

# The co-occurrence of leukemoid reaction and hypercalcemia in a patient with endometrial cancer: A case report and literature review

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## Abstract

Paraneoplastic syndromes are rarely seen in gynecological tumors especially in endometrial cancer. Early identification of paraneoplastic syndromes plays a significant role in the treatment and prognosis of cancer. Here, we reported a rare case with endometrial cancer with a 2.7 cm × 2.2 cm × 3.4 cm lesion in the posterior cervix presenting leukemoid reaction and hypercalcemia as paraneoplastic syndromes simultaneously. During the progress of the endometrial cancer, her leukocyte level rose up to  $60.7 \times 10^9/L$  after anti-infection treatment. Meanwhile, the patient represented a series of severe clinical situation including hypercalcemia, hypokalemia, metabolic alkalosis, and respiratory failure. Finally, the patient died of respiratory circulatory failure 2 weeks later. In addition to symptomatic treatment, possible treatment targeted on the primary tumor as early as possible might help to improve the clinical prognosis.

## Keywords

Endometrial cancer, paraneoplastic syndromes, leukemoid reaction, hypercalcemia

## Introduction

Endometrial cancer (EC) is one of the most common gynecologic malignancy in female reproductive system. It has been reported that there were about 320,000

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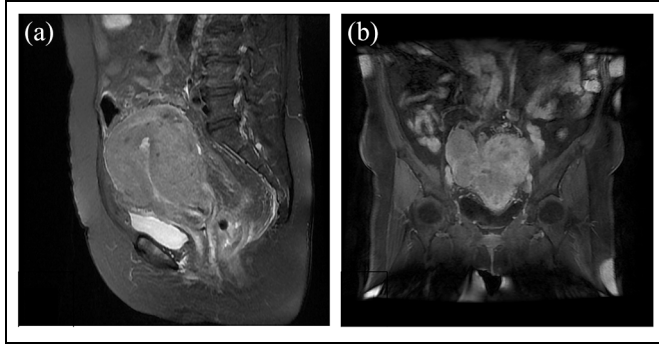
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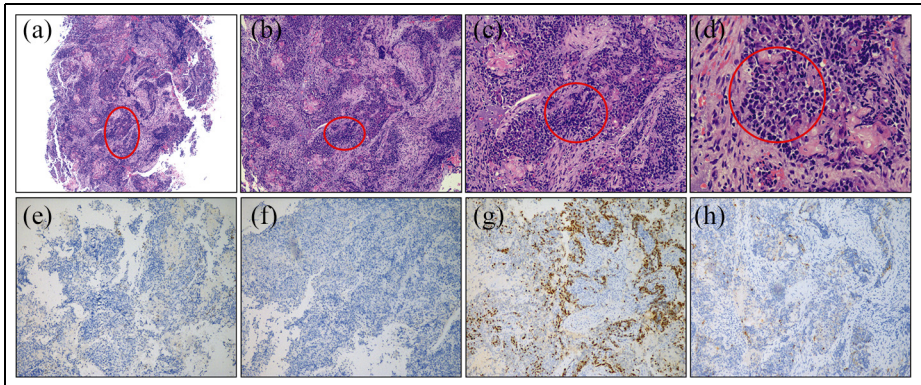


**Figure 1.** Magnetic resonance imaging of primary and recurrent cervical mass: (a) the arrow indicated a 2.7 cm × 2.2 cm × 3.4 cm lesion in posterior cervix accompanied by disappearance of the posterior fornix and (b) the arrow indicated a 68 mm × 63 mm × 58 mm mass in the vaginal cuff.

patients suffering from endometrial cancer and 76,000 died each year around the world.<sup>1</sup> Paraneoplastic syndromes (PNS), which caused by hormones, cytokines and autoimmune responses around the para-carcinoma cells are common in malignant tumors. PNS could influence multiple systems leading to severe life-threatening outcomes.<sup>2</sup> Leukemoid reaction and hypercalcemia are two of the paraneoplastic syndromes in malignant cancers.<sup>3-5</sup> In 1989, Hiller described two patients with humoral hypercalcemia diagnosed endometrial carcinoma.<sup>6</sup> Early awareness of the PNS in certain gynecological malignancy types would benefit for earlier monitoring the progress of the disease. Here we reported a rare endometrial cancer case presenting the PNS of leukemoid reaction and hypercalcemia at the same time.

## Case report

A 66-year-old women was admitted to our hospital on July 2nd, 2018 due to the intermittent minor vaginal bleeding for more than 2 years' duration. She was previously diagnosed hypertension and well controlled with the administration of CCB. The patient had previously undergone cesarean section and transabdominal myomectomy. On physical examination: BMI 27.34 kg/m<sup>2</sup>, no swollen lymph nodes, no common Cushing syndrome was found, increased uterus as large as 8-week-pregnancy. Transvaginal ultrasonographic examination demonstrated the endometrium was thickened by 10 mm with multiple uterine fibroids. The routine blood test indicated: WBC:  $9.7 \times 10^9$ /L, neutrophils: 73.2%, lymphocytes: 19.6%, hemoglobin: 153 g/L, platelet:  $180 \times 10^9$ /L, normal blood clotting function. On July 6th, magnetic resonance imaging (MRI) revealed nonuniform signal in pelvic cavity indicating a 2.7 cm × 2.2 cm × 3.4 cm lesion in the posterior cervix (Figure 1). Dilation and curettage (D&C) HE morphology and immunohistochemical indicated:



**Figure 2.** HE and immunohistochemical (ER, PR, Ki67, and CgA) staining of the patient's endometrial tumor tissue slices: (a–d) irregular nests of neoplastic cells gathered in the uterine section (50 $\times$ , 100 $\times$ , 200 $\times$ , 400 $\times$ ), (e) negative ER immunohistochemical staining 100 $\times$ , (f) negative PR immunohistochemical staining 100 $\times$ , (g) positive Ki67 immunohistochemical staining 100 $\times$ , and (h) negative CgA immunohistochemical staining 100 $\times$ .

Negative CgA, ER, PR staining, and Ki-67 70% positive which suggested Grade 3 low-differentiated endometrial carcinoma (Figure 2). Multiple pelvic lymph nodes, para-aortic, and retroperitoneal lymph nodes were noted. Tumor makers analysis on July 23th indicated: SCCA: 12.6 ng/mL, CEA: 31.09 ng/mL, CA125: 46.11 U/mL, CA199: 746 U/mL.

Before the total abdominal hysterectomy, an infection was noted due to elevated leukocytes level combined with low-grade fever (37.4°C). The patient was first systemic treated with ceftriaxone and ornidazole. However, the level of WBC elevated to  $34.2 \times 10^9/L$  in 5 days (July 25th) and the temperature was fluctuated around 37.5°C. Five days later the antibiotics were changed to cefoperazone-sulbactam combined with fosfomycin. Meanwhile, oral potassium supplement treatment was ordered for hypokalemia (3.1 mmol/L). On July 28th, routine blood tests showed that the leukocytosis went up to  $47.9 \times 10^9/L$  and neutrophils rose up to 90.3%, lymphocytes went down to 6.3%. The peripheral blood smear indicated: neutrophilic segmented granulocyte: 83%, lymphocyte: 5% with myelocytes and metamyelocytes. After clinical consultation, hematologists considered there was a possibility that she might suffer from chronic granulocytic leukemia. She was treated with hydroxycarbamide and sodium bicarbonate tablets. Before the bone marrow aspiration on July 31th, the patient began to appear strong chest tightness, shortness of breath. The laboratory examinations suggested severe hypokalemia (1.6 mmol/L), combined with metabolic alkalosis (PH 7.66,  $HCO_3^-$  36.4 mmol/L, BE 15.9 mmol/L), as well as severe hypoxemia (PaO<sub>2</sub> 52 mmHg, SaO<sub>2</sub> 93%). Later, the patient was transferred to ICU to receive further treatment. The result of laboratory examination before ICU was shown in Table 1.

**Table 1.** Laboratory data before entering ICU.

	Normal values	Date				
		07-06	07-20	07-23	07-26	07-31
WBC	4–10 × 10 <sup>9</sup> /L	9.7	23.5	28.5	34.2	51.9
Neutrophils (%)	50%–70%	73.2	90.1	87.9	92.1	89.8
Nymphocyte (%)	20%–40%	19.6	6.5	7.7	4.1	6.9
Potassium	3.5–5.3 mmol/L		3.5	3.1		1.6
PCT	<0.25 ng/mL		0.12		0.15	
CRP	0–8 mg/L		25	46	44	82

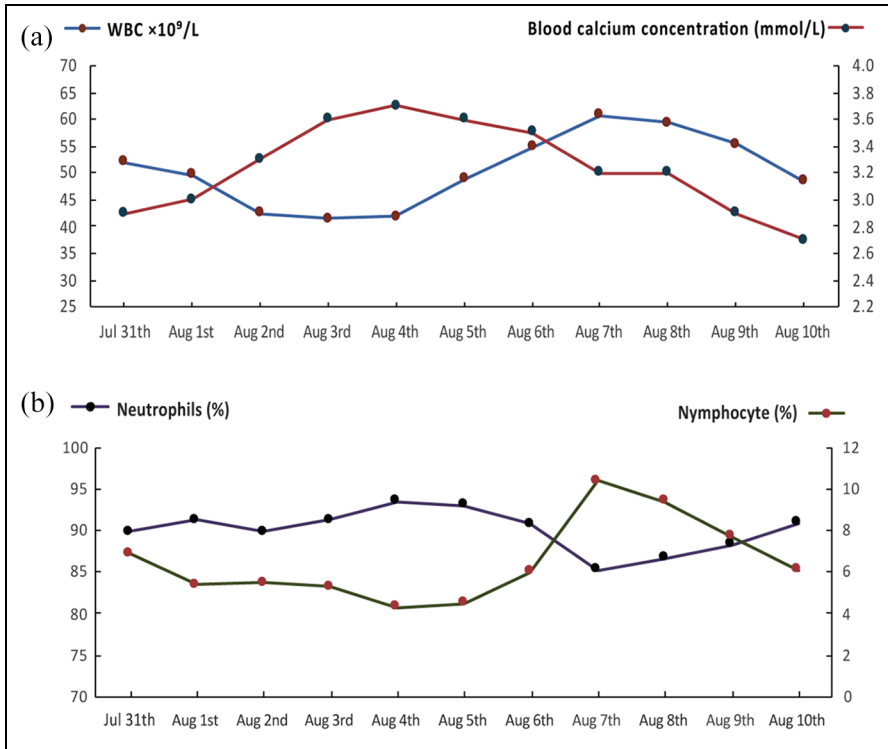
On the first day of admission to ICU, PaO<sub>2</sub> was maintained at 50–75 mmHg after receiving NPPV. PaO<sub>2</sub> elevated to 160 mmHg on the second day with HFNC and NPPV intermittent treatment. Blood biochemical examination still revealed severe hypercalcemia (2.9 mmol/L) and hypophosphatemia (0.3 mmol/L). The patient's hypoxemia was improved after noninvasive positive pressure ventilation. However, all methods including diuresis, calcitonin intravenous injection, and oral diphosphonate were unable to rectify her blood calcium level. During the treatment, the calcium peak reached at 3.7 mmol/L accompanied with extremely high level of leukocyte, which rose to 60.7 × 10<sup>9</sup>/L. Dynamic changes of serum calcium, leukocytes; neutrophils and lymphocytes ratios were shown in Figure 3. Results of bone marrow biopsy were shown in Table 2. All data above indicated that there was no possibility that the patient was suffering from chronic granulocytic leukemia.

During ICU treatment, the patient's uterus continuously enlarged to two fingers above umbilicus. Meanwhile, she was gradually developed deterioration of respiratory, circulation, and consciousness. Considering that all the symptoms of the patient were caused by terminal stage of endometrial cancer that couldn't be reversed, her family decided to give up further treatment. The patient died of respiratory failure 2 weeks later after entering ICU unfortunately.

## Discussion

### *Leukemoid reaction in malignant tumor*

IR is one of the physiological paraneoplastic syndromes triggered by altered immune response to a neoplasm which is really rare in gynecologic malignant tumor. The occurrence of paraneoplastic leukemoid reaction was considered to be related with cytokines (such as G-CSF, GM-CSF, IL-1 $\alpha$ , IL-6) secreted by tumor tissues.<sup>7,8</sup> In addition to promoting the increase of white blood cells, cytokines also directly accelerate the growth of tumor tissues via paracrine. In our case, there were no significant increases in PCT and other infection indicators, no particular drugs were used during previous treatment. However, the level of leukocytes kept



**Figure 3.** Dynamic changes of serum calcium, leukocytes, neutrophils, and lymphocytes ratios during the treatment process.

**Table 2.** Result of bone marrow aspiration.

Test	Results
Flow cytometric test	No increase of CD34 + primitive/immature cells, normal in immunophenotyping analysis. Mature granulocytes account: 91.7%, normal in immunophenotyping analysis
Fusion gene test	P210 <sup>BCR-ABL</sup> negative (-) P190 <sup>BCR-ABL</sup> negative (-) P230 <sup>BCR-ABL</sup> negative (-)
Chromosomal karyotype analysis	No abnormal chromosome (number or structure) detected associated with tumor

rising remarkably during anti-infection treatment. Meanwhile, the tumor grew progressively. No typical CML symptoms were observed in bone marrow tests. Taken together, we believed the abnormal changes in hemogram and myelogram were paraneoplastic leukemoid reactions caused by endometrial cancer. According to

**Table 3.** Pathoclinical features in the cases of endotremial cancer with hypercalcemia.

Author	Pathology	Serum Ca <sup>2+</sup> level	Treatment accepted	Outcome
Visnyei et al. <sup>14</sup>	EC <sup>ω</sup>	3 mmol/L	Bisphosphonate	Discharged
Nehru et al. <sup>15</sup>	SS <sup>&amp;</sup>	4.8 mmol/L	Chemotherapy + radiation	DOD <sup>#</sup>
Sachmech et al. <sup>16</sup>	PSC <sup>Δ</sup>	3.2 mmol/L	Surgery + chemotherapy	Discharged
Mitchell et al. <sup>17</sup>	EEA <sup>§</sup>	3.7 mmol/L	Bisphosphonate + calcitonin	DOD
Current report	NC <sup>Φ</sup>	3.7 mmol/L	Bisphosphonate + calcitonin	DOD

EC<sup>ω</sup>: endometrioid carcinoma; SS<sup>&</sup>: stromal sarcoma; DOD<sup>#</sup>: dead of disease; PSC<sup>Δ</sup>: papillary serous carcinoma; EEA<sup>§</sup>: endometrioid endometrial adenocarcinoma; NC<sup>Φ</sup>: neuroendocrine carcinoma.

the report of Granger and Kontoyiannis,<sup>9</sup> patients diagnosed with PLR have a case-fatality rate up to 76% within 12 weeks, 89% within 1 year, the remaining 10% of the patients who survived more than 1 year have received aggressive chemotherapy or surgery for the tumor. Patients with hyperleukemia also showed a tendency to metastasize which might be related to the formation of tumor pre metastatic niches mediated by tumor secreted G-CSF and myeloid derived suppressor cells (MDSC). Clark et al.<sup>10</sup> reported a 65-year-old PLR symptom with recurrent endometrial cancer after surgical treatment appeared abnormal leukocyte elevation ( $51.4 \times 10^9/L$ ) and red blood cells/platelets myelosuppression during chemotherapy with elevated GCSF level. Eight months after PLR occurred, the patient died due to the intolerance to chemotherapy.

### *Hypercalcemia in malignant tumor*

Hypercalcemia or humoral hypercalcemia of malignancy (HHM) is a common paraneoplastic syndrome, with the incidence of 10% in cancer patients.<sup>11</sup> Symptoms could range from mild thirst and nausea to life-threatening conditions such as kidney failure and coma. Laboratory tests reveal elevated blood calcium levels, low level of PTH, and elevated PTHrP levels accounted for approximately 80% of all tumor-associated hypercalcemia.<sup>12</sup> The prognosis of tumor-associated hypercalcemia is often poor, with a 30-day mortality rate up to 50%. HHM is commonly seen in solid tumors such as lung cancer, breast cancer, and bladder cancer but it is fairly rare in female malignant tumors. According the literature, approximately two-third of the ovarian small cell carcinoma would co-occur with hypercalcemia.<sup>13</sup> In endometrial cancer, the occurrence of hypercalcemia is very rare, only few cases combined with HHM have been reported<sup>14-17</sup>(Table 3). In our case, although the serum calcium level dropped after receiving medications, her condition was getting worse since the primary tumor was incapable to treat effectively. After all possible treatments failed, hypocalcemia treatment termination (hypercalcemia would lead to coma to death) might be an appropriate and more humane approach.

## Conclusion

In conclusion, we reported a rare case of a patient who had endometrial cancer co-occurred with two paraneoplastic syndromes (leukemoid reaction and hypercalcemia). For this kind of patients, the prognosis would be extremely poor without effectively anti-tumor therapy.

## Authors' contribution

Zhendong Xu is in charge of the project and the writing of the thesis. Weimin Tao completed the collection and analysis of relevant literature, as well as writing the paper. Qin Yan, Yao Zhou, Yanli Wang and Zhiqiang Liu are the main participants in the treatment process, and involved in the data collection process.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethics approval

Ethical approval to report this case was obtained from \*Shanghai First Maternity and Infant Hospital (KS20203)\*.

## Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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