CASE REPORT

[18F]fluoro-2-deoxy-D-glucose ([18F]FDG) positron emission tomography imaging of thymic carcinoid tumor presenting with recurrent Cushing’s syndrome

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Abstract
We report a case of a young woman with Cushing’s syndrome (CS), in whom although endocrine investigations and negative pituitary imaging were suggestive of ectopic ACTH secretion, the results of inferior petrosal sinus (IPS) sampling after corticotropin-releasing hormone (CRH) stimulation were suggestive of pituitary ACTH hypersecretion. 111In-labelled octreotide and high-resolution computer tomography (CT) revealed a lesion possibly responsible for the ACTH source in the thymus. Thymectomy confirmed concomitant ectopic CRH and probable ACTH production by a thymic neuroendocrine carcinoma. After an 8-year remission period the patient developed a clinical and biochemical relapse. A high-resolution computed tomography (CT) scan of the thorax showed a 2-cm nodule in the thymic bed, which was positive on a [18F]fluoro-2-deoxy-d-glucose ([18F]FDG) positron emission tomography (PET) scan. However, a repeated thymectomy did not result in remission. A repeat [18F]FDG PET study showed persistent disease in the thymic bed and also uptake in the adrenals. The patient underwent bilateral adrenalectomy, which resulted in clinical remission. A further [18F]FDG PET scan 8 months later showed no progression of the thymic tumor and confirmed complete excision of the adrenals. This is a rare case of concomitant CRH and ACTH secretion from a thymic carcinoid tumor; the case illustrates the usefulness of functional imaging with [18F]FDG PET in the diagnosis, management and follow-up of neuroendocrine tumors.

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Case report
A 25-year-old woman initially presented with recent-onset depression, hirsutism, acne and bruising suggestive of Cushing’s syndrome (CS); clinical examination revealed arterial hypertension (170/120 mmHg) and mild proximal myopathy. Subsequent investigations showed hypokalemic alkalosis (serum K+, 2.3 mmol/l (normal range 3.5–5.0 mmol/l); HCO₃⁻, 32 mmol/l (normal levels 24±2 mmol/l)), marked hyperandrogenemia (testosterone, 12.5 nmol/l (normal range 0.5–2.5 nmol/l)), normal fasting glucose concentrations and autonomous hypercortisolism (elevated 24-h urinary free cortisol (UFC) of 4064 nmol per 24 h (normal range 20–300 nmol per 24 h), serum midnight cortisol of 1161 nmol/l and inadequate cortisol suppression to a formal low-dose dexamethasone suppression test).

An ectopic source of adrenocorticotropic hormone (ACTH) secretion was suggested by a marked elevated plasma ACTH concentration (1350 ng/l (normal values < 25 ng/l)), and a failure to suppress serum cortisol following a high-dose dexamethasone suppression test (HDDST). Inferior petrosal sinus (IPS) sampling after corticotropin-releasing hormone (CRH) stimulation, however, was more in keeping with Cushing’s disease than with ectopic ACTH production as it showed a brisk ACTH increment following CRH administration (Table 1); a pituitary magnetic resonance imaging (MRI) scan was normal. An initial computed tomography (CT) scan of the thorax was normal but scintigraphy with octreotide 111In-[D-Phe1]-DTPA-octreotide (111In-pentetreotide, Mallinckrodt Medical, St. Louis, MO, USA) showed tracer activity in the thymus (Fig. 1A). A further high-resolution CT showed a 2-cm thymic nodule in the upper mediastinum. Whole-body catheterization and sampling did not reveal an ectopic ACTH source. However, a greater than 3:1 CRH gradient suggestive of ectopic CRH production between the left brachiocephalic vein (BCV) and superior vena cava (SVC) and their simultaneous peripheral samples (BCV, 90 pg/ml and SVC, 100 pg/ml vs 30 pg/ml respectively) was shown. Based on the above findings a working diagnosis of a neuroendocrine tumor of the thymus (thymic carcinoid tumor) secreting CRH was made.

The patient underwent a mediastinotomy and thymectomy. A central firm nodule within the thymus
Table 1 Inferior petrosal sinus (IPS) sampling with CRH stimulation.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Left IPS</th>
<th>Right IPS</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>479</td>
<td>1110</td>
<td>364</td>
</tr>
<tr>
<td>3</td>
<td>1500</td>
<td>1960</td>
<td>434</td>
</tr>
<tr>
<td>8</td>
<td>990</td>
<td>1900</td>
<td>490</td>
</tr>
<tr>
<td>15</td>
<td>526</td>
<td>1760</td>
<td>498</td>
</tr>
</tbody>
</table>

was totally excised. Histopathology revealed a well-differentiated neuroendocrine carcinoma with tumor invasion into the lymphatic lumina, which stained positively for neuron-specific enolase (NSE), chromogranin A and synaptophysin, ACTH and CRH. The patient made an uneventful recovery and a repeat 111In-pentetreotide scan 2 weeks later showed no tracer uptake in the mediastinum.

Following a prolonged remission the patient presented 8 years later with depression and typical features of CS, suggestive of disease relapse. Further investigations revealed a plasma potassium concentration of 3.6 mmol/l, serum testosterone of 6.8 mmol/l and a 24-h UFC of 32 078 nmol per 24 h. Imaging with 111In-pentetreotide scan was negative whereas a high-resolution CT scan of the mediastinum showed a possible 2-cm nodule in the thymic bed. Positron emission tomography (PET) using [18F]fluoro-2-deoxy-D-glucose ([18F]FDG) showed increased tracer uptake in the pre-aortic region, implying a metabolically active lesion and prominent uptake of tracer by the adrenals (Fig. 1B and C).

Following a repeated thoracotomy, the histology of the remaining tumor showed relatively monomorphic cells with round nuclei, eosinophilic cytoplasm and prominent nucleoli, mitotic figs. and areas of necrosis. Both vascular and lymphatic invasion was seen. Immunohistochemistry was positive for chromogranin A, synaptophysin, ACTH and cytokeratin but not CRH. Post-operatively, there was little clinical improvement and serum cortisol levels remained elevated. A repeat [18F]FDG PET study showed two small glucose avid areas of uptake adjacent to the thymic bed and persistent avid uptake by the adrenals (standardized uptake values of 5.9 for left and 6.1 for right adrenal). Further thoracic surgery was not thought possible and the patient underwent a successful bilateral adrenalectomy, which lead to clinical and biochemical remission. Plasma ACTH levels remained high. A further [18F]FDG PET study 8 months later showed ongoing activity in the thymic bed but no progression (Fig. 1D); she remains well 2 years after her adrenalectomy.

**Discussion**

The present case describes an extremely rare case of an ectopic CRH and most probably ACTH co-secreting neuroendocrine tumor manifested as CS; it identifies the usefulness of radionuclear methods in identifying the ectopic source. Although the presenting clinical picture, biochemical findings and negative pituitary imaging were suggestive of ectopic ACTH hypersecretion, this was not substantiated by the results of IPS after CRH stimulation, which were indicative of pituitary ACTH hypersecretion. Subsequent investigation using 111In-labelled octreotide initially revealed the original ectopic source of ACTH secretion while imaging with PET revealed the presence of recurrent disease thus directing to the appropriate treatment. Therefore, the possibility of aberrant hormonal secretion from neuroendocrine tumors should always be considered, particularly when there are confounding biochemical results; in such cases the application of thin-section and spiral CT of the chest should be used as a first line of investigation. If this proves negative, or in cases with small ambiguous lesions where there is a need for confirming their neuroendocrine origin, functional imaging (i.e. 111In-labelled octreotide and/or PET) can be extremely helpful in establishing the correct diagnosis (1).

IPS sampling has been claimed to exert an almost 100% sensitivity and specificity in establishing the source of ACTH hypersecretion in cases of ACTH-dependent CS (2–5). In our case, although the results obtained from the other investigations were consistent with ectopic ACTH CS, IPS revealed a central-to-peripheral ACTH gradient of > 3 after CRH stimulation, consistent with Cushing’s disease (2). As these results were originally conflicting we investigated the possibility of the presence of a factor that could de-suppress the pituitary corticotrophs such as CRH, by exerting a stimulating effect. Ectopic CRH secretion, although very rare, has been very well described before and it is a well-established pitfall of IPS when used for the differential diagnosis of ACTH-dependent CS (6–9). This suspicion was reinforced further when imaging with 111In-labelled octreotide revealed a possible neuroendocrine tumor in the anterior mediastinum, which was confirmed on subsequent CT imaging. Following whole-body catheterization and sampling, a CRH gradient between the left BCV and SVC and their simultaneous peripheral samples (BCV, 90 pg/ml and SVC, 100 pg/ml vs 30 pg/ml respectively) was revealed as indicated from the localization studies. Although sampling from the vena cava did not reveal a gradient for ACTH, we speculate that there was ACTH co-secretion because of the positive immunostaining of the excised tumor.

The difference in peripheral plasma ACTH levels observed at the initial evaluation and during the IPS/peripheral sampling can be explained by the spontaneous fluctuations of CRH secretion by the tumor.

To date, approximately 58 cases of neuroendocrine carcinomas of the thymus associated with CS (mostly attributed to ACTH production) have been reported in...
the literature (10, 11). Ectopic CRH production, from various tumors, has been documented and these included: a medullary thyroid carcinoma, bronchial carcinoids, a pheochromocytoma, a retropancreatic tumor, a hypothalamic gangliocytoma and small cell carcinoma of the lung and prostate (6–9, 12–15). There have been two reports of thymic CRH production (16, 17). In such cases functional imaging coupled

Figure 1 Patient with thymic carcinoid tumor. (A) $^{111}$In-pentetreotide scan shows tracer uptake in the thymus (curved arrow). (B and C) $^{18}$F]FDG PET images: coronal sections show $^{18}$F]FDG avid thymic lesion (large arrow) and a further coronal section more posteriorly shows high uptake in the adrenal glands (small arrows). (D) $^{18}$F]FDG PET study acquired post-thymectomy and post-adrenalectomy shows activity in residual tissue (large arrow).
with conventional imaging has recently been used to localize endocrine tumors. In this particular case, prior to repeated thymectomy, [18F]FDG PET scintigraphy and high-resolution CT were the only modalities that detected recurrent tumor. [18F]FDG PET imaging identified the primary site but failed to localize the site of recurrence, which probably reflects either reduced number or lack of somatostatin receptors in the metastatic lesions. Following the repeated thymectomy, [18F]FDG PET was the only modality that continued to show residual tumor, which was in keeping with the patient’s clinical picture: the high metabolic turnover of the adrenals was also clearly demonstrated. It has been shown that only 5% of normal adrenals are seen on the [18F]FDG PET scan. When co-registered [18F]FDG PET/CT studies are quantified the adrenal has been shown that only 5% of normal adrenals are seen on the [18F]FDG PET scan. When co-registered [18F]FDG PET/CT studies are quantified the adrenal localization and follow-up.

PET using [18F]FDG reflects the glucose turnover in a lesion. Increased tracer uptake implies increased metabolic activity of a lesion. This imaging technique plays an important role in identifying cancer stages and the investigation of tumor recurrence (19, 20). [18F]FDG PET imaging has a high sensitivity, specificity and accuracy (70–95%) depending on the type of tumor being investigated (19). However, application of this imaging modality in neuroendocrine tumors is limited because they are mostly well differentiated with a low metabolic rate and therefore cannot be efficiently visualized with FDG (21, 22). PET imaging using [11C]5-hydroxytryptophan ([11C]5-HTP) or [11C]L-DOPA has been shown to be more sensitive for visualization of carcinoids and other neuroendocrine tumors (20, 23–25). Recent technological development in hardware allows simultaneous data acquisition of [18F]FDG PET and CT in one sweep. Thus fusion of the two images allows accurate localization of small functional and non-functional lesions. In our case, this well-differentiated CRH/ACTH secreting tumor was well visualized with [18F]FDG due to increased metabolic activity. There have been two other case reports where [18F]FDG PET has been used to localize a thymic carcinoid tumor (26) and an ectopic ACTH-secreting bronchial carcinoid tumor (27).

In summary, this is a rare case of CRH and probable ACTH co-secretion of a well-differentiated neuroendocrine carcinoma, where in addition to conventional imaging functional scintigraphic imaging with [11C]pentetreotide and [18F]FDG PET was used for tumor localization and follow-up.

References


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