Case report

Paraneoplastic Cushing's syndrome and hypercalcemia arising from metastatic endometrioid endometrial adenocarcinoma: A case report

Evelyn Mitchell\textsuperscript{a}, Marcia Ciccone\textsuperscript{a}, Bing Zhang\textsuperscript{b}, Arnold Tsai\textsuperscript{b}, Laurie L. Brunette\textsuperscript{a,}\textsuperscript{⁎}

\textsuperscript{a} Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, USA
\textsuperscript{b} Department of Medicine, Keck School of Medicine, University of Southern California, USA

ARTICLE INFO

Keywords:
Endometrial cancer
Cushing's syndrome
Paraneoplastic syndrome
Hypercalcemia

1. Background

Paraneoplastic syndromes (PNS) encompass a constellation of abnormalities not attributable to direct organ involvement from an underlying malignancy. These disorders accompany up to 8% of cancers (Pelosof and Gerber, 2010). Occasionally, symptom onset precedes tumor diagnosis and may therefore facilitate early detection and intervention (Pelosof and Gerber, 2010). Alternatively, spontaneous or undiagnosed paraneoplastic syndromes can occur in patients awaiting or undergoing cancer treatment and induce acute and critical decompensation. A comprehensive review categorized PNS into endocrine, neurologic, dermatologic, rheumatologic, and hematologic manifestations (Pelosof and Gerber, 2010). While some syndromes, such as paraneoplastic hypercalcemia, are easily identified and corroborate an undetected cancer, others may appear to be common benign conditions or develop independent of an underlying malignancy, complicating tumor workup.

Malignancy-associated hypercalcemia is one of the earliest described (Mallory, 1941) and most prevalent paraneoplastic syndromes (Mundy and Guise, 1997). Other common paraneoplastic endocrine syndromes (PNES) include syndrome of inappropriate antidiuretic hormone (SIADH), Cushing's syndrome, and hypoglycemia. Given their contribution to morbidity and mortality of the underlying malignancy, swift recognition and aggressive management of PNES are paramount to improving outcome. Here, we present the second published case of a patient with Cushing’s syndrome, along with paraneoplastic hypercalcemia, arising from an endometrial adenocarcinoma (Morton, 2017).

2. Case report

A 56-year-old female with no past medical history was referred to gynecologic oncology after presenting to our emergency department with pelvic pain and postmenopausal vaginal bleeding. She noted abdominal pain, increased abdominal girth, and trace bilateral leg edema, but was otherwise asymptomatic. Labs were notable for elevated calcium of 10.8 mg/dL, platelet count of 386,000/mm\(^3\), CA 125 of 430 U/mL, and HE4 at 1606 pmol/L, along with decreased potassium to 3.2 mmol/L. Imaging revealed bilateral adnexal masses, omental nodularity, and retroperitoneal lymph node enlargement. Endometrial biopsy showed FIGO grade 3 endometrioid endometrial adenocarcinoma. Three weeks later, while awaiting medical clearance and surgical planning, she presented to our emergency department with five days of progressive weakness, worsening abdominal pain, and anasarca, rendering her unable to ambulate. The patient was hypertensive to 160/89 mmHg and had gained ten kilograms in three weeks. Physical exam was remarkable for plethoric facies, hirsutism, central adiposity with striae, diffuse abdominal tenderness, and significant pitting bilateral leg edema. Laboratory tests identified potassium of 2.7 mmol/L, creatinine of 1.09 mg/dL, and glucose of 213 mg/dL. She was admitted to the internal medicine service, and additional workup revealed low parathyroid hormone (PTH) with elevated PTH-related protein (PTHrP). Aggressive intravenous hydration, calcitonin, calcitriol, ergocalciferol, and bisphosphonate were administered for paraneoplastic...
hypercalcemia.

Presence of Cushingoid features on physical exam, which were absent three weeks prior, prompted an evaluation of the hypothalamic-pituitary-adrenal (HPA) axis. A serum cortisol was 98.8 μg/dL at 4 PM on admission (normal range 2–14 μg/dL) and 105.2 μg/dL at 8 AM the following morning (normal range 5–25 μg/dL), confirming loss in cortisol diurnal variation. Adrenocorticotropic hormone (ACTH) was obtained and was significantly elevated to 822 pg/mL (normal range 6–50 pg/mL). The loss of feedback inhibition on ACTH secretion supported ectopic ACTH secretion; thus, ketoconazole was initiated to reduce cortisol levels (Fig. 1). Brain magnetic resonance imaging was negative for a pituitary tumor, confirming ACTH secretion by an ectopic source. Her endometrial biopsy stained negative for ACTH on immunohistochemical testing. Due to her acute decompensation, she no longer remained a surgical candidate, and a weekly neoadjuvant chemotherapy regimen of carboplatin AUC2 and albumin-bound paclitaxel 100 mg/m2 (selected instead of paclitaxel to minimize the intravenous steroid required for premedication) was initiated. Daily allopurinol was initiated for tumor lysis syndrome after a uric acid of 9.3 mg/dL was detected on day 2 of her first cycle. Repeat ACTH level after one dose of chemotherapy declined to 627 pg/mL (Fig. 1).

Later in her hospital course, the patient developed uptrending alkaline phosphatase and bilirubin, compatible with a cholestatic pattern of liver injury. Ketoconazole was discontinued for its known hepatotoxicity. Cortisol rebounded immediately, inducing hypernatremia refractory to high-volume free water (Fig. 1). The patient became obtunded, aspirated, and required intubation for desaturation. Ketoconazole was restarted after consensus among specialists. However, the patient developed toxic epidermal necrolysis, suspected secondary to chemotherapy, allopurinol, or the underlying malignancy, and was transitioned to comfort care.

3. Discussion

Paraneoplastic endocrine syndromes (PNES) typically present after cancer diagnosis. Mechanisms of hormone synthesis and secretion by malignant cells continue to remain elusive, but ectopically-produced signaling substances are mostly peptides and less frequently steroids, amines or thyroid hormones (Kaltsas et al., 2010; Dimitriadis et al., 2016). Per diagnostic criteria, PNES resolves with successful tumor treatment and may return with recurrence (Dimitriadis et al., 2017). Despite inconsistent correlation between PNES and cancer stage or prognosis, their emergence can drastically debilitate the patient and alter treatment plans, as demonstrated by our case.

Unlike most PNES, paraneoplastic Cushing’s syndrome typically presents before cancer detection and arises from neuroendocrine lung
tumors (bronchial carcinoids and small cell lung cancers) 50–60% of the time (Pelosof and Gerber, 2010). Other reported sites of malignancy include thymus, gastrointestinal, thyroid, pancreas, and adrenals.

Paraneoplastic Cushing’s syndrome rarely accompanies gynecologic cancers, but has been reported in ovarian and cervical primaries, most commonly those with neuroendocrine tumors (Ashour et al., 1997). It has been noted in two prior small cell endometrial carcinomas and one endometrioid ovarian carcinoma (Crawford et al., 1994). After a PubMed search of “ectopic cushing endometrial cancer,” “paraneoplastic cushing’s syndrome,” and “ectopic cushing’s syndrome,” we encountered reports in related diagnoses describing ectopic cushing’s in conjunction with two small cell endometrial cancers, one endometrioid ovarian carcinoma, one endometrial adenocarcinoma. This is, therefore, the second published case of paraneoplastic Cushing’s syndrome in an endometrial adenocarcinoma (Morton, 2017). Of note, since our patient never underwent surgical management, we cannot exclude the possibility of synchronous ovarian cancer or ovarian cancer with metastasis to the endometrium, though ectopic ACTH in the setting of epithelial ovarian cancer has only been noted in two prior case reports. 

In all previously reported cases of ectopic Cushing’s, (Khan et al., 2011; Parsons and Rigby, 1958; Crawford et al., 1994; Sato et al., 2010) features of hypercortisolism emerged unexpectedly and even manifested for the first time with recurrence of a previously treated ovarian adenocarcinoma (Crawford et al., 1994). Given its rarity among gynecologic tumors, a low index of suspicion may delay workup and management.

Negative immunohistochemical staining for ACTH expression, as in our case, does not preclude malignancy as the source of ectopic ACTH production. As demonstrated in other case reports, if only a small subset of tumor cells secretes hormone, (Khan et al., 2011) it may be missed on tissue sampling. For example, a case report of a recurrent endometrioid adenocarcinoma of the ovary revealed a tumor containing numerous chromogranin immunoreactive endocrine cells as well as small foci of ACTH immunoreactivity; ACTH immunoreactivity was found in the poorly differentiated areas of the surgically resected tumor before the onset of clinical Cushing’s syndrome (Crawford et al., 1994). Our patient never underwent surgical resection or autopsy; the stain for ACTH was done only on clinic EMB, and ACTH may have been missed on sampling.

Furthermore, variability in ACTH staining among non-gynecological tumors has been demonstrated. In a study of 18 tumors causing ectopic Cushing’s syndrome, only 10 stained positive for ACTH or its precursor (Coates, 1986). The authors proposed that if tumor cells secrete hormones rapidly, the remaining storage concentrations may be too small to be detected by immunohistochemistry (Coates, 1986).

Given PNES’ responsiveness to treatment of the underlying malignancy, the patient’s reduction in ACTH level after chemotherapy also supports a diagnosis of paraneoplastic Cushing’s syndrome, in addition to a loss of cortisol diurnal variation, markedly elevated ACTH levels, and negative MRI findings for pituitary secreting adenoma.

Concurrent PNES or chronic medical conditions can further confound diagnosis. In all published cases, death followed onset of signs and symptoms within weeks to months unless the primary tumor was removed. Therefore, the development of paraneoplastic Cushing’s syndrome in patients with gynecologic malignancies who are not surgical candidates portends a poor prognosis. For small-cell lung cancer, paraneoplastic Cushing’s syndrome is also associated with accelerated decompensation and poorer response to chemotherapy (Nagy-Mignotte et al., 2014; Dimopoulos et al., 1992). Whether these findings can be extrapolated to other malignancies is unknown, but is worthwhile to pursue with retrospective studies, especially for resectable tumors where the source of ectopic hormone production may be removed. If the development of paraneoplastic Cushing’s syndrome is indeed an indicator of treatment futility, then perhaps heightened vigilance, early detection, and aggressive surgical management may prevent or decelerate the acute decompensation of cancer patients and improve outcome. Though we will never know if it would have changed her outcome, with the benefit of the insight her case provided, we may have considered earlier surgical management for our patient in spite of her medical risk profile.

Author contribution

All authors (Mitchell, Ciccone, Brunette, Tsai, Zhang) had equal contribution.

Financial support and conflict of interest disclosure

No financial support to declare.

Authors have no disclosures or conflicts of interest. All authors had equal contribution.

Declaration of competing interests

There are no conflicts of interest.

References

Agha, A.A., Verschraegen, C.F., Kudelka, A.P., et al., 1997. Paraneoplastic syndromes of gynecologic neoplasms. J. Clin. Oncol. 15 (3), 1272–1282.

Coates, et al., 1986. Immunocytochemical study of 18 tumours causing ectopic Cushing’s syndrome. J. Clin. Pathol. 39, 955–960.

Crawford, S.M., Pyrah, R.D., Ismail, S.M., 1994. Cushing’s syndrome associated with recurrent endometrioid adenocarcinoma of the ovary. J. Clin. Pathol. 47 (8), 766–768.

Dimitriadis, G.K., Weickert, M.O., Randeva, H.S., et al., 2016. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocr. Relat. Cancer 23 (9), R423–R436.

Dimitriadis, G.K., Angelousi, A., Weickert, M.O., et al., 2017. Paraneoplastic endocrine syndromes. Endocr. Relat. Cancer 24 (6), R173–R190.

Dimopoulos, M.A., Fernandez, J.F., Samaan, N.A., et al., 1992. Paraneoplastic Cushing’s syndrome as an adverse prognostic factor in patients who die early with small cell lung cancer. Cancer 69 (1), 66–71.

Kalsnes, G., Androulakis, I.I., de Herder, W.W., et al., 2010. Paraneoplastic syndromes secondary to neuroendocrine tumours. Endocr. Relat. Cancer 17 (3), R173–R193.

Khan, M.I., Waguespack, S.G., Habra, M.A., et al., 2011. Acute-onset ectopic adrenocorticotropin hormone syndrome secondary to metastatic endometrioid carcinoma of the ovaries as a fatal complication. J. Clin. Oncol. 29 (16), e462–e464.

Mallory, T.B., 1941. Case records of the Massachusetts General Hospital: case 27461. N. Engl. J. Med. 225, 789–791.

Morton, A., 2017. Ectopic Adrenocorticotropic syndrome. Intern. Med. J. 47, 1328–1329.

Mundy, G.R., Guise, T.A., 1997. Hypercalcemia of malignancy. Am. J. Med. 103 (2), 134–145.

Nagy-Mignotte, H., Steshova, O., Vignoud, L., et al., 2014. Prognostic impact of paraneoplastic cushing’s syndrome in small-cell lung cancer. J. Thorac. Oncol. 9 (4), 497–505.

Parsons, V., Rigby, B., 1958. Cushing’s syndrome associated with adenocarcinoma of the ovary. Lancet 272, 992–994.

Pelosof, L.C., Gerber, D.E., 2010. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin. Proc. 85 (9), 838–854.

Sato, H., Kanai, G., Kajiwara, H., et al., 2010. Small-cell carcinoma of the endometrium presenting as Cushing’s syndrome. Endocr. J. 57 (1), 31–38.