Published in final edited form as:

Clin Nucl Med. 2015 July ; 40(7): 576–578. doi:10.1097/RLU.0000000000000806.

Ectopic ACTH and CRH co-secreting tumor localized by 68Ga-DOTA-TATE PET/CT

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Abstract

Diagnosis of ectopic adrenocorticotrophic hormone (ACTH) and corticotropin releasing hormone (CRH) co-secreting tumors causing Cushing syndrome (CS) is challenging, since these tumors are rare and their diagnosis is frequently confused with Cushing disease (CD), due to the effect of CRH on the pituitary. We report a case of a 21-year-old male who was referred to our institution with persistent hypercortisolemia and CS after undergoing unnecessary transsphenoidal surgery (TSS). 68Ga-DOTA-TATE PET/CT revealed increased tracer uptake in the thymus which was histologically proved to be neuroendocrine tumor (NET) staining positive for ACTH and CRH. Imaging with 18F-FDG PET/CT was not diagnostic.

Keywords

Cushing syndrome; 68Ga-DOTA-TATE PET/CT; 18F-FDG PET/CT; ectopic ACTH/CRH tumor; thymus

A 21-year-old male presented with sudden onset of rapid weight gain, central adiposity, facial plethora, fatigue, loss of muscle mass, insomnia, anxiety and decreased libido. The patient's initial work-up was consistent with CD, and subsequently TSS was performed which failed to correct his hypercortisolemia and clinical symptoms. Histology showed that

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Disclosure: All authors have nothing to disclose

the removed tissue was normal pituitary with no evidence of adenoma. After referral to our institution the patient underwent thorough work-up including measurement of plasma CRH and ACTH levels, 24-hour urinary-free cortisol (UFC), serum cortisol before and after high-dose dexamethasone suppression test (HDDST), CRH stimulation test, inferior petrosal sinus sampling (IPSS), cross-sectional imaging (CT, MRI) and functional imaging with combined PET/CT using 68Ga-DOTA-TATE (somatostatin analogue) and 18F-FDG (glucose analogue). 68Ga-DOTA-TATE PET/CT revealed increased uptake by a thymic nodule (1a-axial) which was also identified on CT (1c-axial, 1d-sagittal) and MRI (1e-axial) scans, suggesting a thymic carcinoid. Selective catheterization of a thymic vein was performed showing a step up for ACTH. The patient also underwent 18F-FDG PET/CT, but didn't show increased glucose metabolism by the tumor (1b-axial). Total thymectomy was performed and a thymic NET was revealed.

Histological examination showed an atypical carcinoid in the thymus gland (hematoxylin & eosin) (2a) with extensive lymphovascular invasion 40x (2b). Formal mitotic count revealed 9 mitotic figures per 50 high power field with several atypical mitotic figures (arrow) 40x (2c). Cells showed focally positive immunostaining for CRH 40x (2d), and diffuse for ACTH 20x (2e) and chromogranin A 20x (2f), characteristic for neuroendocrine neoplasia. Post thymectomy the patient's cortisol and ACTH levels remained elevated with persistent CS, probably due to micrometastatic disease, leading to bilateral adrenalectomy. The patient was discharged with hydrocortisone and fludrocortisone replacement and the recommendation for treatment with octreotide. Ectopic ACTH-secreting tumors, most of which have neuroendocrine origin, account for 8% to 18% of all causes of CS [1, 2]. However ectopic ACTH/CRH co-secreting or CRH-secreting tumors causing CS are very rare with only a few cases reported in the literature [3–7]. Localization of these tumors is challenging, and the optimal imaging approach is not yet established. 18F-FDG PET/CT has limited value in detecting NETs especially in well-differentiated tumors with low proliferative activity [8–11]. However, since the majority of NETs overexpress somatostatin (SST) receptors, they can be effectively targeted and localized using radiolabelled SST analogues [12]. Recent studies have demonstrated the incremental diagnostic information provided by PET/CT using 68Ga-DOTA-conjugated peptides (SST analogues) in patients with NETs [13–15]. This was also proven by the presented patient, in whom 68Ga-DOTATATE PET/CT successfully revealed the underlying NET causing CS. This case elucidates the demanding diagnostic work-up of patients with CS due to ectopic ACTH/CRH co-secreting tumors, since the secretion of CRH stimulates the pituitary gland leading towards erroneous diagnosis of CD and unnecessary TSS. Somatostatin receptor imaging using positron emitting radioisotope labeled SST analogues, contributes to the early diagnosis and accurate management of these patients.

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FIGURE 1.

FIGURE 2.