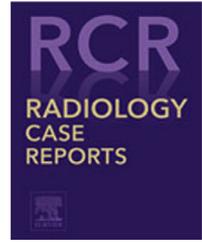


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Case Report

Ectopic Cushing syndrome caused by a pancreatic neuroendocrine tumor: A case report

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ARTICLE INFO

Article history:

Received 14 March 2020

Revised 6 April 2020

Accepted 7 April 2020

Available online 26 May 2020

Keywords:

Ectopic Cushing syndrome
Pancreatic neuroendocrine tumor
Adrenocorticotropin hormone
CT scan
Mediastinal lipomatosis

ABSTRACT

Cushing syndrome is a disorder that occurs when the body is exposed to a higher than normal level of the hormone cortisol. It is most commonly caused by exogenous glucocorticoids, and less commonly due to endogenous sources. Ectopic adrenocorticotropin hormone (ACTH) syndrome is one of the rare causes of endogenous Cushing syndrome engendered by oversecretion of ACTH from a tumor outside of the pituitary or adrenal glands. We present a case of a 74-year-old male with uncontrolled type 2 diabetes mellitus who was suspected of having Cushing syndrome on chest CT due to increasing mediastinal lipomatosis and enlarging bilateral adrenal glands. Cushing syndrome was confirmed based on clinical features and biochemical tests. Further investigation revealed an ACTH-producing functional neuroendocrine tumor of the pancreas causing ectopic Cushing syndrome.

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Introduction

Cushing syndrome is a disorder that occurs as a result of long-term exposure to a high level of the stress hormone cortisol, which is normally secreted by the adrenal glands. It is most commonly exogenous by taking prescribed glucocorticoid drugs or less commonly endogenous due to some derangement in the normal pituitary-adrenal system or ectopic tumors out of this axis, such as the pancreas [1,2]. A pancreatic neuroendocrine tumor (PNET) is the second most common malignancy of the pancreas, which could be the source of different hormones such as insulin, glucagon, and ACTH [3].

We report a rare case of ectopic Cushing syndrome due to an ACTH-producing PNET.

Case Report

A morbidly obese 74-year-old male with a history of uncontrolled diabetes mellitus type 2 complicated by diabetic foot infection, hypertension, hyperlipidemia, obstructive sleep apnea, and frequent cellulitis presented with left ankle swelling, bilateral upper extremity weakness, recurrent falls, and forearm rashes. The exam of the lower extremities revealed 3+ edema in the bilateral calves, redness, and venous stasis

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<https://doi.org/10.1016/j.radcr.2020.04.009>

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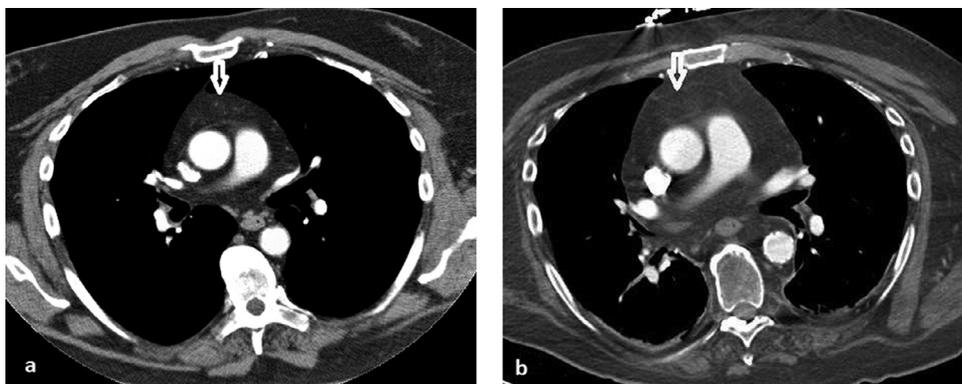


Fig. 1 – Mediastinal lipomatosis (arrow) on contrast-enhanced chest CT. (a) Three years before the admission. (b) At the time of the admission. Note increasing mediastinal lipomatosis compared to the previous CT.

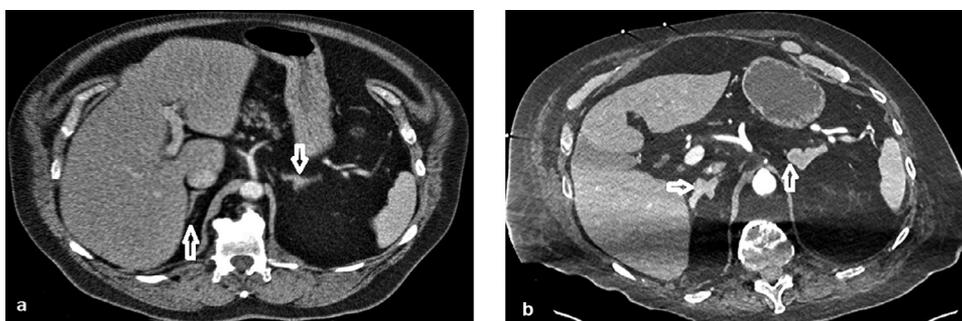


Fig. 2 – Upper abdomen through the adrenal glands included in chest CT. (a) Three years before the admission. Normal size adrenal glands on contrast-enhanced CT scan (arrows). (b) At the time of the admission. Interval development of extensive nodular thickening of both adrenal glands, compatible with nodular adrenal hyperplasia (arrow).

without ulceration, pain, crepitus, and bulla. Purpura and skin thinning were noted on the chest and forearm. Neck and shoulder fullness and central obesity were also observed. The patient cited fatigue but denied cold intolerance, hair loss/hair thinning, or constipation. He denied a family history of endocrine tumors, specifically pituitary, parathyroid, gastrointestinal, pancreatic, or adrenal tumors. He was admitted to our hospital due to concern for left lower extremity cellulitis. On the day of admission, he was afebrile, tachycardic, with a pulse rate of 109. His blood pressure was 121/50 mmHg, and his peripheral capillary oxygen saturation was 94% on room air. Laboratory evaluation demonstrated a leukocytosis to $11.09 \times 10^9/L$ and a lactate of 3.0 mmol/L (normal: 0.5–1 mmol/L), C-reactive protein was elevated to 55.3 mg/L (normal: below 3.0 mg/L), B-type natriuretic peptide was elevated to 620 pg/mL (normal: less than 100 pg/mL); troponins were negative. Laboratory results also revealed that the patient had chronic hypokalemia and iron deficiency anemia. Blood culture showed group B streptococcus bacteremia secondary to left lower extremity cellulitis, which was significantly improved by a 2-week course of antibiotics.

A chest CT scan was performed to rule out superior vena cava syndrome because of facial and neck swelling. The chest CT showed mediastinal lipomatosis and prominent pericardial fat pads, which had increased compared to a prior chest

CT performed 3 years before admission for another reason (Fig. 1a, b). Chest CT also showed interval development of diffuse enlargement of the bilateral adrenal glands (Fig. 2a, b), and diagnosis of Cushing syndrome was suspected.

An endocrinologist was consulted for evaluation for hypercortisolism. A dexamethasone suppression test resulted in a cortisol level of 70 ug/dL (normal: 10–20 ug/dL). The ACTH level was 144 pg/mL (normal: 10–60 pg/mL), late-night serum cortisol was 81.7 ug/dL (normal: less than 5 ug/d), 24-hour urine free cortisol was significantly elevated, and the biochemical evaluation strongly suggested Cushing disease. Carbohydrate antigen (CA) 19-9 was elevated to 184 (normal: 0–37 U/mL).

The patient's pituitary MRI showed a 5-mm hypoenhancing lesion in the mid-posterior aspect of the pituitary gland with no stalk deviation or mass effect on the optic chiasm (Fig. 3). Cushing disease caused by pituitary adenoma does not typically cause this degree of hypercortisolism. Furthermore, pituitary incidentalomas are very common. Therefore, the possibility of ectopic ACTH-secreting tumor was considered, and CT of the abdomen and pelvis was performed. It revealed a hypervascular mass in the pancreatic uncinate process (30 × 37 × 40 mm), highly suspicious for a primary PNET (Fig. 4a, b). It was suspected that this PNET was the source of ACTH-dependent Cushing syndrome, and the pituitary lesion was thought to be more likely an incidental finding. A whole-

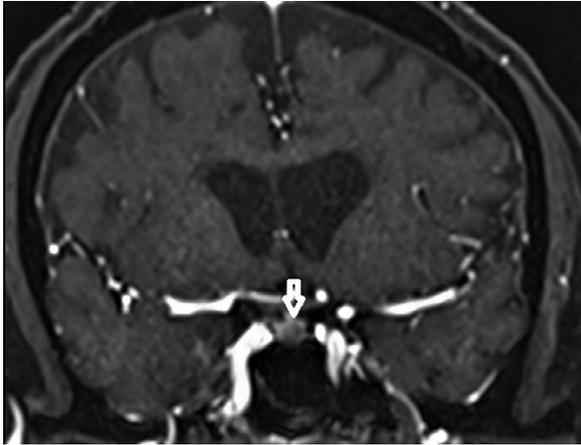


Fig. 3 – Coronal T1-weighted postcontrast brain MRI shows a 0.4 cm x 0.5 cm hypoenhancing focus within the mid-posterior aspect of the pituitary gland.

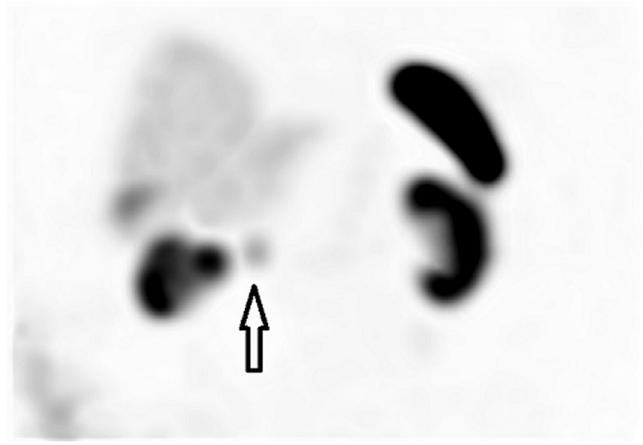


Fig. 5 – Indium-111 OctreoScan AP view of 3D SPECT image reveals radiotracer activity within the pancreatic mass in the uncinate process (arrow), suggestive of a neuroendocrine tumor.

body and SPECT-CT indium-111 OctreoScan demonstrated radiotracer activity within a pancreatic mass, highly suggestive of a neuroendocrine tumor (Fig. 5).

The pancreas was evaluated by endoscopic ultrasound. It showed a hypoechoic mass in the pancreatic uncinate process. Fine needle aspiration of the pancreatic mass via endoscopic ultrasound revealed that the neoplastic cells were positive for synaptophysin and chromogranin with a Ki-67 of approximately 15%. ACTH immunostain was reactive in the neoplastic cells, confirming the pancreatic tumor as the source of ACTH.

Surgery was consulted for potential surgical management of the pancreatic mass. However, surgical management was thought to be a poor option due to severe deconditioning. Regarding medical treatment, octreotide was considered, but deemed likely to be ineffective in controlling hypercortisolism; therefore, mifepristone, a glucocorticoid receptor blocker, was started.

The patient's course was complicated by recurrent cellulitis and resultant bacteremia presumably from skin breakdown as well as *Clostridium difficile* colitis from long-term antibiotics and septic shock. Despite aggressive resuscitative efforts, he arrested and was declared dead.

Discussion

We present one of the rare cases of ectopic ACTH syndrome caused by a neuroendocrine tumor of the pancreas. Cushing syndrome was initially suspected on a chest CT scan by increasing mediastinal lipomatosis and the development of diffuse enlargement of the bilateral adrenal glands. Mediastinal lipomatosis refers to excessive deposition of mature adipose tissue in the mediastinum, usually associated with corticosteroid therapy, obesity, or Cushing syndrome.

Ectopic ACTH syndrome develops as a result of tumors outside of the pituitary gland, which secretes either ACTH and/or corticotropin-releasing hormone leading to a clinical presentation that resembles Cushing disease, characterized by hirsutism, hypertension, muscular wasting, osteoporosis, truncal-central obesity, diabetes mellitus, and osteoporosis [4]. PNETs, which arise from islet cells, are uncommon tumors of the pancreas. The most well-known hormones secreted by functional PNETs include gastrinoma and insulinoma; however, in rare cases, they can produce ACTH [5]. Hormonal profile and imaging studies are necessary to confirm the diag-

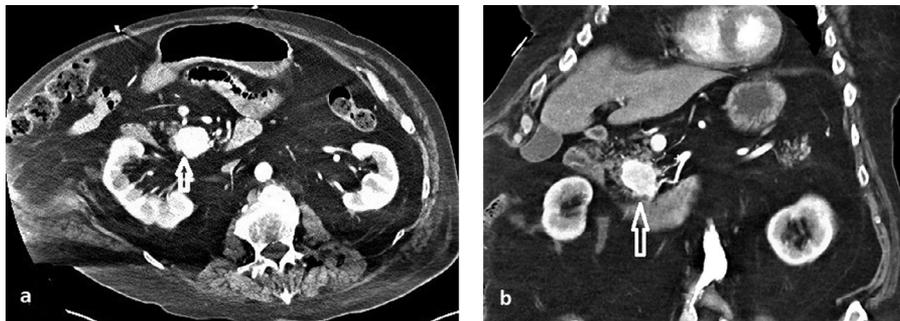


Fig. 4 – (a) Axial arterial phase and (b) coronal venous phase contrast-enhanced CT images of the abdomen demonstrate markedly enhanced 30 x 37 x 40 mm mass in the pancreatic uncinate process (arrow).

nosis of an ACTH producing PNET. Management of a PNET includes surgical and medical treatments. If tumors are resectable, the best option is surgery; otherwise, the main focus should be on medicine such as octreotide and mifepristone [6]. There are few reports about pancreatic endocrine tumors that start producing ACTH in the course of the disease. Kondo et al. [7] reported one of the first cases in this regard in 2009. The patient was a 64-year-old woman who presented with extensive generalized edema and fatigue. The tumor in the head of the pancreas with metastases to the liver was revealed by CT. Typical Cushingoid signs with markedly elevated plasma ACTH and cortisol levels, hypokalemia, and hyperglycemia confirmed the diagnosis of ectopic ACTH syndrome. A combination of treatments with metyrapone, transarterial chemoembolization, and somatostatin analog effectively decreased ACTH and cortisol levels and also addressed hyperglycemia.

In another case report, Petal et al. [8] described a 44-year-old female with a past history of diabetes mellitus, hypertension, and hyperlipidemia who arrived at the hospital with complaints of progressive fatigue and bilateral lower extremity weakness and abdominal striae over a few months. An elevated level of cortisol and ACTH with a large mass in the tail of the pancreas detected in an abdominal CT scan established diagnosis of ectopic Cushing syndrome. Two months after initiation of octreotide, ACTH and urinary free cortisol levels returned to normal, and radioembolization was done for the patient without immediate complication.

Recently, Byun et al. [5] reported a case of a 40-year-old Korean female admitted to the hospital with ophthalmologic discomfort, osteoporosis, and hypokalemia. Laboratory results showed elevated levels of ACTH and cortisol not suppressed by high-dose dexamethasone. A 1.8-cm pancreatic tail mass was confirmed by endoscopic ultrasonography, which verified autonomous ACTH production by venous sampling. Laparoscopic distal pancreatectomy was undertaken for the patient without any clinical complications, which brought her ACTH level back to normal.

Compared to the available case reports in the literature, our patient was unique in terms of presenting with nonspecific symptoms and was suspected for Cushing syndrome on chest CT based on the finding of interval development of bilateral adrenal hyperplasia and increasing mediastinal lipomatosis and pericardial fat pads. Following confirmation of the diag-

nosis of ectopic ACTH syndrome by PNET by laboratory results and imaging studies, the patient was put on mifepristone. However, the course of treatment was left uncompleted because of the patient's poor condition, and the patient passed away due to complications of sepsis.

Acknowledgment

The authors thank senior science writer Edmund Weisberg, MS, MBE, who helped us to review and edit the article.

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