CASE REPORT

Use of In-111 pentetreotide scintigraphy in the diagnosis of a midgut carcinoid causing Cushing’s syndrome

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Abstract

A 57-year-old man presented with clinical features of hypercortisolism and was diagnosed with ACTH-dependent Cushing’s syndrome. Biochemical testing showed partial suppression of urinary free cortisol with high dose dexamethasone. Initial computed tomography (CT) of the chest and abdomen, and magnetic resonance imaging of the pituitary were negative. In-111 pentetreotide scintigraphy with single photon emission computerized tomography revealed two ‘hot’ lesions in the abdomen which were then confirmed by subsequent directed thin-slice abdominal CT and small bowel barium study. At surgery, two segments of ileum, adjoining mesentery and lymph nodes were resected. Histopathology was consistent with a malignant carcinoid tumor of the ileum which stained intensely for ACTH. Plasma ACTH, and serum and urinary cortisol normalized postoperatively. To our knowledge, this is the first reported case of ileal carcinoid tumor causing Cushing’s syndrome with premortem diagnosis. Another unique feature of this case is that In-111 pentetreotide scan provided the decisive clue to localization of the tumor.

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Introduction

As many as 10–15% of all cases of Cushing’s syndrome (CS) are reported to be due to an ectopic production of adrenocorticotropic hormone (ACTH) (1). Localization of an ‘occult’ neoplasm causing ectopic ACTH syndrome frequently poses a diagnostic challenge. Inferior petrosal sinus sampling for ACTH with corticotropin-releasing hormone (CRH) stimulation represents the ‘gold standard’ in differential diagnosis of CS, providing the most accurate and reliable means of distinguishing pituitary from non-pituitary ACTH-dependent CS (2). However, it does not help to localize the source of ectopic ACTH secretion. Computed tomography (CT) and magnetic resonance imaging (MRI) of the chest and abdomen have been reported to be the best localization methods currently available (3, 4). Detection of a lesion by the above imaging procedures, however, does not indicate its function. Selective venous sampling for such localization is invasive and cumbersome. A majority of neuroendocrine tumors including carcinoids and small cell lung cancers express somatostatin receptors (5, 6). This has allowed for in vivo visualization of such tumors using the radiolabeled somatostatin analog, octreotide.

In the following case report, we describe the occurrence of CS caused by ectopic secretion of ACTH by an ileal carcinoid tumor localized by In-111 pentetreotide scintigraphy.

Methods

Hormonal assays

Serum cortisol was measured by fluorescence polarization immunnoassay (TDxFLx; Abbott Laboratories, Abbott Park, IL, USA), urine free cortisol was measured by HPLC (Nichols Institute, San Juan Capistrano, CA, USA) and plasma ACTH was measured by a highly sensitive immunoradiometric assay (Nichols Institute).

In-111 pentetreotide scintigraphy

The patient was injected with 6.0 mCi In-111 pentetreotide (Octreoscan) intravenously and planar images were obtained at 4, 24, and 96 h on a dual-headed scanner using medium energy collimators. Single photon emission computerized tomography (SPECT) was performed at 24 and 96 h using a 128 × 128 matrix.
acquisition size and 40 stops at 6° increments. The images were then prefiltered with a Butterworth filter using a critical frequency of 0.3 cycles/cm and a power factor of 10, with ramp backprojection filter.

Case report

A 57-year-old caucasian male presented with a two-month history of abdominal pain, fatigue, swelling of the face and feet, difficulty in climbing stairs, a fifteen-pound weight gain, worsening hypertension, and melena. There were no symptoms suggestive of carcinoid syndrome. On upper GI endoscopy, he was noted to have multiple gastric ulcers and candidial esophagitis. Past medical history was significant for hypertension for ten years which was being treated with metoprolol. Physical examination revealed a blood pressure of 190/86 mm Hg, bilateral exophthalmos, edema of the lower extremities, a dorsocervical fat pad, proximal muscle weakness, and abdominal distension. Laboratory data revealed the following values: hemoglobin, 139 g/l; hematocrit, 0.4; white blood cell count, $12 \times 10^9$/l (polymorphonuclear cells, 0.74; lymphocytes, 0.22; eosinophils, 0); serum sodium, 140 mmol/l; serum potassium, 2.8 mmol/l; chloride, 99 mmol/l; CO$_2$ content, 32 mmol/l; BUN (blood urea nitrogen), 11.36 mmol/l; creatinine, 70.67 μmol/l; random glucose, 7.89 mmol/l; calcium, 2.0 mmol/l; albumin, 32 g/l. Endocrine testing revealed the following values: a.m. serum cortisol, 1428 nmol/l (normal (N): 170–680 nmol/l); a.m. plasma ACTH, 45.35 pmol/l (N: 1.98–11.45 pmol/l); serum cortisol after 1 mg overnight dexamethasone, 1204.2 nmol/l; urinary free cortisol (by HPLC), basal-8699.52 mmol/24 h (N: <138 mmol/24 h), and after two days of high dose dexamethasone (2 mg q 6 h) 3441.72 mmol/24 h; urinary 5-hydroxyindole acetic acid (5HIAA), 49.6 μmol/24 h (N: 10.4–41.8 μmol/24 h).

MRI of the pituitary, and initial CT imaging of the abdomen and chest (regular 1-cm sections with IV contrast) were negative. Planar In-111 pentetreotide scanning showed abnormal radiopharmaceutical localization in the right abdomen at 4, 24 and 96 h. The 96-h images were obtained to confirm the lesion and to ensure any excreted activity cleared the bowel (Fig. 1). In-111 pentetreotide scanning with SPECT revealed ‘hot lesions’ in the abdomen antero-inferior to the lower pole of the right kidney. A subsequent, carefully guided, thin-sliced CT of the abdomen (5-mm sections in the area directed by the scintigraphy) showed three enlarged mesenteric lymph nodes at the level of the lower pole of the right kidney (thick arrow) and a suspicious filling defect in a loop of ileum (thin arrow).
enlarged mesenteric lymph nodes at the level of the lower pole of the right kidney that corresponded with these ‘hot spots’, and a suspicious filling defect in a loop of ileum (Fig. 2). A small bowel barium study showed a fixed mass in a bowel loop corresponding to the CT finding (Fig. 3).

At surgery, two portions of ileum (6.0 and 75.0 cm long) along with the adjoining mesentery and lymph nodes were excised. There were no visible hepatic metastases. Histopathological examination of the specimens revealed ten foci of carcinoid tumor originating in the submucosa of the ileum. Several foci involved the mucosa and two also involved the serosa. Eight of sixteen mesenteric lymph nodes were positive for metastatic carcinoid. The tumor stained strongly for ACTH (Fig. 4). CRH staining was negative.

Endocrine testing done two weeks post-operatively revealed the following values: a.m. serum cortisol, 184.2 nmol/l; urinary free cortisol, 85.6 mmol/24 h; a.m. plasma ACTH, 14 ng/l; urinary 5HIAA, 18.8 µmol/l. His symptoms resolved after surgery and he was doing well on replacement hydrocortisone therapy six months after surgery. Repeat endocrine testing was normal.

**Discussion**

Localization of ‘occult’ ectopic ACTH-producing tumors is frequently a clinician’s nightmare. The most commonly reported neoplasms causing occult ectopic ACTH syndrome are bronchial carcinoids followed by thymic carcinoids and pancreatic islet cell tumors (3, 7, 8). Midgut carcinoids causing CS are much less common, and the previously reported cases have been carcinoids of the appendix (9–11) and a single case of ileal carcinoid which was diagnosed at autopsy (12).

Bilateral inferior petrosal sinus sampling is an extremely useful tool to differentiate between an ectopic source of ACTH and a pituitary corticotrope adenoma, with reported sensitivity close to 100% (4, 13). However, it does not help to localize the source of ectopic ACTH production. Slowly growing tumors like bronchial carcinoids may remain undetected for long periods of time necessitating repeated imaging procedures. CT scan and MRI of the chest and abdomen are currently the best widely available imaging procedures for this purpose (3, 4). However, the lesions detected by these imaging modalities may be entirely incidental and not responsible for ACTH secretion, necessitating fine needle biopsy, venous sampling, or surgical resection to confirm the nature of these lesions.

More recently, octreotide scintigraphy is being evaluated in the diagnosis of various neuroendocrine tumors. Such tumors have high numbers of somatostatin receptors (5). At least five different somatostatin receptor subtypes have been identified in human tissues with different tissue distribution and binding characteristics (14). The uptake of radiolabeled somatostatin analog octreotide by tumor tissue is highly specific and depends on the expression of appropriate somatostatin receptors. In an *in vitro* study of somatostatin receptor status in tumor tissues of patients with carcinoid tumors, using autoradiographic techniques with iodinated somatostatin analogs, 87% (54/62) of these patients were found to have somatostatin receptor-positive tumors (6). (\(^{111}\text{In-DTPA-o-Phe}^1\))octreotide (In-111 pentetreotide) is the radionuclide of choice and has largely replaced (\(^{123}\text{I-Tyr}^3\))octreotide in diagnostic imaging as several technical and supply difficulties are encountered with the use of the latter (15). These include the short half-life of \(^{123}\text{I}\), inefficient labeling and the lack of a Food and Drug Administration approved radiopharmaceutical for general distribution. In addition, the hepatobiliary clearance of (\(^{123}\text{I-Tyr}^3\))octreotide results in substantial background radioactivity in the upper abdomen, obscuring lesions in these sites. The addition of SPECT imaging has improved spatial resolution and definition of the relationship of such tumors to surrounding anatomical landmarks. Unlike
the CT or MRI, octreotide scintigraphy indicates the functional nature of the suspected lesion.

The reported sensitivity of octreotide scintigraphy in detecting primary gastroenteropancreatic tumors is around 80–90% and in detecting gastroenteropancreatic carcinoid tumors is 80–100% (16–22). It should be noted that although somatostatin scintigraphy has the advantage of combining functional and morphological approaches, it may not always be possible accurately to point out the source of ACTH since a variety of pathologic entities (breast cancer, malignant lymphomas, adenocarcinoma, granulomatous or autoimmune diseases) can be visualized using this procedure (19).

The sensitivity of octreotide scintigraphy in localizing occult ACTH-secreting tumors remains unknown. Several recent reports have evaluated the use of this technique for localization of tumors in patients with ectopic ACTH-dependent Cushing’s syndrome. In the largest series by de Herder et al. (23), eight out of ten ACTH-secreting tumors were identified with octreotide scintigraphy. In this series, only one of ten was a truly occult tumor, and this one was not identified by octreotide scintigraphy. Reviewing published reports so far, eight of ten (including the present case) ‘occult’ tumors which were not visualized by standard radiographic imaging could be localized by this technique (23–31). Of the eight visualized tumors, five were bronchial carcinoids (26, 28–31), one was an epigastric neuroendocrine tumor (27), one was a pancreatic islet cell tumor (24), and one was an ileal carcinoid (present case). From the published data, the size of the primary tumor first localized by pentetreotide scanning ranged from 6 to 25 mm, the largest one being a pancreatic islet cell neoplasm (24), which was not localized by initial CT or MRI but later confirmed by endoscopic ultrasonography after localization with the pentetreotide scan. Because octreotide scintigraphy provides functional information about a lesion, it can be useful in confirming a suspected lesion seen on CT. In the case reported by Ollaro et al. (28), the patient had concomitant pulmonary mycosis which made interpretation of the CT difficult, although in retrospect there was a lesion on CT which corresponded to the area labeled by octreotide. In the two cases that were not visualized by scintigraphy, one was a presumed recurring bronchial carcinoid (23) and the other was of uncertain origin (25). The cost of a whole-body In-111 pentetreotide scan including SPECT in our hospital (UW Hospital and Clinics) is about $2300.00 which is very close to the cost of CT, abdomen and pelvis ($2200.00) and less than the cost of MR imaging of the chest and abdomen ($3400.00). Thus, in cases of CS due to ‘occult’ ectopic ACTH and/or CRH secretion, In-111 pentetreotide scintigraphy has the potential of becoming the imaging modality of choice.

In contrast to the wide range of hormones found in foregut carcinoids, midgut carcinoids mainly secrete serotonin and tachykinins (32, 33). Midgut carcinoids causing ectopic ACTH syndrome are rare, and the only previous reported case of ileal carcinoid causing CS was diagnosed at autopsy (12).

We have reported a very rare case of ACTH-producing ileal carcinoid tumor. The initial localization of this tumor was provided by In-111 pentetreotide scintigraphy and was able to direct further evaluation of the patient. Early identification of the source of ectopic ACTH production resulted in early treatment and an apparent surgical cure of this metastatic ileal carcinoid.

References
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