

CT and 111In-pentetreotide SPECT of hilar ACTH-producing neuroendocrine tumor associated with Cushing's syndrome and massive bilateral adrenal gland hyperplasia

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ABSTRACT

We present the clinical, laboratory, computed tomography (CT), single photon emission computed tomography (SPECT), and histopathological findings of a patient with adrenocorticotrophic hormone (ACTH) dependent Cushing's syndrome with massive bilateral adrenal gland hyperplasia due to a hilar ACTH-producing well-differentiated neuroendocrine carcinoma.

CASE REPORT

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A 29-year-old previously healthy man presented with symptoms and signs of Cushing's syndrome. His family noticed that he had a rounder looking face, and he noticed that he began to become tired during work as an auto mechanic. On initial physical examination, he had mild hypertension (blood pressure 150/90) and a cushinoid appearance with moon facies, truncal obesity, and multiple red striae in the torso. The serum cortisol level was elevated at 48.7 ug/dl (normal range 5-25 ug/dl), and there was no prior history of use of steroid-containing medications or other exogenous source of corticosteroids. His serum ACTH level was also elevated to greater than 130 pg/ml (normal range 7-69 pg/ml). No pituitary, hypothalamic, or other abnormalities were seen on head magnetic resonance imaging (MRI) (Figure 1A), and inferior petrosal sinus sampling for ACTH was negative.

Contrast-enhanced CT examination of the chest demonstrated a nonspecific 1 cm soft tissue attenuation

enlarged right hilar lymph node (Figure 1C), which demonstrated avid uptake of radiotracer on a separate 111In-pentetreotide SPECT scan (Figure 1B and 1D), indicating the presence of somatostatin receptors. CT images through the upper abdomen demonstrated massive smooth enlargement of the adrenal glands in keeping with bilateral adrenal hyperplasia (Figure 1E). Surgical removal of the right hilar mass and right upper lobe was subsequently performed. Histopathology demonstrated a well-differentiated neuroendocrine carcinoma confined to the right hilar lymph node without involvement of the lung parenchyma (Figures 2A - B). Immunohistochemistry revealed diffuse and strong positive ACTH staining of the tumor with lymphovascular involvement (Figure 2C). Repeat contrast-enhanced CT examination 7 months post surgery showed normalization of bilateral adrenal gland size (Figure 1F). Normalization of serum cortisol and ACTH levels also occurred as well.

DISCUSSION

Cushing's syndrome is a hormonal disorder in which there is excessive production of corticosteroids, either due to exogenous or endogenous causes. If left untreated, the morbidity and mortality rates of the syndrome are high (1) Cushing's syndrome due to an endogenous cause has an incidence of 5-6 cases per million individuals (2), 85% of which are adrenocorticotropic hormone (ACTH) dependent, where an excess of ACTH overstimulates the production and secretion of cortisol from the adrenal glands. A major cause of ACTH dependent Cushing's syndrome is Cushing's disease, comprising 70% of cases, which is due to a hyperfunctioning pituitary gland tumor such as an adenoma. The other 15% of cases of ACTH dependent Cushing's syndrome are related to a non-pituitary ectopic source of ACTH production, most often due to small cell lung carcinoma and neuroendocrine tumors.

Neuroendocrine tumors are rare, with annual age-adjusted incidence of 5.25/100,000 in 2004 (3), can occur in any location where endocrine precursor cells are found, and can be classified by their associated clinical syndromes related to increased production and secretion of specific hormones, although more than one hormone may be produced simultaneously (4). These hormones include ACTH, calcitonin, gastrin, glucagon, growth hormone, insulin, somatostatin, among others. Besides Cushing's syndrome, a clinical syndrome causing by increased ACTH, carcinoid syndrome (in which main symptoms are flushing and diarrhea) occurs from high serotonin secretion. Gastrin hypersecretion is associated with increased gastric acid production, causing Zollinger-Ellison syndrome with symptoms and signs of disease including peptic ulcers and diarrhea.

Differential diagnoses of bilateral enlarged adrenal glands include Cushing's syndrome, adrenal tumors and adrenal metastases. Cushing's syndrome with associated bilateral adrenal gland hyperplasia, particularly when smooth in configuration, is either pituitary, mainly due to adenomas, or non-pituitary ACTH secretion (5). Ectopic ACTH secretion occurs with lung cancer, neuroendocrine tumors and less common due to thymomas, pancreatic islet cell tumors and medullary thyroid cancer. On the other hand, adrenal tumors and adrenal metastases may cause of ACTH independent Cushing's syndrome and could present with bilaterally enlarged adrenal glands, although in these cases the enlarged adrenal glands tend to have a multinodular appearance (6).

SPECT imaging following the intravenous administration of 111In-pentetreotide, a single gamma emitting somatostatin analog, can be utilized to detect somatostatin receptor rich tumors such as neuroendocrine tumors (7).

In our patient described above, smooth bilateral adrenal gland hyperplasia seen on CT, implied the presence of ACTH dependent Cushing's syndrome. Furthermore, 111In-pentetreotide SPECT imaging was useful to localize the somatostatin receptor rich neuroendocrine tumor (8), which was also the non-pituitary source of ACTH production.

TEACHING POINT

In order to find a cause of ACTH dependent Cushing's syndrome due to Neuroendocrine tumors, multi-imaging modalities are needed. Massive bilateral adrenal gland hyperplasia indirectly implies increased ACTH production and brain MRI helps to rule out pituitary tumors, which is a common cause for ACTH dependent Cushing's syndrome. Combined 111In-pentetreotide SPECT/CT locates the site of the tumor by detecting somatostatin receptors which are often plentiful in Neuroendocrine tumor.

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FIGURES

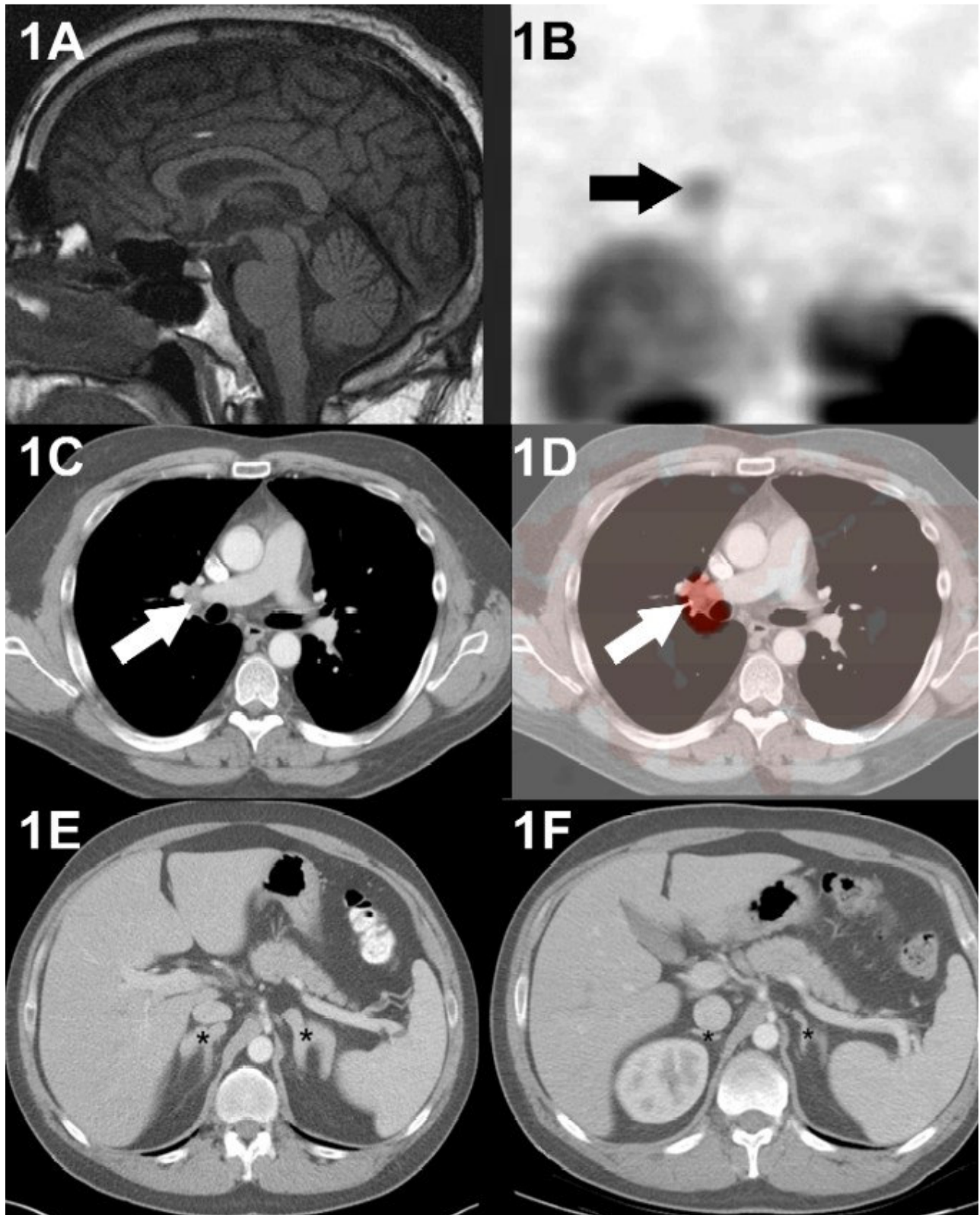


Figure 1: 29-year-old man with hilar ACTH-producing neuroendocrine tumor associated with Cushing's syndrome and massive bilateral adrenal gland hyperplasia. (A) Sagittal T1-weighted MR image of the brain shows no pituitary or hypothalamic abnormality. Contrast-enhanced axial CT image through chest during the parenchymal phase of enhancement reveals (C) nonspecific 1 cm soft tissue attenuation right hilar lymph node (white arrow). Coronal SPECT image of the chest (B) at 24 hours post administration 6.1 mCi of ¹¹¹In-pentetreotide (Octreoscan) shows avid uptake of radiotracer in right hilar region (black arrow) corresponding with right hilar lymph node on chest CT, indicating somatostatin receptor rich lesion. The fused ¹¹¹In-pentetreotide axial SPECT and axial CT images of the chest (D) are shown the tracer-avid right hilar lymph node (white arrow). Contrast-enhanced CT image through upper abdomen (E) demonstrates bilateral massive smooth enlargement of adrenal glands (*) in keeping with adrenal hyperplasia. (F) Contrast-enhanced CT image through upper abdomen 7 months following surgical resection of right hilar lymph node shows normalization of bilateral adrenal gland size (*).

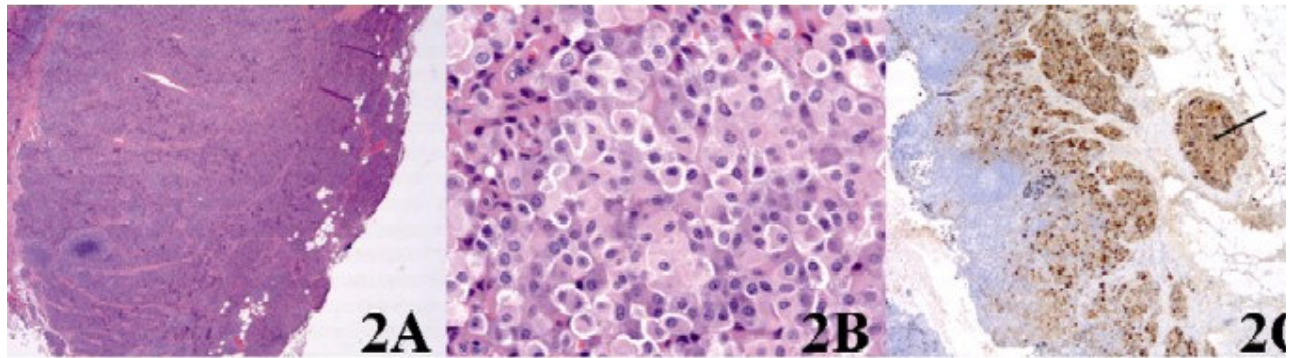


Figure 2: 29-year-old man with hilar ACTH-producing neuroendocrine tumor associated with Cushing's syndrome and massive bilateral adrenal gland hyperplasia. (A) Histopathologic image shows well-differentiated neuroendocrine carcinoma confined to right hilar lymph node without involvement of lung parenchyma (H&E, x25). (B) Higher power image reveals mixture of acidophil and basophil cell types without significant cellular atypia, necrosis, or increased mitoses (H&E, x400). (C) Immunohistochemistry image reveals diffuse and strong positive ACTH staining of tumor with lymphovascular involvement (arrow) (ACTH, x50).

ABBREVIATIONS

CT = Computed Tomography
SPECT = Single Photon Emission Computed Tomography
ACTH = Adrenocorticotrophic hormone

KEYWORDS

Bilateral adrenal gland hyperplasia; ¹¹¹In-pentetreotide (Octreoscan); Cushing's syndrome

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