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Case Report

Cushing's syndrome due to atypical carcinoid of the mediastinum ☆,☆☆

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ABSTRACT

Ectopic Cushing's syndrome, caused by a neuroendocrine tumor (NET), is a rare finding. NETs of the mediastinum are extremely rare. NETs arising from the anterior mediastinum are generally aggressive. They are widely characterized at clinical presentations, and may be asymptomatic or present with atypical symptoms. Prognosis is often poor due to their local recurrence and distant metastasis despite a multimodal approach. A 33-year-old male patient was admitted to our department with a femoral soft tissue abscess, diabetes, and hypokalemia. He had no typical features of Cushing's syndrome. However, with a few simple tests, that is, a basal hormone profile, and low-dose and high-dose dexamethasone suppression tests, we diagnosed this complicated condition of ectopic adrenocorticotrophic hormone (ACTH) secretion. Thoracic computed tomography revealed an anterior mediastinal mass of 35 × 22 mm. A surgical excision of the tumor was proposed, and intra-operative pathology consultation returned positive for the suspected NET. Immunohistochemically, the tumor cells were positive for CK, CD56, Chromogranin, Synaptophysin, S100, and CD117. No thymic tissue was found. The Ki-67 was 4%. A diagnosis of primary NETs of the mediastinum, intermediate grade (G2), of atypical carcinoids according to WHO 2015 was established. This patient survived with no sequelae, no distant metastasis, no recurrence, and without adjuvant radiotherapy or chemotherapy 2 years after surgery thanks to earlier diagnosis and prompt surgical intervention. Mediastinum ectopic ACTH-secreting tumors are a rare type of cancer. According to recent research, these tumors frequently display

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more aggressive behavior and are linked to endocrinopathies. It is noted that patient might have a better outcome and a longer survival time due to earlier detection and complete resection of malignancies.

Core tip

It is unusual to encounter ectopic Cushing's syndrome, which is brought on by neuroendocrine tumors (NETs). Mediastinal NETs are quite uncommon. The majority of NETs that originate in the anterior mediastinum are aggressive. They might be asymptomatic or exhibit aberrant symptoms during clinical presentations, and they are broadly described. Despite a multimodal treatment, the prognosis is frequently poor because to their local recurrence and distant metastases.

Introduction

Neuroendocrine tumors (NETs) derive from neuroendocrine cells and may arise in various organ of the body. Ectopic Cushing's syndrome (ECS) refers to Cushing's syndrome (CS) that results from extra-pituitary secretion of adrenocorticotrophic hormone (ACTH) and/or, anecdotally, corticotrophin-releasing hormone. The ECS originate primarily from NETs of the lung, accounting for 50% [1,2]. NETs arising from the mediastinum are extremely rare; they often originate from the thymus gland (10%) or paraganglionic structures (10%) [3]. NETs account for 2%-4% of all anterior mediastinal neoplasms [4].

The NETs are grades in 3 grades: Grade 1, Grade 2, and Grade 3 corresponding to low-grade, intermediate-grade, and high-grade [5]. Typical lung and thymic carcinoids inherently reflect G1. Atypical carcinoids reflecting G2 correspond to intermediate-grade and well-differentiated NETs. Atypical carcinoid tumors are aggressive and clinically exhibit local recurrence or distant metastasis.

We report a relatively rare case of ECS in a patient with an atypical carcinoid tumor of the mediastinum. The key to successful treatment of this functional tumor rests in early detection and resection of the mediastinal mass.

Case presentation

A 33-year-old male was admitted to the hospital because of a chief complaint of pain in right thigh for several days. The patient had history of newly diagnosed diabetes 2 months prior. He is currently being treated with Metformin 850 mg/day. There was no personal and family history of other diseases. On physical examination, he had a mass that was red and warm to touch on the lower third of his thigh. He was 170 cm in height and 53.5 kg in weight, body mass index was 18.5 kg/m^2, and had a blood pressure of 120/80 mmHg on admission. He was afebrile. Notably, he presented with multiple pustules all over the body. He had no typical Cushing's syndrome features.

Laboratory results revealed hyperglycemia and hypokalemia.

Initial laboratory findings were significant: Glucose 11.8 mmol/L (normal: 4.1-5.8 mmol/L), HbA1C 7.6% (normal: 4.8-5.9%), K 2.2 mmol/L (normal: 3.4-4.5 mmol/L), and sodium/chloride within normal range. He was noted to have a WBC of 9.5 G/l and a CRPhs of 5.6 mg/dL (normal $<$ 0.5 mg/dL). Ultrasonography and soft magnetic resonance imaging showed a collection of fluid in the lower third of the right thigh, measuring 100 $\times$ 15 mm. The patient was diagnosed with a right femoral soft tissue abscess, diabetes, and hypokalemia. The soft tissue abscess and resultant infection were well controlled after incision. Cultured pus revealed methicillin-resistant *Staphylococcus aureus*. The patient was treated with vancomycin. Glycemia was controlled by an Insulin Basal - Bolus regimen with a total insulin dose of 0.8 UI/kg/day. However, the patient's glycemia remained unstable. Potassium was not controlled despite potassium replacement of 5-6 g/day. We performed laboratory tests to diagnose the cause of hypokalemia, including a 24-hour urinary potassium which was 104 mmol/L suggesting renal potassium loss. Arterial blood gases and thyroid function tests were normal. A random serum cortisol was elevated at 1664 nmol/l (normal: 120-620 nmol/L), and the ACTH was 854 pg/mL (normal: 7.2-63 pg/mL) (Table 1).

A low-dose overnight dexamethasone suppression test (DST) and a high-dose DST (8 mg) were ineffective at suppressing serum cortisol levels (1551 nmol/L and 1550 nmol/L, respectively). Serum ACTH remained elevated after high-dose DST 894 pg/mL (normal: 7.2-63.3) (Table 1). Results of the DST suggested an ectopic ACTH-producing tumor. Pituitary magnetic resonance imaging confirmed that he had no pituitary tumor. Inferior petrosal sinus sampling was not available. Further investigation warranted a CT of the chest, abdomen, and pelvis for determination of an ectopic ACTH-producing tumor. CT of the chest showed an anterior mediastinal mass measuring 35 $\times$ 22 mm with a regular border and no calcification.

Table 1 – The results of basal hormonal levels and after suppression tests.

	Cortisol (Normal: 120-620 nmol/L)	ACTH (Normal: 7.2-63 pg/mL)
Basal serum cortisol, ACTH	1664	854
Low-dose overnight DST (1 mg/day)	1551	841
High-dose DST (8 mg/day)	1550	894

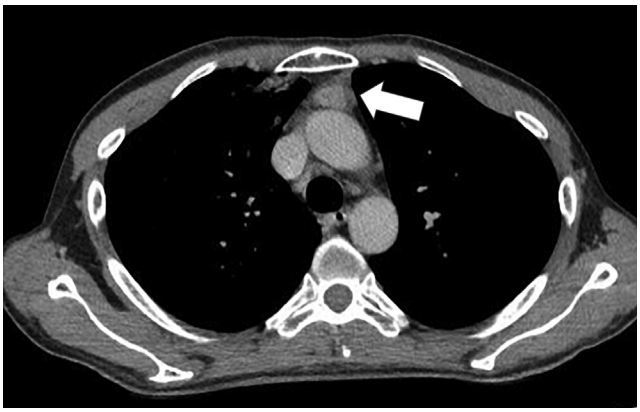

Fig. 1 – Axial thorax computerized tomography, axial view, showed an anterior mediastinal mass measuring 35 x 22 mm with regular border, without invasion and lymphadenopathy.

There was no lymphadenopathy or evidence of metastatic disease (Fig. 1).

The patient underwent complete resection of the anterior mediastinal mass. Intra-operative pathology consultation returned positive for a NET. Histopathology definitively confirmed an atypical carcinoid, grade 2 with negative margins. The tumor cells were positive for CK, CD56, Chromogranin, Synaptophysin, S100, CD117, Ki-67 (4%), and negative for thymic markers (p63) (Fig. 2). Synaptophysin, CD56, and Chromogranin are the immunohistochemical markers for the diagnosis of NETs.

Table 2 – Hormone levels after surgery.

	Cortisol (Normal range: 120-620 nmol/L)	ACTH (Normal range: 7.2-63 pg/mL)
1 day after surgery	356	55.9
2 years after surgery	254	30.2

ACTH and cortisol levels dropped significantly and returned to normal day one post-operatively (Table 2). Potassium returned to normal without medical treatment. Two months post-operatively, glycemia was normal without insulin or oral diabetic medications. At 2-year follow-up in the clinic, the patient had complete resolution of the disease with normal ACTH, cortisol, potassium and glycemia levels (Table 2), and had no recurrence on chest CT imaging.

Discussion

Overall, NETs are classified into well-differentiated NETs and poorly differentiated neuroendocrine carcinomas. NETs are classified into 3 grades: Grade 1, Grade 2, and Grade 3 corresponding to low-grade, intermediate-grade, and high-grade [5]. Typical lung and thymic carcinoids inherently reflect G1,

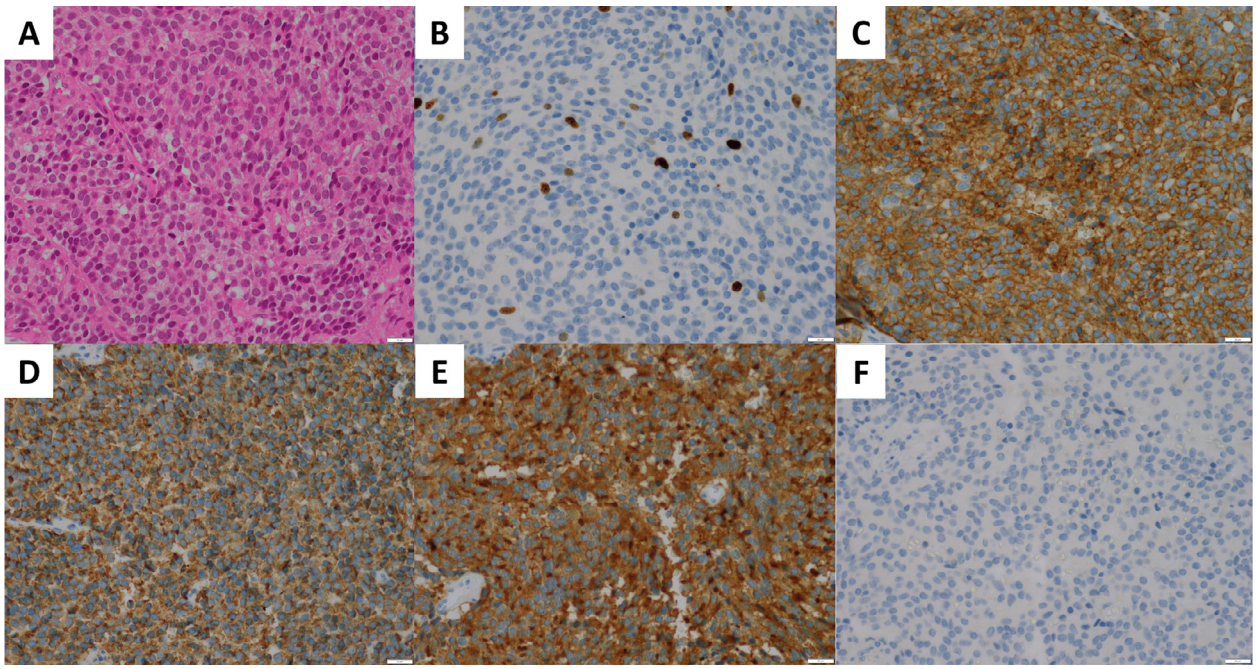

Fig. 2 – (A) The atypical carcinoid tumor (Hematoxylin and eosin staining, x400 magnification). Uniform tumor cells with nested and rosette-like growth patterns, round to oval nuclei, "salt and pepper" chromatin, eosinophilic cytoplasm. (B) The Ki-67 index was 4%. (C) Immunohistology showing specimen was positive for CD56. (D) Immunohistology showing specimen was positive for Chromogranin. (E) Immunohistology showing specimen was positive for Synaptophysin. (F) Immunohistology showing specimen was negative for p63.

and atypical carcinoids reflect G2. They are classified into well-differentiated NETs. Neuroendocrine carcinomas include large-cell neuroendocrine carcinomas, and small-cell carcinomas reflecting G3 are classified into poorly differentiated NETS. Atypical carcinoid tumors correspond to intermediate-grade and well-differentiated NETs. Criteria to distinguish these tumors are based on mitoses and necrosis. A typical carcinoid can be diagnosed with bifocal necrosis and/or 2-10 mitoses per 10 HPF [5].

NETs can arise from multiple organs of the body. While they are more frequently localized in the gastro-enterohepatic or respiratory system, they can present in the mediastinum, as was the case with this patient. NETs of the mediastinum are very rare; they account for 2%-4% of all mediastinal tumors [4].

Mediastinal NETs may originate from neuroendocrine elements within the thymus (most frequently), from aorticopulmonary and paravertebral paragangliomas, from misplaced embryonal structures within the mediastinum, and from ectopic or supernumerary parathyroid glands [4,6,7]. However, the origin, nomenclature and classification of mediastinal NETs have been the source of much controversy in the literature.

Clinically, NETs of the mediastinum may be asymptomatic, or manifest local symptoms due to compression or invasion of mediastinal structures, or systemic symptoms of endocrinopathies [8]. In asymptomatic cases or nonspecific symptoms, diagnosis of mediastinal tumors may be delayed.

We describe the case of Ectopic Cushing's syndrome due to an extremely rare atypical carcinoid NET in the mediastinum. It has been reported only in limited number [9].

In this case, the patient had no specific symptoms of Cushing's syndrome. However, he had several complications of excessive glucocorticoids, including hyperglycemia, hypokalemia, and a femoral soft tissue abscess. The patient's morning cortisol levels were found to be severely elevated. ACTH had reached a peak value. Serum cortisol levels and ACTH were not suppressed by low-dose DST. To discriminate ectopic ACTH secreting syndrome from classic Cushing's disease, a high-dose dexamethasone suppression test can be used; a suppression of more than 50% of the basal cortisol level can be observed in more than 80% of patients with Cushing's disease [10].

In this patient, serum cortisol levels and ACTH were not suppressed at high-dose DST, indicative of ectopic ACTH secretion. Pituitary MRI was normal. Thoracic CT is important to define the characteristics of the tumor and surround structures. In this case, thoracic CT revealed a mediastinal mass. A definitive diagnosis was based on intra-operative histopathology consultation and immunophenotypic markers.

The main differential diagnosis of mediastinal atypical carcinoid is thymic tumor. Atypical thymic carcinoids are more aggressive, and the survival rate is low, with overall mortality was 60% [11]. In the present case, no thymic tissues were identified within the lesion. Immunohistochemistry was negative with thymic marker (p63), and positive for NETs (CD56, Chromogranin, Synaptophysin), with Ki-67 4%.

Primary NETs of the mediastinum are characterized by a poorer prognosis due to their high propensity for local recurrence and earlier distant metastases [11]. In atypical carcinoid, regional lymph node metastases were found in 50% and distant metastases in 25% of patients [12]. The treatment options are surgical resection of the tumor, chemotherapy, somatostatin analogues, and radiotherapy. In the literature, some cases of mediastinal NETs have been treated by a combination of chemotherapy and Y-DOTATOC [13]. Interferons IFN-α, IFN-γ have been used in the pharmacological management of NETs. The tumor response rates are modest, while the adverse effects are significant.

In this case, because of the locality of the disease, no invasion or lymphadenopathy, surgery was the preferred treatment. The patient had complete resolution of symptoms after surgery and no recurrence on 2-year follow-up. Further, with earlier diagnostic and timely surgical intervention, the patient survived with no sequelae, no distant metastasis or recurrence, without adjuvant radiotherapy neither chemotherapy 2 years post-surgically. The key to successful treatment of this functional tumor rests in early detection and resection of the mediastinal mass.

Conclusions

Ectopic ACTH secreting tumors of the mediastinum are rare malignancies. Current literature suggests that these tumors often express a more aggressive behavior and are associated with endocrinopathies. We presented a case of a young male who presented with nonspecific Cushing's symptoms, but was experiencing several complications cause by excessive glucocorticoids. Because of earlier recognition and complete resection of malignancies, this patient had a better outcome and survival.

Author's contributions

Vu BN and Mac-Thi T contributed equally to this article as co-first authors. Vu BN and Mac-Thi T: Case file retrieval and case summary preparation. Mac-Thi T and Nguyen MD: preparation of manuscript and editing. All authors read and approved the final manuscript.

CARE Checklist (2016) statement

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-access

Availability of data and materials

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Our institution does not require ethical approval for reporting individual cases or case series.

Consent for publication

Not applicable.

Patient consent

Informed consent for patient information to be published in this article was obtained.

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