Uterine Carcinoma With Complex Reasons for Hypercalcemia: a Case Report and Review of the Literature

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Case report

Keywords: Ectopic parathyroid hormone (ectopic PTH), parathyroid hormone-related protein (PTH-rp), large-cell neuroendocrine carcinoma (LCNEC), endometrial cancer

Posted Date: March 6th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-287350/v1

Abstract

Introduction: Large-cell neuroendocrine carcinoma (LCNEC) is a seldom seen histological subtype of endometrial cancer with aggressive behavior and poor prognosis. Among current literatures, no one was found to be hormonally functional.

Case presentation: We reported a rare case of endometrial LCNEC expressing both parathyroid hormone (PTH) and parathyroid hormone-related protein (PTH-rp). With ectopic PTH secreted into the blood stream, the hypercalcemia caused by malignant existence and osseous metastasis were concealed and misled initially.

Literature review: Systematic literature search of previously reported uterine large cell neuroendocrine carcinomas and ectopic PTH-secreting neuroendocrine tumor (NET) cases were conducted in PubMed/MEDLINE databases respectively. We identified 55 cases of uterine LCNEC and 7 cases of PTH-secreting NET. Clinicopathologic characteristics, treatment and prognosis of all collected cases were summarized.

Conclusion: Although quite rare, endometrial cancer can be functional and secret ectopic hormone, causing confusing clinical features. This case demonstrated the challenge in diagnosing malignancy-associated refractory hypercalcemia.

Introduction

Neuroendocrine carcinoma (NEC) arises mostly from the lung and can be occasionally detected in the gastrointestinal and urogenital tract. When it comes to female genital organs, it occurs more frequently in the cervix and ovary, but rarely involves the endometrium[1, 2]. Most were reported to be small-cell type, while large cell neuroendocrine carcinomas (LCNECs) were extremely rare[3]. Despite its low incidence, LCNEC has high malignant degree, early metastasis tendency and usually carries poor prognosis. It can be solitary or co-occur with other histological types such as endometroid adenocarcinoma[4], serous carcinoma[5] and malignant mixed Mullerian tumor (MMMT)[1], etc. The clinical manifestations of endometrial LCNEC cases resemble endometrial adenocarcinoma, including abnormal uterine bleeding and abdominal pain. This might be the first case of endometrial LCNEC with hypercalcemia presented as the main manifestation. And regretfully, the diagnosis was misled initially by elevated parathyroid hormone (PTH) level and finally determined by a palliative hysterectomy.

Case Presentation

A 53-year-old female (gravida1, para1), presented to the Department of Nephrology due to thirsty, polydipsia, polyuria and gradually developing swelling of the limbs and face for more than one month. Medical history was notable for two months of lumbago, along with radiating pain to both lower extremities, which had been diagnosed as lumbar disc herniation, with ibuprofen ineffective to relieve the symptom. Personal and family history were otherwise unremarkable. On examination, she had edema of face and both lower limbs. High blood pressure (173/104 mmHg) was found while other vital signs were within normal ranges. Initial laboratory and ultrasound findings indicated acute kidney injury (AKI) (serum creatinine 157 umol/L; blood urea nitrogen 22.6 mmol/L; no significant increase in the size of the kidneys and cortical thickness), and drug-induced interstitial nephritis was presumed.

Nevertheless, after admission, profound hypercalcemia (Calcium: 4.47 mmol/L, N 2.10–2.55 mmol/L) and elevated level of PTH (280.1 pg/mL, N 12.0–88.0 pg/mL) suggested that the cause of AKI was dehydration from Hypercalcemic crisis. Hemodialysis was performed immediately, followed with intravenous fluids, diuresis, salmon calcitonin and pamidronate disodium. After symptomatic treatment, her blood pressure dropped back to normal with renal function recovery (serum creatinine 72 umol/L, blood urea nitrogen 7.4 mmol/L**).** However, recurrent symptoms, hypercalcemia and gradually increased level of PTH (280.1 pg/ml-486.0 pg/ml-1316.0 pg/ml) raised the possible diagnosis of primary hyperparathyroidism (PHPT). Upon further examination, neck ultrasound, Tc99m methoxyisobutylisonitrile (Tc99m-MIBI) scintigraphy scanning and chest computerized tomography all failed to localize a possible primary/ectopic parathyroid adenoma or hyperplasia lesion. The patient was transferred to Endocrinology Department due to unexplained hypercalcemia and hyperparathyroidism.

Further neck and chest ^{18}F-fluorocholine positron emission tomography-computed tomography (^{18}F-FCH PET/CT) still failed to identify specific overactive PTH secretion areas. Simultaneously, bone metabolic indexes such as serum osteocalcin (33.67 ng/ml) and total Procollagen Type I N-terminal Propeptide (77.69 ng/ml) indicated the existence of osteolytic destruction. Given the results above, endocrinologists got down to the possibility of ectopic PTH-secreting tumor and re-reviewed the medical history in detail: 1. left hip joint post-activity pain for more than two months; 2. perimenopause woman with menstrual disorder for nearly one year. Accordingly, hip X-ray was performed and revealed bone destruction of left ischium and inferior ramus of pubis. Transvaginal ultrasonography showed the intrauterine abnormal echo. The attention was finally attached to osseous metastatic tumor of gynecologic origin. Abdominopelvic magnetic resonance imaging (MRI) showed crumby-structured thickened endometrium and a 7 cm × 5 cm mass in the left ischium and pubis, both heterogeneously enhanced with obscure boundary, accorded with the manifestation of endometrial malignant tumor metastasizing to left obturator, also consistent with ^{18}F-fluorodeoxyglucose PET/CT scan findings (Fig. 1). Nevertheless, subsequent colposcopy and directed biopsy of the cauliflower-like neoplasm at the external orifice of cervix revealed endometrial adenocarcinoma.

After multi-disciplinary team consultation, PHPT was excluded. Bone metastases of gynecologic tumor and ectopic secretion of PTH were thought to work together and lead to refractory hypercalcemia. However, the source of PTH was still inconclusive since endometrial adenocarcinoma is a nonendocrine tumor, with no relevant case reported so far. Definite diagnosis still remained pending.

Although it was hard to explain the relationship between the tumor feature and PTH secretion, initial chemotherapy was recommended due to the advanced disease. One week after the initiation of chemotherapy with nedaplatin (100 mg/m^2) and paclitaxel (175 mg/m^2), the patient's pain resolved, her high serum calcium and PTH levels gradually dropped back to normal (Calcium: 2.37 mmol/L, PTH: 89.7 pg/ml) and remained within the normal limits during treatment

(six months). Following two cycles of chemotherapy, the enlarged uterus and tumor were evaluated (physical examination and MRI) to be reduced partially. Palliative surgery of hysterectomy and bilateral salpingo-oophorectomy was recommended through multidisciplinary approaches and performed because of persistent vaginal spotting.

Intraoperative exploration revealed slightly enlarged irregular uterus with several subserous grey-white lesions involving the anterior-fundal wall, about 0.3cm-1cm in diameter. Dense adhesion of left infundibulopelvic ligament and sigmoid colon extended to left pelvic wall. No obvious abnormality was found in bilateral adnexa, omentum and bowel. Gross findings showed diffuse grey-white cauliflower-like lesions in the uterine cavity, 1–2 cm in size, with whole myometrial infiltration to the serosa layer. Whereas a polypoid neoplasm of about 3cm × 3cm × 2cm located in the upper endocervical canal was noted, with the gross appearance completely different from that of the uterine body. Post-operative pathology confirmed two distinct histologic types: endometrioid carcinoma and large cell neuroendocrine carcinoma (LCNEC), which were markedly different both visually and microscopically (Fig. 2). The diagnosis of LCNEC was supported by immunostaining for neural cell adhesion molecule (CD56), synaptophysin (Syn) and Chromogranin A (CgA). Deep myometrial and lymphavascular invasion were observed in LCNEC but not in endometroid carcinoma. Additionally, differential distribution of estrogen receptor (ER) and progesterone receptor (PR) between LCNEC (stromal) and endometroid carcinoma (glandular) was observed. To explore the reason of hypercalcemia and elevated PTH level, immunohistochemistry (IHC) staining was performed, and positive expression of PTH and PTH-related protein (PTH-rP) was detected in LCNEC other than in endometroid carcinoma (Fig. 2). Despite postoperative adjuvant chemotherapy and radiotherapy, the patient succumbed to the disease 12 months after diagnosis from recurrent hypercalcemia.

Literature review

In the systematic literature search of PubMed database using the search terms ((‘endometrium’[All Fields] OR ‘uterine’[All Fields]) AND ‘neuroendocrine carcinoma’[All Fields]), 539 citations were initially obtained (final search date 2020-12-01). After excluding literatures irrelevant or lacking of essential clinicopathological information, a total of 30 English language articles were identified eligible[1–30]. As shown in Table 1, more than 85% of endometrial LCNEC occurred in patients over 50 years, with a median age of 58 years (range 37 years ~ 88 years), which mostly appeared as abnormal bleeding and abdominal pain, similar to the presentation of other uterine carcinomas. Less common symptoms including dyspnea and dizziness caused by metastasis[17]. Except for a patient with psychosis caused by anti-*N*-methyl-d-aspartate receptor encephalitis[20], none of them presented as paraneoplastic syndrome. This type of aggressive malignancy is often diagnosed at advanced stage, with more than 70% of patients suffering wide metastasis. Of the 55 cases reported, preoperative diagnosis was achieved in only 4 cases[5, 12, 21, 28], since the pathological patterns based on small biopsy specimens were insufficient. In addition, the radiologic findings were nonspecific[12] and there is no NEC specific biomarkers[3]. Due to the resemblance of pathologic morphology features between LCNEC and other poorly-differentiated carcinoma, undifferentiated sarcoma and MMMT[1], postoperative immunohistochemistry based on a larger specimen serves as the most useful method for diagnosis, with at least one positive neuroendocrine marker detected in previous reported cases. LCNEC appeared simultaneously with other histological types at times, most frequently with endometrioid carcinoma (22 cases, 40%), followed by small-cell neuroendocrine carcinoma (7 cases, 12.7%) and serous carcinoma (4 cases, 7.3%). Relatively rare mixed histologic components including clear cell carcinoma[17], MMMT[1] and low-grade endometrial stromal sarcoma[29]. LCNEC tends to be aggressive and have strong propensity for metastasis[1]. Some patients with combined components of malignancies exhibited only distant LCNEC metastasis[8, 16]. Standard management has not been established due to its rarity, so is has been treated in the same way as other endometrial carcinoma. Except for 3 terminal-stage patients who accepted palliative care, most patients received surgery with or without adjuvant therapy. Hysterectomy and bilateral salpingo-ophorectomy were performed at minimum. Further procedures included lymphadenectomy, omentectomy, tumor cytoreduction and appendectomy. As for adjuvant therapy, 33 (60%) patients received chemotherapy, 18 (32.7%) patients combined with radiotherapy, and 6 (10.9%) patients received radiotherapy only. Chemotherapy regimen was available for 18 patients, and platinum in combination with etoposide, irinotecan or paclitaxel were generally used. However, despite the multi-modality approach of treatment, the prognosis is still poor. Of the 55 cases reported, more than half of the patients experienced recurrence or progression in 2 years. 25 cases progressed rapidly with a survival of less than 2 years, even in 5 patients with early-stage disease.

Table 1
Clinicopathologic features of currently reported uterine LCNEC

Case	Author	Age	FIGO Stage	Presenting complaint	Biopsy pathology	Surgery	Postoperative pathology	Neuronal Markers	Adjuvant treatme
1	Erhan et al.	52	IC	AUB	NA	HystBSO	LCNEC	Syn, NSE	CT (EPcis) + RT
2	Mulvany et al.	50	IIIC	AUB	NA	HystBSO, OMY, LND	LCNEC	Syn, NSE	CCRT (EPcar)
3	Mulvany et al.	80	IC	AUB	NA	HystBSO, LND	LCNEC, EC G3	CgA, NSE	None
4	Mulvany et al.	77	IIB	AUB	NA	HystBSO	LCNEC, EC G1	Syn, CgA, CD56, NSE	RT
5	Mulvany et al.	79	IIIA	AUB	NA	HystBSO, Obx, Pbx	LCNEC, EC G1	CgA, CD56, NSE	RT
6	Mulvany et al.	88	IIIC	AUB	NA	HystBSO, LND	LCNEC, EC G3, SCNEC with squamous differentiation	CgA, CD56, NSE	RT
7	Posligua et al.	59	IIIB	AGC	High-grade NEC	Modified radical HystBSO, OMY, LND	LCNEC, papillary SC	Syn, CD56, NSE	CT (NA) + RT
8	Albores-Saavedra et al.	42	IC	AUB	None	Radical hysterectomy	LCNEC	Syn, CgA, CD56	CT (EPcis)
9	Froio et al.	58	IB	AUB	Cancer of mesodermal origin	HystBSO, LND	Carcinosarcoma with LCNEC histology	Syn, CgA	None
10	Terada et al.	40	IB	AUB	Sarcomatous, undifferentiated carcinoma	HystBSO, LND, OMY	LCNEC with sarcomatous changes	Syn, CD56	CT (NA)
11	Deodhar et al.	70	IB	AUB, abdominal pain	None	HystBSO, OMY	LCNEC	Syn, CgA, CD56	CT (EPcis)
12	Shahabi et al.	59	IIIC2	AUB	Poorly differentiated endometrial carcinoma	HystBSO, OMY,LND, APPY, tumor cytoreduction	LCNEC	Syn, CgA, CD56, NSE	Sandwich chemoradiothera (TC)
13	Makihara et al.	73	IVB	Lumbago,abdominal distention	LCNEC	None	None	Syn, CgA, NSE	Palliative care
14	Makihara et al.	73	IIIC	AUB, heavy discharge	Adenocarcinoma with solid poorly differentiated component	HystBSO, OMY, LND	LCNEC	Syn, CgA, CD56	CT (IP)
15	Nguyen et al.	71	IVB	AUB	Extensive necrosis and apoptosis	Radical HystBSO, OMY, LND, tumor cytoreduction	LCNEC	Syn, CgA, CD56	None
16	Chougule et al.	55	IB	AUB	Moderately differentiated adenocarcinoma	HystBSO, LND	LCNEC	Syn, CgA, CD56	None
17	Konishi et al.	54	IIIC1	AUB	Poorly differentiated endometrial carcinoma	Modified radical HystBSO, LND, OMY	LCNEC	Syn, CgA, CD56	CT (IP)
18	Matsumoto et al.	51	IIIA	Cancer screening	Adenosquamous carcinoma with neuroendocrine differentiation	Radical HystBSO, OMY, LND	LCNEC, EC G1	Syn, CgA, CD56	CT (IP)

AGC, atypical glandular cells; APPY, appendectomy; AUB, abnormal uterine bleeding; AWD, alive with disease; CCRT, concurrent chemoradiotherapy; CP, cyclophosphamide/cisplatin; CT, chemotherapy; DOD, died of disease; EC, endometrioid carcinoma; EPcar, etoposide/carboplatin; EPcis, etoposide/cisplatin; hysterectomy with bilateral salpingo-oophorectomy; IP, irinotecan/cisplatin; LND, lymph node dissection; MMMT, malignant mixed Mullerian tumor; NA, not av evidence of disease; NSE, neuron-specific enolase; Obx, omental biopsy; OMY, omentectomy; Pbx, peritoneal biopsy; RT, radiotherapy; SC, serous carcinoma; S neuroendocrine carcinoma; STbx, soft tissue biopsy; TC, paclitaxel/carboplatin; TP, paclitaxel/cisplatin.

Case	Author	Age	FIGO Stage	Presenting complaint	Biopsy pathology	Surgery	Postoperative pathology	Neuronal Markers	Adjuvant treatme
19	Ono et al.	41	II	Vaginal mass	None	Hysterectomy	LCNEC, EC G3	Syn, CgA, CD56	CT (TC)
20	Pocrnich et al.	54	IA	NA	NA	HystBSO	LCNEC	CgA	RT
21	Pocrnich et al.	65	IA	AUB	NA	HystBSO,LND	LCNEC, SCNEC, EC G3	Syn, CgA, CD56	RT
22	Pocrnich et al.	84	IB	AUB, abnormal Pap smear	NA	HystBSO,LND	LCNEC, EC G2	CD56	RT
23	Pocrnich et al.	66	IB	AUB	NA	HystBSO,LND	LCNEC, EC G2	Syn	CT (NA) + RT
24	Pocrnich et al.	55	IB	AUB	NA	HystBSO	LCNEC, EC G2	Syn, CgA	NA
25	Pocrnich et al.	47	II	AUB	NA	HystBSO,LND	LCNEC, EC G2	Syn, CgA	CT (NA) + RT
26	Pocrnich et al.	51	II	AUB, abnormal Pap smear	NA	HystBSO,LND□Obx	LCNEC, EC G2	Syn, CgA	CT (NA) + RT
27	Pocrnich et al.	68	IIIA	AUB	NA	HystBSO	LCNEC, SCNEC, EC G2	Syn, CgA, CD56	CT (NA) + RT
28	Pocrnich et al.	69	IIIA	AUB	NA	HystBSO,LND	LCNEC	CgA	CT (NA) + RT
29	Pocrnich et al.	59	IIIB	Abnormal Pap smear	NA	HystBSO,LND	LCNEC, SC	Syn, CD56	CT (NA) + RT
30	Pocrnich et al.	54	IIIB	AUB	NA	HystBSO,LND	LCNEC, EC G2	Syn, CgA	CT (NA) + RT
31	Pocrnich et al.	68	IIIB	AUB	NA	HystBSO, LND, APPY	LCNEC, SCNEC, EC G3, clear cell carcinoma	Syn	CT (NA) + RT
32	Pocrnich et al.	52	IIIC1	AUB	NA	HystBSO, LND	LCNEC	CgA	CT (NA) + RT
33	Pocrnich et al.	55	IIIC2	AUB	NA	HystBSO, LND	LCNEC	Syn, CD56	None
34	Pocrnich et al.	63	IIIC2	NA	NA	HystBSO, LND, Obx	LCNEC	Syn, CgA, CD56	NA
35	Pocrnich et al.	87	IVB	AUB	NA	HystBSO, Obx	LCNEC, SCNEC, EC G3	Syn	CT (NA)
36	Pocrnich et al.	59	IVB	Dizziness	NA	HystBSO, LND	LCNEC, EC G2	Syn, CgA	CT (NA) + RT
37	Pocrnich et al.	55	IVB	AUB, abdominal pain	NA	HystBSO, APPY, STbx	LCNEC, SCNEC	Syn, CgA, CD56	NA
38	Pocrnich et al.	37	IVB	AUB	NA	HystBSO, Obx, Pbx	LCNEC, SCNEC	Syn, CgA	CT (NA)
39	Pocrnich et al.	80	IVB	Dyspnea	NA	HystBSO, Pbx	LCNEC	Syn, CgA	None
40	Pocrnich et al.	55	IVB	AUB	NA	HystBSO, LND, Obx	LCNEC	Syn	CT (NA)
41	Ariura et al.	61	IB	AUB	None	Modified radical HystBSO, OMY, LND	LCNEC, EC G1	Syn, NSE	None

AGC, atypical glandular cells; APPY, appendectomy; AUB, abnormal uterine bleeding; AWD, alive with disease; CCRT, concurrent chemoradiotherapy; CP, cyclophosphamide/cisplatin; CT, chemotherapy; DOD, died of disease; EC, endometrioid carcinoma; EPcar, etoposide/carboplatin; EPcis, etoposide/cisplatin; hysterectomy with bilateral salpingo-oophorectomy; IP, irinotecan/cisplatin; LND, lymph node dissection; MMMT, malignant mixed Mullerian tumor; NA, not av evidence of disease; NSE, neuron-specific enolase; Obx, omental biopsy; OMY, omentectomy; Pbx, peritoneal biopsy; RT, radiotherapy; SC, serous carcinoma; S neuroendocrine carcinoma; STbx, soft tissue biopsy; TC, paclitaxel/carboplatin; TP, paclitaxel/cisplatin.

Case	Author	Age	FIGO Stage	Presenting complaint	Biopsy pathology	Surgery	Postoperative pathology	Neuronal Markers	Adjuvant treatme
42	Kobayashi A et al.	52	IIIC2	Abdominal pain, rapid uterine enlargement	Poorly differentiated carcinoma or carcinosarcoma	HystBSO, LND	LCNEC	Syn, CgA, CD56	CCRT (IP)
43	Kobayashi M et al.	44	IIIC1	AGC, psychosis	None	Tumor cytoreduction	LCNEC, EC	Syn, CgA, CD56	Comprehensive immunomodulat therapy, CT (TC)
44	Yi-An et al.	51	IVB	AUB, pelvic mass	MMMT	HystBSO, OMY, tumor cytoreduction	LCNEC with superficial focal MMMT	Syn, CgA, CD56	CT (EPcis)
45	Ogura et al.	52	IIIC2	AUB	LCNEC	None	LCNEC	Syn, CD56	Palliative care
46	Guimarães et al.	75	IIIA	AUB, abdominal pain	Epithelioid malignant neoplasm	Extended total HystBSO	LCNEC with melanocytic differentiation	Syn, CgA, CD56	CT (CP) + RT
47	Suh et al.	61	IIIB	Abdominal pain, uterine mass	Failed biopsy	HystBSO, OMY	LCNEC	Syn, CD56	CT (EPcis) + RT
48	Hu et al.	54	IIIC2	AUB	Malignant tumor	Radical HystBSO, LND	LCNEC, SC	Syn, CgA, CD56	Sandwich chemoradiothera (EPcis)
49	Jenny et al.	56	IVB	AUB, pelvic pain	No endometrial tissue	HystBSO	Uterine LCNEC, ovarian endometrioid adenocarcinoma G1	Syn	Planned EPcis
50	Sekine et al.	56	IV	Metrorrhagia	None	None	LCNEC, EC	CgA	Palliative care
51	Lee et al.	62	NA	AUB	Low-grade EC	NA	LCNEC, low-grade EC	Syn, CD56	None
52	Akgor et al.	70	IVB	AUB	NA	HystBSO, LND, Obx	LCNEC	Syn, CgA, CD56	None
53	Hardy et al.	47	IVB	Abdominal pain, distension, anorexia, loss of weight	LCNEC	Modified supralevator posterior exenteration, partial posterior vaginectomy, OMY, Hartmanns procedure	LCNEC, high-grade SC	Syn, CgA	CT (TP)
54	Rivera et al.	48	IIIA	Abdominal pain, girth	Severe acute and chronic endometritis and pyometra	HystBSO, tumor cytoreduction	LCNEC, low-grade endometrial stromal sarcoma	Syn, CgA	CT (EPcis)
55	Shopov et al.	76	IIIC	AUB, abdominal pain	Insufficient sample	HystBSO, LND, partial OMY	LCNEC	Syn, CgA, CD56	CT (EPcis)

AGC, atypical glandular cells; APPY, appendectomy; AUB, abnormal uterine bleeding; AWD, alive with disease; CCRT, concurrent chemoradiotherapy; CP, cyclophosphamide/cisplatin; CT, chemotherapy; DOD, died of disease; EC, endometrioid carcinoma; EPcar, etoposide/carboplatin; EPcis, etoposide/cisplatin; hysterectomy with bilateral salpingo-oophorectomy; IP, irinotecan/cisplatin; LND, lymph node dissection; MMMT, malignant mixed Mullerian tumor; NA, not av evidence of disease; NSE, neuron-specific enolase; Obx, omental biopsy; OMY, omentectomy; Pbx, peritoneal biopsy; RT, radiotherapy; SC, serous carcinoma; S neuroendocrine carcinoma; STbx, soft tissue biopsy; TC, paclitaxel/carboplatin; TP, paclitaxel/cisplatin.

Likewise, we searched PubMed using the search terms ((‘PTH’[All Fields]) OR (‘parathyroid hormone’[All Fields])) AND ((‘neuroendocrine carcinoma’[All Fields]) OR (‘neuroendocrine tumor’[All Fields])). After screening the abstract of 354 citations we initially obtained, only 7 PTH-secreting LCNEC cases were identified[31–37]. In the 7 cases summarized below (Table 2), the tumor appeared to mainly affect females, and more than half of them originated from the digestive system. In most patients, the presentation of hypercalcemia-associated clinical symptoms, such as fatigue, nausea, polyuria and polydipsia, in combination with elevated serum calcium and PTH, led to the misdiagnosis of PHPT initially. Several techniques have been used to confirm the origin of ectopic PTH, including immunohistochemistry, Sestamibi radionuclide scan and quantitative RT-PCR. Among 6 cases using IHC as the confirmation tool, 3 were insufficient, and the diagnosis was inferential[35–37]. Except for well-differentiated NETs, the prognosis of PTH-secreting NEC was extremely poor, 3 out of 5 patients died of rapid progression of disease within 6 months[31, 33, 37].

Table 2
Summary of previously reported ectopic PTH-secreting neuroendocrine tumor cases

Case	Author [erf]	Age (yr) /sex	Initial presentation	PTH and calcium	Initial diagnosis	Primary site	Final pathology	Metastasis	IHC staining	Confirmat of PTH originatio
1	Ohira et al.	33/F	Lower abdominal pain and general fatigue	Elevated	Left adnexal mass	Ovarian	NEC with component of endometrioid adenocarcinoma	None	Syn, CgA, PTH	IHC
2	Vacher-Coponat et al.	58/F	Confusional syndrome	Elevated	PHPT	Pancreas	NET	Liver	NA	Sestamibi radionucli scan
3	VanHouten et al.	74/F	Nausea, fatigue, polyuria, and polydipsia	Elevated	Decompensated PHPT or ectopic PTH productive malignancy	Pancreas	Poorly differentiated NET	Liver and retroperitoneal lymph nodes	PTH,PTH-rp□NA for NET marker	IHC, quantitati RT-PCR
4	Kandil et al.	71/F	Depression and fatigue	Elevated	Recurrent PHPT	Right thyrothymic ligament	NET	None	CgA, PTH	IHC
5	Doyle et al.	28/F	Nausea, fatigue, abdominal pain, and weight loss	Elevated	PHPT or MEN1	Pancreas	SCNEC	Liver	NA	PTH reduc after tumc regressior
6	Lu et al.	65/M	Increased foam in urine	Elevated	Ectopic parathyroid adenoma	Mediastinal	Carcinoid	None	NA	PTH declinatio after rumc excision
7	Kwon et al.	44/M	None	Elevated	Hepatic mass	Liver	HCC and NEC	Bone	Syn, CgA, CD56	None

IHC: immunohistochemistry; HCC, hepatocellular carcinoma; MEN I, Multiple endocrine neoplasia type I.

Discussion

We reported the unique case of combined LCNEC and endometrioid adenocarcinoma of the endometrium with hormonal function. Ectopic secretion of PTH and PTH-rp together with osseous metastasis contributed to hypercalcemia as the main clinical manifestation.

Primary LCNEC of the endometrium is a rare but vicious malignancy that corresponds to less than 1% of endometrial neoplasms, with a total of 55 cases reported currently. Due to limited number of cases, the diagnostic criteria for endometrial LCNEC haven't been well established. According to the World Health Organization (WHO) classification of lung tumors, LCNEC is defined as large-cell carcinoma (large cell size with low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/or frequent nucleoli; high mitotic activity: usually > 10 mitotic counts in 2 mm^2 of viable tumor [10HPF]), with neuroendocrine histological patterns (organoid nesting, palisading, rosettes and trabeculae) and at least one positive immunohistochemical neuroendocrine markers (Syn, CgA, or CD56) [2, 38, 39]. The pathologic features of LCNEC closely resemble other poor-differentiated tumor. Therefore, it is relatively difficult to differentiate from these tumors pre-operatively through small biopsy specimens[1, 4], with only 4 cases diagnosed based on biopsy[5, 12, 21, 28, 40] among current literatures. Besides, neuroendocrine neoplasm often co-exists with other pathologic types such as endometrioid adenocarcinoma, serous adenocarcinoma and sarcomatoid carcinoma, etc. In certain uncommon cases, different preoperative biopsy site can lead to misdiagnosis of pathologic type[1]. As for this case, the diagnosis was delayed by confusing coexistence of hypercalcemia and high PTH level, and its deep corner location, which was covered by the co-existed component of endometroid carcinoma located at the out orifice of cervix.

Neuroendocrine neoplasms occasionally synthesize and secrete bioactive substances, causing distinct clinical syndromes[31, 32, 34, 35, 37]. However, no case of functional endometrial LCNEC has been reported so far. Similar to the manifestation of endometrial adenocarcinoma, primary endometrial LCNECs mostly appeared as abnormal bleeding and abdominal pain, less common symptoms including dyspnea, dizziness and psychosis. In this case, neuroendocrine tumor secreted ectopic PTH, biochemically mimicking the manifestation of PHPT. Initially, concurrent hypercalcemia with progressively increased level of PTH despite management made us presume the diagnose of primary hyperparathyroidism. However, we failed to find any positive lesion from parathyroid or elsewhere through directed imaging examinations or functional assays. Under this circumstance, elevated PTH was highly suspected to be produced by neoplasm and was testified by MRI and biopsy. The lacking evidence of PHPT, reduced PTH level following anti-tumor treatment and positive PTH immunohistochemistry worked together to prove the fact that endometrial neuroendocrine tumor was the source of elevated PTH. Through reviewing related literatures, although quite a few cases of hypercalcemia due to ectopic PTH production of malignancies have been described[34], only seven cases of PTH-secreting neuroendocrine tumor have been reported so far[31–37], with the present case being the first one originated from endometrium. Nevertheless, A paradoxical result of elevated serum PTH level and fairly weak positive PTH staining was noticed, similar to several cases reported previously, who present

with elevated PTH and negative PTH expression in immunohistochemistry. This might suggest that the LCNEC tumor cells secrete PTH into circulation soon after synthesis[35–37, 41, 42] other than storing it in cells.

This woman was firstly noted by her hypercalcemia, a common metabolic disorder with multiple etiologies. PHPT serves as the most common cause[43], followed by malignancy [44–46]. The majority of malignancy-associated hypercalcemia was induced by parathyroid hormone-related protein (PTH-rp). Osseous metastases of malignant tumor might as well cause osteolysis and lead to hypercalcemia[46, 47]. However, these patients usually presented with suppressed PTH level in response to hypercalcemia[35]. In this case, the positive immunohistochemical staining for PTH-rp confirmed the effect of PTH-rp on blood calcium. That is, both PTH and PTH-rp in LCNEC worked together with direct bone resorption of osseous metastasis and contributed to hypercalcemia.

Currently, data regarding uterine LCNEC is limited to case reports and the optimal therapeutic regimen has not been proposed. According to previous literatures, except for a tiny minority with end-stage disease, most of the patients received primary surgery with or without adjuvant chemotherapy and radiotherapy. As for chemotherapy, the regimens for lung neuroendocrine carcinoma[2], including irinotecan/platinum and etoposide/platinum, were referred for most of the cases. Due to the scarce information of the biological activity for endometrial LCNEC, only 2 cases received or planned to receive octreotide as adjuvant targeted therapy[11, 13]. For this case, considering the advanced stage and the repeatedly hypercalcemia, chemotherapy with paclitaxel and nedaplatin, a regimen usually utilized in endometrial carcinoma, was employed as the primary management. As expected, such choice was proved feasible since chemotherapy controlled the symptoms, normalized the serum calcium and provided opportunity for surgery, which made the final diagnosis determined. However, despite the multi-modality approach of treatment, the prognosis was still poor. Further research is needed to define a standard treatment protocol for women with LCNEC of the gynecological system due to its aggressive behavior and poor prognosis.

Conclusion

Malignancy-associated hypercalcemia usually arises from PTH-rp secretion. For those without, bone metastasis with osteolytic destruction would be another reason, which is usually accompanied by suppressed PTH level. It is rare to see such case of whom PTH, PTH-rp and lytic osseous metastasis coexist and contribute to the hypercalcemia. The component of LCNEC is thought to be responsible, since most symptoms and anormal levels of serum calcium and PTH returned by effective treatment.

Declarations

Ethics approval and consent to participate

Ethical approval is not required as a written informed consent was obtained for publication of this case report and accompanying images.

Consent for publication

A signed consent for publication from the patient’s husband has been obtained.

Availability of data and materials

Not applicable as all information and data are presented in the manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Natural Science Foundation of China [No. 81572562].

Authors' contributions

All the authors mentioned above contributed to the report. Yue-xi Liu was responsible for collecting the clinical data and writing the manuscript. Xing Wei and Xiao-mei Zhang were responsible for collecting the clinical data. Zhi-hong Wang was responsible for giving endocrinological suggestions of this case. Ruo-nan Li was responsible for histological staining for PTH and PTH-rp, Bin Liu was responsible for reviewing all immunohistochemistry results and discussion. Linghu Hua was responsible for the intellectual content of the report. All authors read and approved the final manuscript.

Acknowledgments

None.

Data availability statement

The datasets used during the current report available from the corresponding author on reasonable request.

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Figures

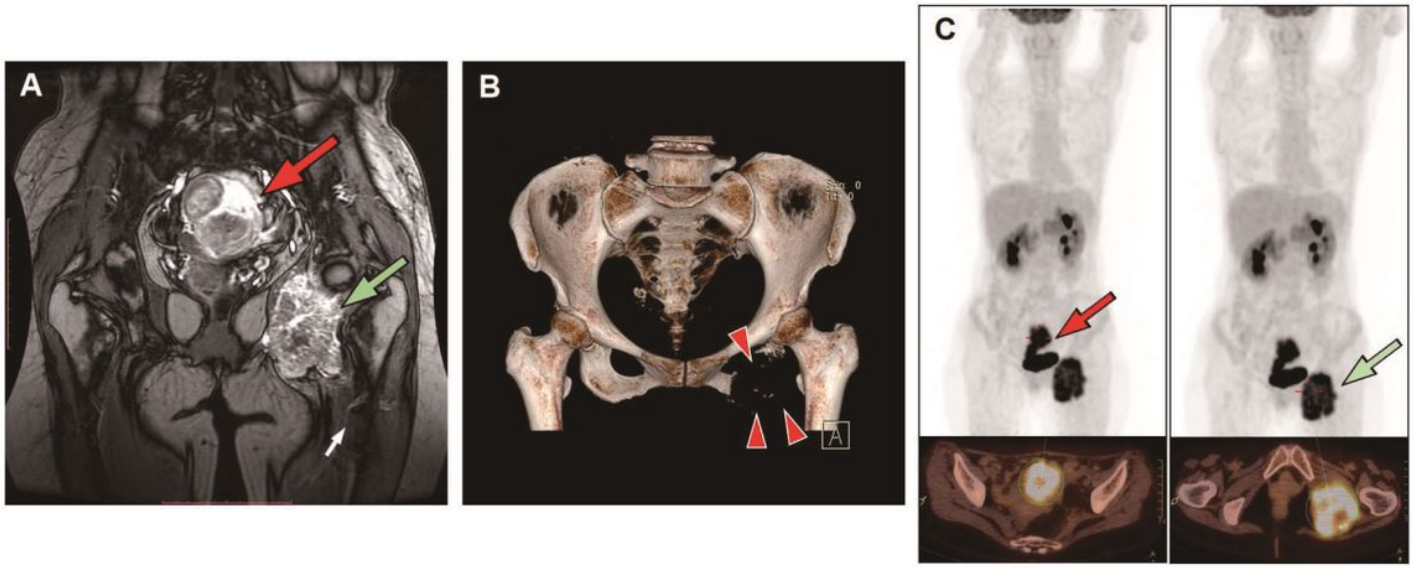

Figure 1

Imaging findings. Foci of endometrial (red arrow), obturator area (green arrow) and osseous involvement (arrow head) were identified through MRI (A), CT(B) and PET-CT (C), respectively.

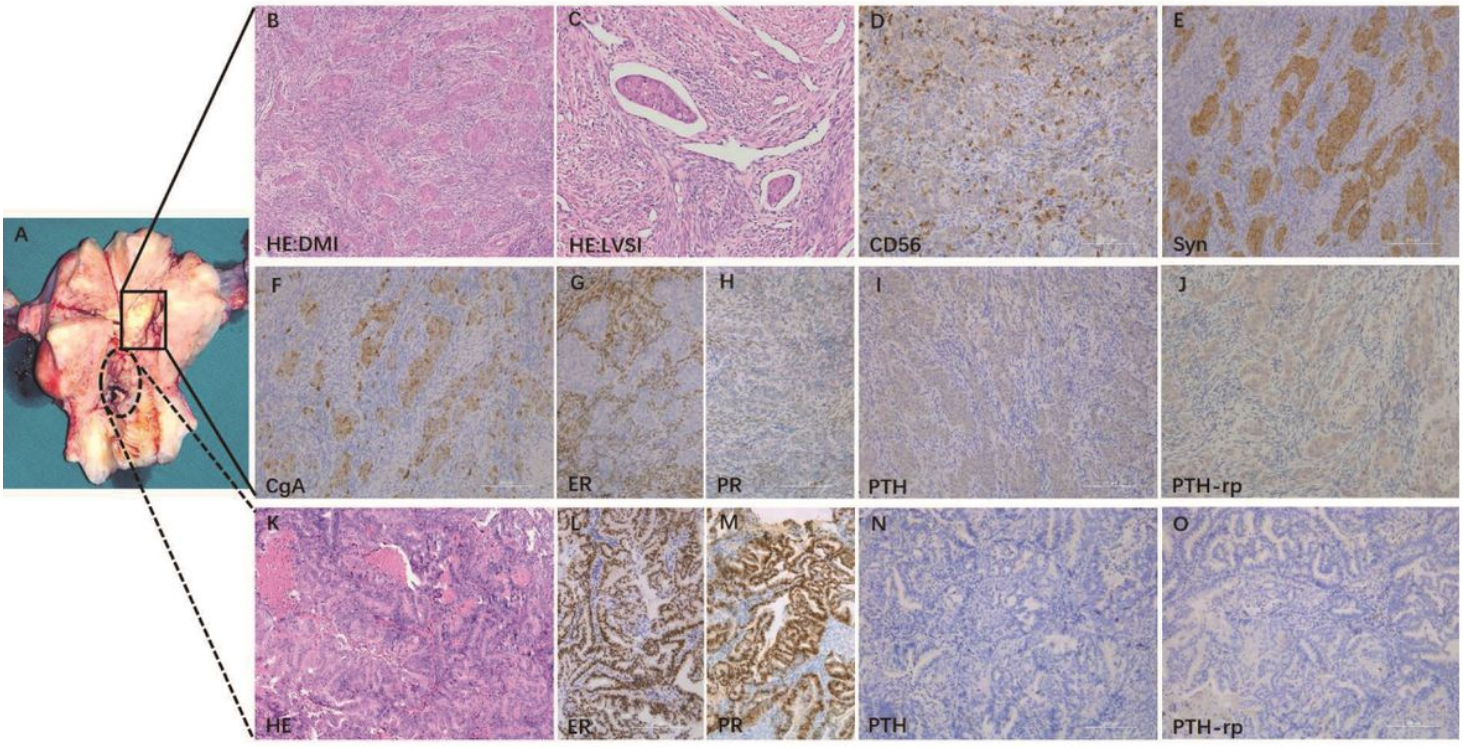

Figure 2

Histopathological findings of post-operative specimen. (A) Gross appearance of the surgical specimen showing diffuse cauliflower-like lesions in the uterine cavity (LCNEC), with a 2cm×3cm lesion noted in the upper endocervical canal (endometrioid carcinoma). (B-J) Histology and immunohistochemical findings of the LCNEC: deep myometrial invasions (B) and lymphovascular invasions (C); positive expression of specific neuroendocrine markers: CD56 (D),

Synaptophysin (E) and Chromagranin (F); negative expression of estrogen receptor (G) and progesterone receptor (H); positivity for both parathyroid hormone (I) and parathyroid hormone-related protein (J). (K-O) Histology and immunohistochemical findings of the endometrioid carcinoma: positivity for estrogen receptor (L) and progesterone receptor (M); negative expression of parathyroid hormone (N) and parathyroid hormone-related protein (O).