellular smears containing a few individual mesothelial cells in a background of lymphocytes and macrophages – no atypical cells present, and negative for bacterial culture.

On the 12th day of admission, the patient's consciousness gradually decreased. A series of investigations were performed and a differential to her condition was drug-induced (Sertraline, Morphine) and septic encephalopathy. She was intubated for 4 days and was successfully extubated after an improvement in consciousness. The patient and her relatives were given counselling regarding her prognosis, and a decision for a "do not resuscitate" (DNR) advance care plan was established. After 17 days of admission, a discharge plan was prepared along with her referral to an oncology gynecologist for further treatment. On the 20th day of admission, during the process of referral, the patient had sudden cardiac arrest.

Discussion

This is a case of hypercalcemia presenting as a paraneoplastic syndrome of clear cell ovarian cancer. Clear cell ovarian carcinoma is one of five histological subtypes of epithelial ovarian cancer: high-grade serous, endometrioid, clear cell carcinoma, mucinous carcinoma and low-grade serous carcinoma[5]. Clear cell ovarian carcinomas are resistant to conventional platinum-based chemotherapy, resulting in a poorer prognosis as compared with the other subtypes[6]. However, if diagnosed and treated in the early stages of the cancer, the prognosis is relatively good. Factors affecting prognosis include the patient's age, advanced cancer stage and presence of vascular invasion – which all suggest a poor prognosis[7]. Tumor markers at the time of diagnosis (e.g., CA-125) do not correlate with prognosis[5].

Treatment choices included surgical procedures such as a total hysterectomy with bilateral salpingo-oophorectomy, peritoneal washing, infra-colic omentectomy as well as bilateral pelvic and para-aortic lymphadenectomy. The current gold standard treatment for advanced stages of ovarian carcinoma is primary cytoreductive surgery, followed by paclitaxel and carboplatin chemotherapy, despite having lower response rates to platinum-based chemotherapy (11-50%) as compared with high grade. Neoadjuvant radiation and chemotherapy are in controversy[5]. In cases of recurrence, limited evidence is available regarding secondary cytoreductive surgery. The standard of treatment for recurrent carcinoma is second line chemotherapy, despite low response rates to treatment – partial response in 9% and stable disease in 19%[5]. Our patient was previously diagnosed with FIGO stage IIIB ovarian clear cell adenocarcinoma, with a

previously complete remission. However, she experienced symptoms of hypercalcemia, including apathy, constipation, anorexia, and her serum calcium level was compatible with severe hypercalcemia (> 14 mg/dL). Differential diagnosis for the etiology of hypercalcemia at presentation were humoral hypercalcemia of malignancy with PTH-rP as the causal agent[8]. However, hypercalcemia in malignancy can sometimes be facilitated through multiple pathophysiology, including non-malignancy related pathways such as hyperparathyroidism. However, laboratory investigations in patients indicated severe hypercalcemia – which is usually highly associated with malignancy. The diagnosis in our patient was PTH-rP mediated hypercalcemia, which was confirmed by laboratory investigations and was hypothesized to be caused by the recurrence of the underlying ovarian clear cell adenocarcinoma. However, due to the circumstances of our patient, hard evidence regarding the recurrence of ovarian clear cell adenocarcinoma was unfortunately not obtained. The prognosis regarding high pretreatment calcium levels and elevated PTH-rP is shown to be poor, with an increased mortality of 30% of each mg/dL of elevated serum calcium[9, 10].

Treatment in this patient was conducted through consultation of both nephrology and endocrine specialists and was in line with the current clinical practice guidelines for severe hypercalcemia[11]. A combination of calcitonin and intravenous bisphosphonate, in addition to aggressive saline hydration, was administered. Patients with severe hypercalcemia usually have associated kidney injury due to multiple mechanisms, such as renal vasoconstriction. Another factor to consider when selecting treatment is the increased risk of using bisphosphonate for renal impairment. Serum calcium levels were lowered as predicted, however our patient died after treatment, most likely from an ongoing abdominal infection.

Hypercalcemia, as a complication of malignancy, should be treated even if the primary cancer is in its advanced stage or is untreatable, to reduce symptoms, decrease the number of hospital admissions and to improve the patients' quality of life.

Through literature review (table 2), PTH-rP has been shown to be associated with disease prognosis. Routine monitoring may be beneficial as a marker for recurrence – for early treatment of second line agents such as salvage chemotherapy or target therapy.

Conclusion

We presented a case of PTH-rp related hypercalcemia in a patient with clear cell ovarian cancer, which was associated with a poor prognosis of the disease. Early recognition and prompt assessment was required due to the recurring nature of this disease.

Acknowledgement

Clinical data, laboratory investigations and imaging studies were provided by Burapha University Hospital. Pathological studies and photographs were kindly provided by the Chonburi Cancer Hospital.

Table 2 The case report of clear cell-ovarian cancer associated with hypercalcemia.

Clinical	Histological Type	Stage (FIGO)	Ca (mg/dL)	PTH (pmol/L)	PTH-rp (pmol/L)	Diagnosis	Treatment	Outcome
63 years, Abdominal distension, and anorexia Bilateral ovarian mass 10.5 cm, 4.5 cm[12]	Clear cell adenocarcinoma	IIIC	15.40	0.95	12.20	PTH-rP related HHM	IV hydration Pamidronate TAH with BSO + CMT	Died in 13 months
49 years, Pelvic mass 24x22x12 cm loss of appetite N/V constipation thirst[13]	Clear cell ovarian adenocarcinoma	IIIC	13.00	0.30	259	PTH-rP HHM	10 mg disodium incadronate IV TAH with BSO + CMT	Recurrence of CA at 3 months after CMT
35 years, Hypercalcemia after C/S 50 days 13.8x7.8 cystic mass Lt. uterus[14]	Clear cell ovarian carcinoma	IC	13.60	1.36	12.20	PTH-rP HHM	Pamidronate, Hydration, Furosemide IV Lt. SO and washing cytology + CMT	Remission
34 years, Lower abdominal mass[15]	Clear cell carcinoma	IV B	13.60	15.10	PTH-rP staining from pathology of metastatic lymph node	PTH-rP HHM	TAH with BSO + CMT Hydration Furosemide Calcitonin	Unknown
56 years, lower abdominal pain, malaise, constipation, bilateral ovarian tumor size 16 and 10 cm[16]	Clear cell adenocarcinoma	Unknown	15.50	-	-	Unknown	TAH with BSO + CMT	Alive 13 months without recurrence
48 years, acute abdominal pain, tumor 10x11x10 cm with partial rupture[17]	Clear cell carcinoma	IIc	14.60	<0.03	6090	PTH-rP HHM	TAH with BSO + CMT Saline hydration, furosemide, calcitonin	Died 1 month after admission
60 years, N/V, weight loss 9 kg[18]	Mixed serous and clear cell carcinoma	IIC	15.70	< 0.03	23.11	PTH-rP related HHM	IV hydration, calcitonin, zoledronic acid	-

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