Case report

Difficulties in diagnosis and treatment of ectopic ACTH-producing tumors of the chest

Chiara Dall’Asta\textsuperscript{a}, Luigi Santambrogio\textsuperscript{b}, Massimo Castellani\textsuperscript{c}, Bruno Ambrosi\textsuperscript{a,*}

\textsuperscript{a}Institute of Endocrine Sciences, University of Milan, Ospedale Maggiore IRCCS – pad. Granelli Via F. Sforza 35, 20122 Milan, Italy
\textsuperscript{b}Unit of Thoracic Surgery, University of Milan, Ospedale Maggiore IRCCS – pad. Monteggia Via F. Sforza 35, 20122 Milan, Italy
\textsuperscript{c}Department of Nuclear Medicine, University of Milan, Ospedale Maggiore IRCCS – pad. Granelli Via F. Sforza 35, 20122 Milan, Italy

Received 18 July 2001; received in revised form 15 October 2001; accepted 18 October 2001

Abstract

It is widely accepted that surgery is the first choice treatment for ACTH-secreting tumors, most of them being lung or bronchial tumors. However, the localization of such lesions is rather difficult and it needs a compelling work-up. Here we present the results of different hormonal and imaging investigations and the surgical outcome of three patients with ectopic Cushing’s syndrome.

Keywords: Ectopic Cushing’s syndrome; \textsuperscript{111}In-pentetreotide scintigraphy; \textsuperscript{18}F-fluorodeoxyglucose positron emission tomography; Pulmonary lobectomy; Thoracic surgery

1. Introduction

The ACTH-dependent Cushing’s syndrome is consequent to ectopic ACTH secretion (EAS) in 15–20% of patients \cite{1}. Once the hypercortisolism has been diagnosed, the endocrine work-up, not constantly confirmatory of the ectopic source, needs to be followed by further investigations. To this purpose, although inferior petrosal sinus sampling (IPSS) helps in excluding a pituitary origin \cite{2}, no information about the source of ectopic ACTH is easily obtained. Lung and bronchial tumors are the most common causative neoplasms, but some of them are not disclosed by conventional imaging owing to their small size and location in the inner middle of the lung \cite{1}.

Nowadays, CT, MRI, somatostatin receptor scintigraphy (SRS) using \textsuperscript{111}In-pentetreotide, and \textsuperscript{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) are the available techniques in order to identify ectopic ACTH-secreting lesions. Here we describe three patients with EAS, in whom the diagnostic work-up was different, as it was the subsequent outcome of thoracic surgery.

2. Case reports

2.1. Case 1

A 61-year-old woman was referred for Cushing’s syndrome. Endocrine work-up revealed elevated urinary free cortisol (UFC); high ACTH/cortisol levels did not rise after CRH and desmopressin tests, as it occurs in EAS \cite{3}; chromogranin A (CgA) levels were high. Brain MRI excluded the existence of a pituitary adenoma. A chest X-ray showed a 3-cm opacity in the right lower lobe of the lung, which was confirmed by CT scan. Bronchoscopy and needle biopsy of the lesion were negative. The patient underwent a right lower lobectomy with mediastinal lymph nodes dissection and an atypical carcinoid tumor without metastases was diagnosed. Immunohistochemistry showed positive staining for ACTH and CgA. Subsequently, hypercortisolemic features disappeared, hormonal findings normalized and 18 months after operation the patient is cured.

2.2. Case 2

In 1992 a 31-year-old woman was referred for Cushing’s syndrome. A pituitary origin was firstly suspected, as brain MRI showed a pituitary microadenoma. High ACTH/cortisol and UFC levels were found. ACTH and cortisol did not rise after CRH and were not suppressed by high-dose dexamethasone test. An IPSS did not show any ACTH gradient.
A chest X-ray revealed a 1.5-cm rounded opacity in the right lung and the MRI confirmed a 1.5-cm nodule with regular margins in the axillary segment of the middle lobe. A mild uptake at SRS was observed in the right lung. After a negative bronchoscopy the patient underwent middle lobectomy. Histology showed a typical bronchial carcinoid with positive immunostaining for ACTH and CgA. A biochemical and clinical remission was achieved. In 1996 abnormal ACTH/cortisol responses to CRH and dexamethasone tests reappeared. The SRS showed two spots of tracer uptake in mediastinum and in right hilum, whereas CT scan was normal. In 1999 hypercortisolemic features reappeared: high ACTH, cortisol, UFC levels were found. In 2000 a FDG-PET showed increased glucose metabolism in the areas with SRS uptake and CT scans confirmed the presence of two micronodular lesions. A complete mediastinal and right pulmonary hilum lymph nodes dissection was performed. Histology demonstrated massive lymphonodal metastases of a neuroendocrine carcinoma, spread to the mediastinal soft tissue with positive staining for ACTH and CgA. Thereafter, the patient underwent chemotherapy and now is in remission.

2.3. Case 3

A 53-year-old man was admitted for Cushing’s syndrome. High ACTH/cortisol levels were stimulated by CRH and desmopressin and not suppressed by high-dose dexamethasone test; UFC and CgA levels were elevated. Brain MRI was normal, while a rounded not homogeneous opacity in the right lung was found at chest X-ray. A CT scan revealed a hyperdense 4-cm lesion in the apical segment of the right lower lobe and a retrosternal goiter (Fig. 1). Although an uptake at SRS was observed on the pulmonary mass as well as on the right thyroidal lobe, the FDG-PET scan showed a focal area of increased uptake only on the pulmonary lesion. The $^{99m}$Tc-pertechnetate thyroid scintigraphy did not show any different uptake between the nodule and the remaining gland and the FNAB was negative. Bronchoscopy and fine-needle biopsy were negative. A right lower lobectomy was performed and no pathological lymph nodes were found. Unexpectedly, at histology an inflammatory pseudotumour was diagnosed (Fig. 1). The hypercortisolism was still persistent and the patient underwent bilateral adrenalectomy.
3. Discussion

In all patients the clinical presentation was typical for an ACTH-dependent Cushing’s syndrome, without any suspect for a malignant paraneoplastic syndrome. However, their different history enables some comments. In case 1 hormonal data undoubtedly pointed to an ectopic ACTH source and chest conventional images revealed the pulmonary lesion: these results did not require further investigations and the patient was successfully operated. By contrast, in case 2, though bearing a pituitary microadenoma, hormonal testing and IPSS were not consistent with the presence of a pituitary corticotropinoma. Therefore, further investigations were performed: the pulmonary lesion disclosed by MRI was confirmed by SRS and identified at surgery as the source of EAS. Notably, in this patient during the post-operative follow-up the SRS, in agreement with hormonal testing, allowed to suspect a relapse, which was reliably confirmed by CT scan only 3 years later. Indeed, the possible recurrence of bronchial carcinoid tumor, often deemed as benign and indolent, has been previously reported [1,4,5].

In patient 3 the ectopic ACTH origin still remains occult, as the lesion detected by different imaging techniques was not a neuroendocrine tumor. This case once again emphasizes the rather difficult localization of ectopic ACTH source. False positive images at SRS have been already described [4–6], but not associated, at our knowledge, with false positive images at FDG-PET. Indeed, the latter procedure may also fail in the differentiation between benign and malignant lesions. Recently, the use of $^{11}$C-5-hydroxytryptophan as tracer in the whole body PET allowed to identify neuroendocrine tumors in three/five patients with suspected EAS [7].

In conclusion, a gold standard technique in localizing ectopic ACTH-producing tumors is not available so far. Besides the low usefulness of bronchoscopy and needle biopsy, false negative and false positive results with either conventional or functional images may be obtained. Owing to the severity of EAS, all available techniques should be used as complementary tools to attempt a precise tumor localization.

References