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Case Report

Ectopic corticotropin-releasing hormone syndrome caused by rectal large cell neuroendocrine carcinoma: a rare case report

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***Abstract*:** Ectopic corticotropin-releasing hormone (CRH) syndrome, a rare subtype of adrenocorticotropic hormone-dependent Cushing syndrome, is associated with tumors of diverse origins. Here, we present a case of a 37-year-old female diagnosed with ectopic CRH syndrome secondary to rectal large cell neuroendocrine carcinoma, a hitherto unprecedented site for CRH-secreting tumors. The patient presented with classical features of Cushing syndrome, supported by laboratory evidence of hypercortisolemia and disrupted diurnal cortisol secretion. Imaging studies ruled out a pituitary adenoma, whereas colonoscopy identified a rectal malignancy. Immunohistochemical staining confirmed the presence of ectopic CRH syndrome. Despite prompt chemotherapy initiation, the patient's condition rapidly deteriorated, highlighting the aggressive nature and dismal prognosis associated with rectal large cell neuroendocrine carcinoma linked to ectopic CRH syndrome. This case underscores the importance of early recognition and comprehensive management to optimize patient outcomes.

Keywords: case report, Cushing syndrome, ectopic CRH syndrome, neuroendocrine carcinoma, rectal large cell carcinoma

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Background

Cushing syndrome (CS) encompasses a spectrum of clinical manifestations resulting from hypercortisolemia. It can present as either exogenous hypercortisolism due to glucocorticoid administration or endogenous hypercortisolism, which is further classified into adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent forms.[1] ACTH-dependent CS accounts for approximately 80%–85% of cases, whereas ACTH-independent CS accounts for 15%–20% of cases. The most prevalent form of ACTH-dependent CS is Cushing disease, which primarily originates from pituitary adenomas.[1–3] However, ACTH-dependent CS can also manifest ectopically, most commonly due to bronchial tumors. This condition, which is known as ectopic ACTH syndrome, is associated with tumors outside the pituitary that autonomously secrete ACTH.[1] Although bronchial tumors are the most frequent source of ectopic CS, they can also arise from neuroendocrine tumors (NETs) such as thymic or pancreatic carcinoids, medullary thyroid carcinoma (MTC), and pheochromocytoma.[4] In rare instances, NETs outside the pituitary co-secrete ACTH and corticotropin-releasing hormone (CRH), leading to CS; this is referred to as ectopic CRH syndrome, and tumors that solely secrete CRH are even rarer.[5–7]

NETs encompass a broad spectrum ranging from well-differentiated typical carcinoids to poorly differentiated carcinomas. Typical carcinoids are low-grade NETs, whereas neuroendocrine

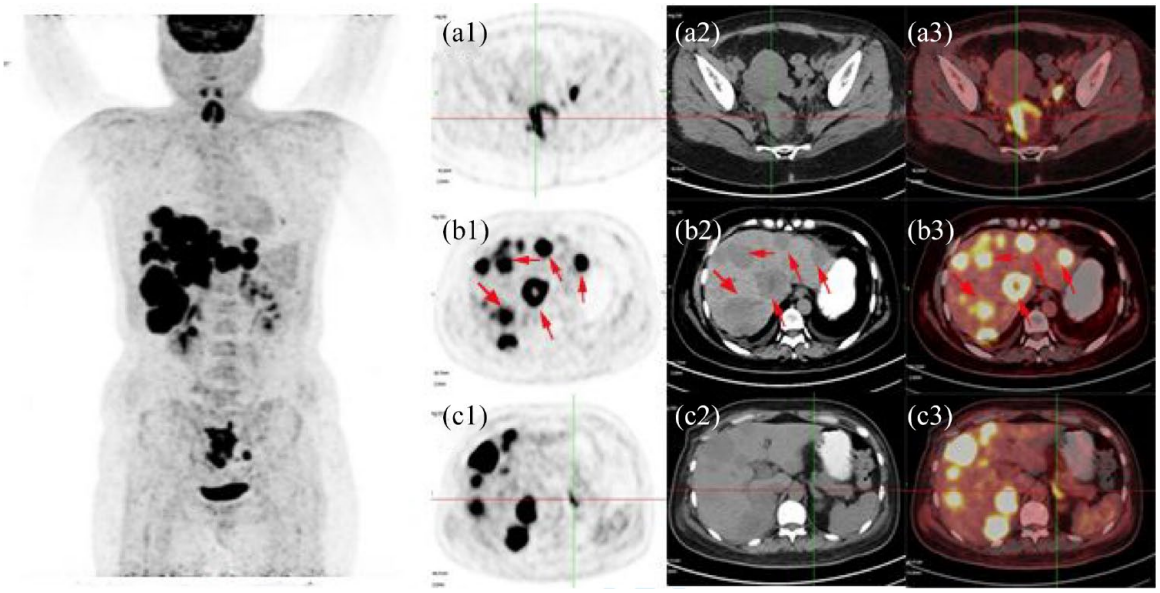

Figure 1. Results of ^{18}F-FDG positron emission tomography-computed tomography. (a1–a3) Rectal tumor. (b1–b3) Liver metastases. (c1–c3) Left adrenal gland with metastasis. See red arrows and intersections.

carcinomas (NECs) are characterized by high cytological grade, a solid growth pattern, numerous mitoses, and frequent necrosis.[8,9] Large cell NEC of the rectum is exceptionally rare, accounting for 0.25% of rectal malignancies.[10] Herein, we report a rare case of ectopic CRH syndrome induced by a large cell NEC of the rectum.

Case presentation

In 2023, a 37-year-old female presented with diarrhea, characterized by 5–6 bowel movements per day of thin, yellowish, soft stools. These symptoms persisted for over a month and were accompanied by rapid weight gain of 5 kg within 20 days. She also experienced intermittent, unexplained abdominal pain during this period. Approximately 20 days before admission, she developed significant fat redistribution, including central obesity with noticeable weight gain, increased abdominal girth, facial rounding, neck thickening, and marked edema in the limbs. She did not present with purple striae. The patient reported significant proximal muscle weakness, although physical examination showed no muscle atrophy and muscle strength remained normal. Menstrual cycles were regular (28 days) without significant abnormalities. Her medical history included hepatitis B virus infection and a prior cesarean section, with no history of prolonged medication or exogenous corticosteroid use.

Enhanced pelvic computed tomography (CT) revealed uneven thickening of the upper rectal wall, with the thickest portion measuring approximately 2.3 cm and involving a length of 5.4 cm of the bowel. Multiple small lymph nodes were observed in the surrounding area, the largest of which had a short diameter of approximately 0.8 cm. Suspicion of rectal cancer with lymph node metastasis arose. On initial consultation with general surgery, laboratory tests indicated persistent hypokalemia, fluctuating between 2.6 and 3.2 mmol/l (normal range 3.5–5.5 mmol/l) despite oral and intravenous potassium supplementation. Further colonoscopy revealed an ulcerative mass occupying half the circumference of the rectal lumen, located 10–15 cm from the anal verge, characterized by a white coating and prone to bleeding. Pathological examination identified a NEC of the large cell type in the rectum. ^{18}F-FDG positron emission tomography (PET)-CT revealed several lesions as follows (Figure 1): (1) Thickening of the upper rectal wall with increased metabolic activity (SUVmax, 17.1), suggestive of rectal cancer with possible invasion through the serosal layer; (2) Multiple lymph nodes anterior to the sacrum located around the rectal lesion and adjacent to the left iliac vessels, with partially increased metabolic activity suggestive of metastasis (SUVmax, 17.8); (3) Multiple nodules and masses with increased metabolic activity within the liver suggestive of

metastasis (SUVmax, 29.8); (4) Small nodules with increased metabolic activity in the basal segment of the left lower lobe of the lung suggestive of metastasis (SUVmax, 4.1), in addition to multiple small nodules in both lungs with partially elevated metabolic activity, indicating a high likelihood of metastasis; (5) Slightly enlarged left adrenal gland with increased metabolic activity (SUVmax, 7.2), with metastasis not ruled out.

Endocrinology examination revealed significant disruption of the diurnal rhythm of cortisol secretion, with plasma ACTH levels peaking at 527 pg/ml (reference range <46 pg/ml), suggestive of ACTH-dependent CS (Table 1). Other relevant laboratory results, including a pituitary profile indicative of hypogonadotropic hypogonadism and normal blood glucose levels, are listed in Table 1. Magnetic resonance imaging (MRI) showed no pituitary adenoma. Tumor markers showed elevated levels of neuron-specific enolase (183 ng/ml↑; reference range 0–16.3 ng/ml), cancer antigen (CA) 19-9 (1002.7 U/ml↑; reference range <37.0 U/ml), and CA125 (45 U/ml↑; reference range <35 U/ml). Immunohistochemical staining of the rectal tumor showed positive staining for P53, synaptophysin (Syn), and CD56, with a Ki-67 labeling index of approximately 70% (Figure 2(b)). The tumor was also positive for CRH (Figure 2(d)) but negative for ACTH (Figure 2(c)), confirming ectopic CRH syndrome caused by rectal large cell NEC.

The patient underwent two cycles of chemotherapy (etoposide plus carboplatin) in the hospital. Three weeks after the first chemotherapy cycle, follow-up tests showed that the 8 am ACTH level was 311 pg/ml, and the cortisol level was 132.5 μg/dl. After the chemotherapy cycles, the patient developed grade III bone marrow suppression, fever, hypoalbuminemia, and coagulation dysfunction. Despite aggressive treatment, her condition rapidly deteriorated and she passed away 1 month post-discharge.

Table 1. Laboratory results.

Parameters	Level	Reference range
Serum cortisol (μg/dl)		5–25
08:00 am	145.6	
4:00 pm	11.0	
12:00 am	10.7	
08:00 am-$_{ODST}$	11.4	
08:00 am-$_{HDDST}$	22.2	
ACTH (pg/ml)		0–46
08:00 am	527	
08:00 am-$_{ODST}$	52	
08:00 am-$_{HDDST}$	101	
FSH (mIU/ml)	6.08	3.3–8.6
LH (mIU/ml)	2.56	1.5–12
Estradiol (pg/ml)	11.53	15.2–127.8
TSH (μIU/ml)	0.47	0.35–5.5
FT3 (pg/ml)	1.81	2.3–4.2
FT4 (ng/dl)	1.02	0.89–1.76
IGF1 (ng/ml)	33	63–223
Glu (mmol/l)	4.8	3.9–6.1
HbA1c (%)	5.5	4.0–6.2

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; Glu, glucose; HbA1c, hemoglobin A1c; HDDST, high-dose dexamethasone suppression test; IGF1, insulin-like growth factor 1; LH, luteinizing hormone; ODST, overnight dexamethasone suppression test; TSH, thyroid stimulating hormone.

Discussion

Ectopic CRH syndrome represents an extremely rare subtype of CS; patients often present with the classical clinical manifestations of CS, such as moon face, buffalo hump, central obesity, purple striae, hypokalemia, and weakness.[1] Most patients with ectopic CRH syndrome experience severe cortisol excess and rapid disease progression within weeks. In addition to the typical clinical presentation, elevated ACTH levels often lead to prominent skin hyperpigmentation, and some patients experience significant muscle loss and weight gain due to the profound catabolic effects of high cortisol levels.[11] In this case, the patient exhibited typical features, including a round face, central obesity, and refractory hypokalemia, which are consistent with the clinical presentation of ectopic CRH syndrome.

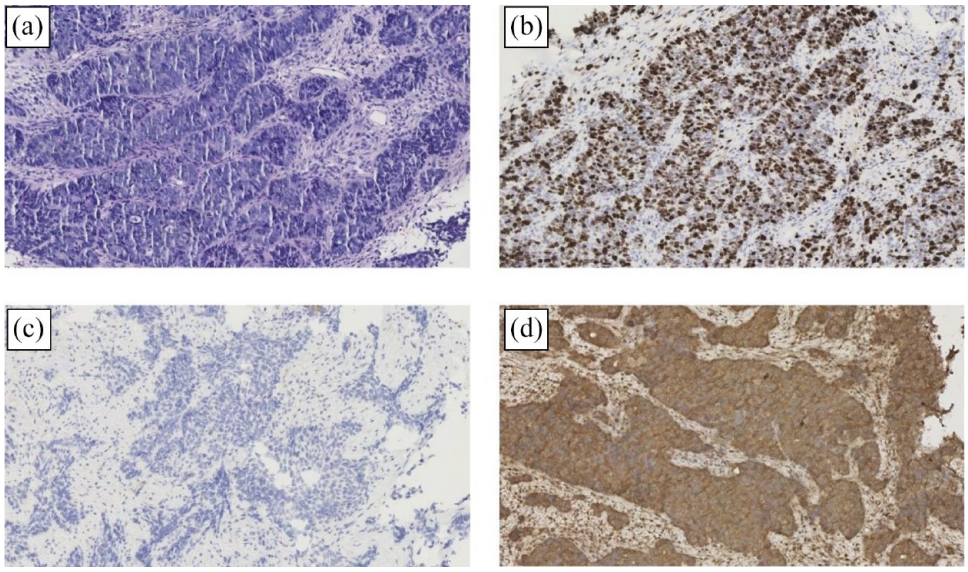

Figure 2. Morphological and immunohistochemical staining of the tumor. (a) Poorly differentiated neuroendocrine carcinoma of the rectum composed of large cells (hematoxylin and eosin ×400). (b) More than 70% of tumor nuclei stained positive for Ki-67 (×400). (c) Negative ACTH immunostaining (×400, ACTH antibody: mouse, ZSGB-Bio, Beijing, China, Cat# ZM0004, RRID: AB_3331651); normal mouse pituitary tissue was used as the positive control. (d) Positive expression of CRH in tumor cells (×400, CRH antibody: rabbit, Solarbio, Beijing, China, Cat# K007404P, RRID: AB_3331648); mouse hypothalamus tissue was used as the positive control.
ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

The diagnosis and evaluation of ACTH-dependent CS can be challenging. Once biochemical assays confirm that ACTH levels are inappropriately high-normal or elevated, the next step is to differentiate between pituitary and ectopic sources. Currently, there is no single laboratory test or combination of tests that can definitively distinguish the source of ACTH.[2] Guidelines recommend integrating results from pituitary MRI, high-dose dexamethasone suppression test (HDDST), and CRH stimulation test (or desmopressin where CRH is unavailable) for determination.[1] However, both HDDST and CRH stimulation tests may yield false suppression results in patients with ectopic tumors. Well-differentiated NETs may also express the corresponding receptors, leading to false positive results. Moreover, the small size of most pituitary microadenomas and many ectopic ACTH-secreting tumors can lead to false-negative results on pituitary MRI, making localization diagnosis even more challenging. When a small pituitary adenoma is detected on MRI, it is not always the source of elevated ACTH, as non-functioning pituitary adenomas account for approximately one-third of all pituitary adenomas.[12] Therefore, guidelines recommend performing bilateral inferior petrosal sinus sampling (BIPSS) to identify the source of ACTH when MRI fails to detect the features of pituitary adenoma, when the adenoma is smaller than 6 mm, or when non-invasive test results are inconclusive.[2] In the present case, although BIPSS was recommended, the patient's rapid disease progression precluded its completion. Furthermore, we did not have the opportunity to measure plasma CRH levels in this patient, as CRH measurement is not routinely performed in clinical practice, especially given the rapid progression of the disease in this case. We also have to recognize that none of the several diagnostic tools recommended in the guidelines to identify the source of ACTH are absolutely reliable, including BIPSS. For instance, Mäkinen et al. reported a case of ectopic CRH secretion from MTC, where the BIPSS suggested pituitary ACTH secretion.[7] However, ^{68}Ga-DOTATOC PET/CT indicated increased uptake in the right thyroid lobe and elevated serum calcitonin levels, confirming MTC. This case underscores the potential for BIPSS to yield false positive results due to ectopic CRH secretion and supports the diagnostic value of measuring circulating CRH

levels, although this test is not routinely available in clinical practice. It is difficult to determine whether the elevated ACTH levels in a patient are due to ectopic ACTH secretion or CRH secretion leading to elevated ACTH levels. Moreover, existing case reports confirm that ectopic tumors can co-secrete both ACTH and CRH. Such cases have been documented in various tumors, including bronchial and thymic carcinoid tumors, pancreatic NETs, MTC, pheochromocytomas, and small cell lung cancer.[5–7,13,14] In addition, the location of ectopic tumors poses a significant clinical challenge. ^{68}Ga-DOTA-TATE PET/CT and ^{18}F-FDG PET/CT have demonstrated high clinical utility for detecting occult or small lesions.[6] In our case, the patient exhibited changes in bowel habits and abdominal pain, with colonoscopy revealing rectal malignancy. The ^{18}F-FDG PET/CT confirmed rectal cancer with multiple organ metastases, and the ACTH immunostaining was negative, whereas CRH immunostaining was positive, supporting the diagnosis of ectopic CRH syndrome due to rectal malignancy. This case highlights the value of immunohistochemical staining as a diagnostic tool for ectopic hormone secretion.

Literature indicates that the most common tumor types recognized as sole sources of ectopic CRH secretion are pheochromocytoma and MTC, followed by bronchial carcinoid, thymic carcinoid, and pancreatic NETs, among others.[15] The case reported herein is a rare instance of ectopic CRH syndrome caused by rectal large cell NEC, a site for which ectopic CRH-secreting tumors have not been previously reported. NECs constitute a subclass of NETs that are rarely found in the gastrointestinal tract.[10,16] Data from the American Surveillance, Epidemiology, and End Results database spanning from 1973 to 2012 indicate that the incidence of gastrointestinal NETs is 0.04 per 100,000 individuals.[17] Most of the literature on NECs is derived from studies focused on small cell lung carcinoma, whereas data specifically addressing rectal NECs remain limited. Rectal NECs account for $<1\%$ of all rectal malignancies, and large cell NEC is particularly rare, highly invasive, and associated with a poor prognosis.[10,18] The 3-year overall survival rate for this condition ranges from 5% to 27%.[10]

The treatment of ectopic CRH syndrome involves tumor control and alleviation of cortisol excess. Ideally, complete resection of NETs secreting ectopic hormones should be performed. In instances where complete surgical resection is not feasible, several options are available for managing cortisol excess. These options include steroidogenesis inhibitors, glucocorticoid receptor blockers, bilateral adrenalectomy, and tumor chemotherapy.[1,11] In the present case, the patient developed ectopic CRH syndrome due to rectal NEC. Given its rarity, clinical evidence is extremely limited. Smith et al. indicated that for most patients with rectal NETs, surgery does not improve survival, especially in the presence of metastases.[19] Retrospective studies show that local surgery combined with adjuvant chemotherapy can significantly improve survival rates, and chemotherapy regimens consisting of etoposide/cisplatin and cisplatin/etoposide are effective.[20–22] The patient presented in this report harbored extensive metastasis at diagnosis and was thus not a surgery candidate. Although potent steroidogenesis inhibitors, such as osilodrostat, have been approved for the treatment of Cushing disease in various countries, the drug is not yet available in China.[23] Additionally, its use is associated with significant risks, particularly adrenal insufficiency, especially in patients with electrolyte disturbances. Given the patient's poor overall condition and the adverse effects following chemotherapy, osilodrostat or glucocorticoid receptor blockers were not used, and treatment focused on chemotherapy. However, the disease progressed rapidly, leading to death within 3 months.

Conclusion

We report an exceedingly rare case of ectopic CS resulting from a CRH-secreting large cell NEC of the rectum. This malignancy is characterized by rapid clinical progression and an extremely poor prognosis, underscoring the importance of early detection and intervention. This case raises awareness of the importance of vigilance and thorough consideration during clinical diagnosis and treatment, as well as the need to address this rare condition to prevent misdiagnosis and mistreatment.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient's husband. A copy of the consent form is available for review by the Editor of this journal.

Author contributions

Yuan Lou: Conceptualization; Data curation; Investigation; Resources; Validation; Visualization; Writing – original draft.

Huan Chen: Validation; Writing – review & editing.

Si-Jia Fei: Validation; Writing – review & editing.

Qing-Hua He: Resources; Writing – review & editing.

Qi Pan: Conceptualization; Supervision; Validation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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