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Management of Occult Adrenocorticotropin-Secreting Bronchial Carcinoids: Limits of Endocrine Testing and Imaging Techniques

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The differential diagnosis and the identification of the source of ACTH in occult ectopic Cushing's syndrome due to a bronchial carcinoid still represents a challenge for the endocrinologist. We report our experience in six patients with occult bronchial carcinoid in whom extensive hormonal, imaging, and scintigraphic evaluation was performed. All patients presented with hypercortisolism associated with high plasma ACTH values. The CRH test and high dose dexamethasone suppression test suggested an ectopic source of ACTH in three of six patients. During bilateral inferior petrosal sinus sampling, none of the patients showed a central to peripheral ACTH gradient. At the time of diagnosis, none of the patients had radiological evidence of the ectopic source of ACTH, whereas pentetreotide scintigraphy identified the lesion in two of four patients. Finally, a chest computed tomography scan revealed the presence of a bronchial lesion in all patients, and pentetreotide scintigraphy identified four of six lesions. In all patients a bronchial carcinoid was found and removed. In one patient with scintigraphic evidence of residual disease after two operations, radioguided surgery, using a hand-held γ probe after iv administration of radiolabeled pentetreotide, was performed; this allowed detection and removal of residual multiple mediastinal lymph node metastases. In conclusion, our data show that there is not a single endocrine test or imaging procedure accurate enough to diagnose and localize occult ectopic ACTH-secreting bronchial carcinoids. Radioguided surgery appears to be promising in the presence of multiple tumor foci and previous incomplete removal of the tumor. (*J Clin Endocrinol Metab* 88: 1029–1035, 2003)

THE ECTOPIC ACTH syndrome accounts for 5–10% of all cases of ACTH-dependent hypercortisolism, and bronchial carcinoids are the most frequent occult source of ectopic ACTH (1). Unlike patients with highly aggressive ACTH-secreting tumors, patients bearing small nonaggressive tumors, such as bronchial carcinoids, may have a clinical course indistinguishable from that of patients with Cushing's disease (2).

As patients with both eutopic and ectopic sources of ACTH may have misleading results when tested with the most accurate noninvasive biochemical tests (*i.e.* the CRH and high dose dexamethasone suppression tests), differential diagnosis relies on the results of ACTH sampling in inferior petrosal sinuses. However, this procedure does not localize the source of ectopic ACTH secretion, whose identification is based on imaging techniques such as computed tomography (CT) and/or magnetic resonance imaging (MRI). Recently [^{111}In]pentetreotide scintigraphy ([^{111}In]PS) has been proposed as a useful tool to localize the source of ACTH in patients with a high suspicion of ectopic syndrome. However, the radiological and scintigraphic techniques may show limited accuracy in detecting ACTH-secreting bronchial carcinoids mainly because of their small size (3–6).

In the literature, patients with bronchial carcinoids are often included in heterogeneous series of ectopic ACTH-secreting tumors, in whom only some of the aforementioned diagnostic procedures have been performed. We report our experience in six patients with ascertained, truly occult, bronchial carcinoid, in each of whom hormonal, conventional imaging, and scintigraphic evaluations were performed.

Abbreviations: BIPSS, Bilateral inferior petrosal sinus sampling; C/P, central to peripheral; CT, computed tomography; MRI, magnetic resonance imaging; PS, pentetreotide scintigraphy.

Subjects and Methods

Of 67 patients with endogenous hypercortisolism seen at our institution between 1991 and 1999, 6 had the final diagnosis of ACTH-secreting bronchial carcinoid, and they were included in this study. These patients (3 women and 3 men), aged 25–65 yr, were referred to the Endocrine Unit for recently diagnosed, severe hypercortisolism; one patient (no. 6) had been previously treated elsewhere by pituitary microsurgery. Epidemiological and clinical data together with basal hormone levels are reported in Table 1. Each patient showed typical stigmata of Cushing's syndrome; particularly 5 of 6 patients complained of severe myopathy, resulting in intense weakness, preventing them from walking, 5 of 6 had hypertension, and 3 of 6 diabetes. Hirsutism was present in all female patients, and the 2 premenopausal women were amenorrheic. Each patient had hypokalemia requiring potassium iv supplementation. Marked osteopenia with vertebral collapses was documented in 4 patients; because of that all of them needed a brace.

In all patients the presence of ACTH-dependent hypercortisolism was established on the basis of supranormal excretion of 24-h urinary cortisol in presence of supranormal ACTH concentration (evaluated, in each instance, in at least three blood samples withdrawn at 20-min intervals). All patients underwent CRH stimulation testing (100 μg ovine CRH, iv; CLINALFA, Laufelfingen, Switzerland) for the determination of plasma ACTH and cortisol (blood samples at −15, 0, 15, 30, 45, 60, 90, and 120 min) and high dose dexamethasone suppression test. Four patients underwent the 2-d test with determination of urinary free cortisol, and two patients underwent the overnight test (8 mg dexamethasone, orally,

TABLE 1. Epidemiological, clinical data and basal hormonal evaluation of the patients studied

Case	Sex/age	Hypertension	Diabetes	Hypokalemia (<3.0 mEq/liter)	Vertebral collapses	ACTH (pmol/liter)[a]	Cortisol (nmol/liter)[a]	Urinary free cortisol (nmol/d)
1	M/33	Yes	Yes	Yes	No	31	938	5794
2	M/25	No	No	Yes	Yes	30	745	3523
3	F/65	Yes	No	Yes	Yes	38	1231	1628
4	F/28	Yes	Yes	Yes	Yes	38	938	9850
5	F/27	Yes	Yes	Yes	Yes	23	690	1007
6	M/29	Yes	No	Yes	No	41	979	2566

Plasma ACTH normal range, 2–11.5 pmol/liter; morning cortisol normal range, 220–690 nmol/liter; urinary free cortisol normal range, 27–220 nmol/d.

[a] Mean of at least three morning determinations.

TABLE 2. Results of hormonal dynamic evaluation and BIPSS in the patients studied

Case	CRH test (100 μg ev)		DDAVP test (5 μg ev)		SMS test (100 μg sc)		HD-DEXA suppression test		BIPSS post-CRH C/P ACTH ratio
	ACTH % increase	Cortisol % increase	ACTH % increase	Cortisol % increase	ACTH % decrease	Cortisol % decrease	8 + 8 mg[a]	Overnight 8 mg[b]	
1	3	15	8	−11	29.2	15.8	0%		0.9
2	−1	30	5		55.7	71.1	85%		1
3	0	−7			30.3	57.1	60%		1
4	−1	−6	77	37	40.6	36.7		23%	1
5	38	8	377	59	54.4	2.7		50%	1
6[c]	0		23.6		26.6	25.9	91%		2.3

[a] Inhibition of 24-h UFC excretion.

[b] Inhibition of morning serum cortisol.

[c] CRH and DDAVP tests performed after adrenalectomy; SMS test, HD-DEXA test, and BIPSS performed after unsuccessful pituitary microsurgery and before adrenalectomy.

administered between 2300–2400 h, with blood sampling at 0830 h pretreatment and 0900 h the next day). Five patients underwent desmopressin stimulation test for ACTH and cortisol determinations (5 μg, iv; Minirin/DDAVP, Ferring Pharmaceuticals Ltd., Malmo, Sweden); blood was sampled at –15, 0, 15, 30, 60, and 90 min after drug administration. CRH and desmopressin stimulation tests for ACTH determination were performed later in the follow-up, after bilateral adrenalectomy in patient 6.

The criteria used to establish the presence of pituitary responsiveness to CRH were an increase in mean plasma ACTH at 15–30 min greater than 35% and/or an increase in mean plasma cortisol at 30–45 min greater than 20% above basal levels (7). For the desmopressin test the criteria used were an increase in mean plasma ACTH at 15–30 min greater than 35% and an increase in mean plasma cortisol at 30–60 min greater than 20% above basal levels. The criterion used to establish pituitary-adrenal suppressibility after high dose dexamethasone was a fall in plasma cortisol or in urinary free cortisol excretion by at least 50% or 90%, respectively (8, 9).

All patients underwent bilateral, simultaneous catheterization of inferior petrosal sinuses for ACTH determination with samples taken at –15, 0, 1, 3, 5, and 10 min after CRH administration, as previously described (10). In each case the procedure was performed during the initial diagnostic work-up while the patients had severe hypercortisolism, before any medical treatment was started. According to the generally accepted criteria, a central to peripheral (C/P) plasma ACTH gradient lower than 2 in basal conditions and/or 3 after CRH was considered consistent with the presence of ectopic ACTH secretion (11). In addition, all patients had ACTH and cortisol assessed after a test dose of 0.1 mg octreotide, sc, to assess the effectiveness of the drug in inhibiting hormonal secretion. ACTH and cortisol changes after drug administration were compared with the hormone values recorded at the same time points during saline infusion on a previous day. The markers of neuroendocrine neoplasia (urinary 5-hydroxyindolacetic acid, serum neuron-specific enolase, and calcitonin) were assessed in each patient. All patients underwent pituitary MRI.

Imaging studies included CT of the chest and the abdomen. Section thickness was 5 mm in the chest and upper abdomen and 10 mm in lower abdomen and pelvis. Oral contrastrographic media and iv nonionic water soluble contrast were given at the radiologist's discretion. In each case the radiologist was aware of the suspicion of ectopic ACTH syndrome. MRI of the chest was performed in two cases (no. 2 and 4).

Total body [^{111}In]PS was performed at least once in all patients. The scans were performed with multiple planar and single photon emission CT images of the head, neck, chest, and abdomen obtained 4 and 24 h after iv administration of 122 MBq ^{111}In-labeled pentetreotide. The assessment of tracer accumulation was made by the same nuclear medicine physician.

Results

Hormonal data

All patients had high serum and urinary cortisol levels and supranormal plasma ACTH values (Table 1). CRH administration did not induce any ACTH and/or cortisol increase in four patients; one patient (no. 5) had a 38% increase in ACTH, and another one (no. 2) had a 30% increase in cortisol. Desmopressin administration determined an ACTH and cortisol response in two of five patients (no. 4 and 5). Two of six patients showed dexamethasone-induced suppression (Table 2).

None of the patients showed a central to peripheral ACTH gradient greater than 2 in basal conditions or greater than 3 after CRH stimulation during bilateral inferior petrosal sinus sampling (BIPSS). The absence of a central to peripheral ACTH gradient was not considered conclusive for ectopic ACTH in patient 2 because of the presence of a right plexiform inferior petrosal sinus. Compared with saline infusion, acute administration of octreotide induced decreases in plasma ACTH and cortisol greater than 30% in three patients (no. 2–4) (Table 2). Apart from BIPSS, endocrine testing suggested ectopic ACTH secretion in three of six patients (no. 1, 3, and 4). The markers of neuroendocrine neoplasia were negative in all patients.

Imaging

Data on the timing and results of the imaging are reported in Table 3. Pituitary MRI was negative in four patients. It

showed an equivocal hypointense area suspicious for a microadenoma in one patient (no. 2) and became suspicious for a microadenoma during the follow-up in another patient (no. 5). At the time of the diagnosis of hypercortisolism, none of the patients had CT (n = 6) or MRI (n = 1) evidence of an ectopic source of ACTH. Two (no. 1 and 4) of four patients who underwent PS showed evidence of abnormal uptake in the chest. This finding suggested that targeted CT scans should be performed in these two patients.

Radiological results

Eventually, CT scan disclosed a chest lesion in all patients. In two cases it was the only imaging technique to reveal the presence of a lesion suggestive for bronchial carcinoid (no. 3 and 5) 8 and 50 months, respectively, after the initial diagnosis. In another two cases (no. 1 and 4), the CT scan, focused on the area of interest, confirmed a previous abnormal PS 12 and 1 month after the initial diagnosis. In patients 2 and 6, the CT scan of the chest identified the ectopic source of ACTH, which was confirmed by PS in the same period, 8 yr after an incorrect initial diagnosis of pituitary adenoma. One or two negative CT scans preceded radiological demonstration of the ectopic source of ACTH in each patient.

Scintigraphic results

PS identified four of six ACTH-secreting tumors; in two cases scintigraphy was not performed at the time of diagnosis, but followed radiological demonstration of the lesion (no. 2 and 6). A pentetreotide scan, performed twice in two patients (no. 3 and 5), was repeatedly negative even after radiological demonstration of bronchial tumors. In no case did PS give false positive results. There was no correlation between the effect of acute administration of octreotide on hormone secretion and tracer uptake by PS (Table 4).

Management and outcome

Data on management and outcome are reported in Table 3. After referral, based on incorrect diagnoses, two patients (no. 2 and 5) underwent unsuccessful pituitary microsurgery; in both cases there was no clear evidence of adenoma, although the tissue removed at surgery was intensely immunoreactive for ACTH in one case (no. 2). Subsequently, one of these patients (no. 5) was treated with pituitary radiotherapy and adrenal steroidogenesis inhibitors, whereas the other (no. 2) underwent bilateral adrenalectomy.

Pending the identification of the ectopic source of ACTH, bilateral adrenalectomy was performed in two additional patients (no. 1 and 6), who showed limited effectiveness of medical treatment with ketoconazole and/or octreotide at tolerated doses, and in another patient (no. 4), who had persistent hypercortisolism after removal of the bronchial carcinoid.

In all patients a bronchial carcinoid was finally found and removed (Table 3). ACTH immunoreactivity of the tissue was documented in all but one case (no. 4). Lymph node metastases were detected at surgery in five of six patients; multiple node metastases were removed in two subsequent operations in patient 4 (see below). Patient 2 underwent chemotherapy because of evidence of atypical carcinoid. A cure was achieved after removal of the primary lesion and metastases in all patients 8–96 months after the diagnosis of hypercortisolism.

In one patient (no. 4) the disease persisted after the first operation; the postoperative persistence of tracer uptake at PS indicated the presence of pathological tissue in the mediastinum not detected at surgery and only subsequently confirmed by radiological studies. The patient underwent a second operation, after which scintigraphic and radiological evidence of residual disease persisted. Lastly, the patient underwent radioguided surgery using an handheld γ probe 24 h after iv administration of a tracer dose of radiolabeled [^{111}In]DTPA-D-Phe^{1}-pentetreotide that allowed detection and removal of residual multiple mediastinal lymph node metastases. Cure and no more evidence of tracer uptake at PS followed. Two additional patients (no. 1 and 2), with positive preoperative scintigraphy, repeated this procedure after removal of the ectopic source of ACTH to exclude the presence of residual tumor or distant metastases; in both cases no uptake of the tracer was recorded.

Eventually, a clear-cut reduction of plasma ACTH levels to normal (no. 1 and 2) or subnormal, low normal (no. 3–6) values was observed in all patients (Table 5); the two who did not undergo adrenalectomy (no. 3 and 5) showed postoperative hypoadrenalism after removal of the bronchial carcinoid. At follow-up patients 2, 3, 4, 5, and 6 were free of disease at 24, 78, 15, 9, and 3 months after surgery, respectively. In patient 1 an increase in plasma ACTH with no radiological or scintigraphic evidence of tumor tissue was observed 1 month after surgery.

Discussion

The present study reports a series of patients with hypercortisolism due to an occult ACTH-secreting bronchial carcinoid; the patients were evaluated at the same institution. There are several case reports in the literature, two large surgical series and a review of previously reported cases, where the diagnostic endocrine work-up was not extensively performed or reported (1, 12, 13). Although not representative of all patients with this disease, the cases reported here show the limits of single diagnostic procedures and offer the opportunity to evaluate their roles in clinical practice.

It is often reported that patients with occult ectopic ACTH syndrome do not show distinctive clinical features compared with patients with Cushing's disease (2, 14, 15). The severity of the clinical and biochemical expression of hypercortisolism observed in our patients suggests that occult ectopic Cushing's syndrome due to bronchial carcinoid may be more severe than pituitary-dependent disease. As previously reported (5, 6, 13), the age at presentation of disease was less than 33 yr in all but one of our patients, confirming that patients with ACTH-secreting bronchial carcinoid are generally younger than patients with ectopic sources of ACTH located elsewhere (1).

Our results confirm that dynamic endocrine testing may be misleading in bronchial carcinoids. In fact, two patients in the present series were responsive to CRH administration, and one of them was also responsive to dexamethasone sup-

TABLE 3. Clinical and pathological work-up of the patients studied

Case	Date work-up	Pentetreotide scan result	Radiological imaging	History and outcome	Pathological and immunohistochemical diagnosis
1	Jan-99	Right midcentral lung field; one focus	Negative abdominal and chest CT	Medical treatment (ketoconazole plus octreotide for 3 months)	
	May-99		Negative chest CT	Bilateral adrenalectomy	
	Jan-00		Positive chest CT; right midcentral lung nodule 12 mm		
	Mar-00			Cured after right lung upper lobectomy	Typical carcinoid, 13 mm; ACTH +; lymph node metastasis in 1/6 N1
	Jun-00	Negative	Negative chest CT	Normalization of ACTH levels	
2[a]	Mar-91		Negative abdominal and chest CT; negative chest MRI	Medical treatment ketoconazole plus octreotide for 2 months	
	Aug-91		Equivocal pituitary MRI	Unsuccessful pituitary surgery	Suggestive but not conclusive for pituitary adenoma ACTH +
	Nov-91		Negative chest CT	Bilateral adrenalectomy	
	Aug/Sep-99	Right midcentral lung; two foci	Positive chest CT; right lung upper lobe nodule 20 mm and hilar lymph node	Right lung upper lobectomy. Normalization of plasma ACTH levels	Atypical carcinoid, 15 mm; ACTH +, NSE +, CgA +, CCK19 +; lymph node metastases in 3/4 N1 and 4/4 N2
	Oct-99	Negative	Negative total body CT	Chemotherapy. Persistence of normal ACTH values	
3[a]	Jan-94	Negative	Negative chest-abdomen CT	Medical treatment: ketoconazole plus octreotide for 8 months	
	Sep-94	Negative	Positive chest CT: right lung upper lobe nodule 20 mm	Upper right lung lobectomy. Reduction of plasma ACTH to subnormal levels; postoperative hypoadrenalism lasting one year	Typical carcinoid, 15 mm; ACTH +, 5HT +, CgA +
	Apr-01		Negative chest CT	Normal ACTH levels	
4	Dec-95	Right paracardiac, two foci	Negative chest-abdomen CT	Medical treatment: ketoconazole plus octreotide for 1 month	
	Jan-96		Positive chest CT: right lung midcentral nodule 1 cm	Excision of right lung inferior lobe nodule; persistence of disease	Typical carcinoid, 18 mm; ACTH −
	Mar-96			Bilateral adrenalectomy	
	Apr-96	Right paracardiac one focus			
	Oct-96		Negative chest CT		
	July-98	Right paracardiac two foci	Positive chest CT: retro-sternal nodule. Positive chest MRI: two retrosternal nodules		
	Apr/Jun-99		Positive chest CT: two retro-sternal nodules	Thymectomy. Persistence of supranormal ACTH	Multiple thymic microfoci of neuroendocrine ACTH + tumor; lymph node metastasis 23 mm
	Nov-99	Right paracardiac one focus (upper mediastinum)	Positive chest CT: anterior mediastinum nodule 10 mm		
	Feb/Apr-00		Positive chest CT: multiple mediastinal pathologic lymph nodes	Radioguided thoracoscopic excision of mediastinal lymph node metastases. Reduction of ACTH to subnormal levels	Multiple lymph node metastases of neuroendocrine tumor 3–15 mm
	Jun-00	Negative		Subnormal ACTH levels	
5	Nov/Dec-95	Negative	Negative chest-abdomen CT. Negative pituitary MRI	Medical treatment: ketoconazole for 3 months. Spontaneous remission of Cushing and hypocortisolism for 18 months	
	Mar-96		Negative total body CT.		
	Sep-98			Recurrence of hypercortisolism	
	Nov-98		Equivocal pituitary MRI	Pituitary microsurgery. Persistence of hypercortisolism. Medical treatment: ketoconazole	ACTH + cells, not conclusive for adenoma

	Mar-99		Pituitary radiotherapy. Persistence of hypercortisolism. Medical treatment: ketoconazole	
	Jan/Feb-00	Negative	Positive total body CT: inferior lobe right lung nodule of 9 mm	Right lung inferior lobectomy. Reduction of ACTH to subnormal values; postoperative hypoadrenalism	Plurifocal typical carcinoid, 2–20 mm; ACTH+, CgA+; lymph node metastases in 2/4 N1
	Oct-00		Negative total body CT.	Hypoadrenalism	
6	Mar-93		Negative chest and abdominal CT	Previous unsuccessful pituitary microsurgery. Persistence of hypercortisolism	Croocke's hyaline degeneration
	May-93			Medical treatment: octreotide for one month	
	July-93			Bilateral adrenalectomy	
	Feb-01		Positive chest CT: left lung inferior lobe 20 mm nodule		
	Apr-01	Left inferior lobe, one focus		Left lung inferior lobectomy. Reduction of ACTH to low normal values	Typical carcinoid 15 mm, ACTH +; lymph node metastasis in 1/6 N1

The medical treatment has been previously reported (J Clin Endocrinol Metab 81:2885–2890, 1996).

TABLE 4. Comparison between hormonal response to acute octreotide administration and results of pentetreotide scintigraphy

Case	Octreotide test (100 μg sc)	^{111}In-pentetreotide scintigraphy
1	No response	Positive
2	Response	Positive
3	Response	Negative
4	Response	Positive
5	No response	Negative
6	No response	Positive

TABLE 5. Plasma ACTH values (picomoles per liter) at basal evaluation and after thoracic surgery

Case	Baseline	After tumor resection
1[a]	31	8.8
2[a]	30	5.5
3	38	1.8
4[a,b]	38	1.5
5	23	1.3
6[a]	41	2.6

Plasma ACTH normal range, 2–11.5 pmol/liter.
[a] Patient previously adrenalectomized.
[b] ACTH value after radioguided mediastinal surgery.

pression. This finding can be expected if one considers that the reported specificity of the CRH test ranges from 88–100% whether cortisol or the ACTH responses are considered (7), and the specificity of the high dose dexamethasone suppression test ranges from 60–100% (3). The choice of cut-off points affects both the sensitivity and the specificity of a test, and the decision to use less stringent criteria improves sensitivity at the expense of specificity. In our series patient 5 would not have been considered to show suppression on a more recent evaluation of a high dose dexamethasone suppression test, suggesting a more strict cut-off point for suppression to avoid misdiagnosing Cushing's disease (16). Even in this case complete diagnostic accuracy is not ensured, as shown by one patient (no. 6) who had 91% suppression on high dose dexamethasone. This is a teaching point that might indicate that even more stringent criteria are bound to lose discriminatory power when the number of patients observed and experience increase, and that the results near the cut-off points should be viewed with some skepticism.

Even if theoretically very uncommon, the occurrence of ACTH-secreting bronchial carcinoids that are suppressed on a high dose dexamethasone suppression test and exhibit responsiveness to CRH does exist in practice, suggesting that one cannot rely on these dynamic tests only (17, 18).

The response to desmopressin administration observed in two patients confirms that this test, as already suggested by others (19–21), is unreliable in the differential diagnosis of Cushing's syndrome. To date it is not known whether the overexpression of vasopressin receptor subtypes V2 and V3, which mediate the ACTH response to desmopressin, is limited to bronchial carcinoids or is extended to other ectopic ACTH sources. Reportedly, the most accurate test in the differential diagnosis of ACTH-dependent Cushing's syndrome is BIPSS (11, 22, 23).

Our data support this evidence, in that no patients showed

a C/P ACTH gradient greater than the commonly accepted cut-off point (11). However, one of our patients did show a C/P ratio that was the highest ever reported in the ectopic ACTH syndrome (11), even higher than the value proposed by Findling *et al.* (22). A C/P ACTH gradient suggestive of pituitary-dependent disease has been reported in patients with ectopic CRH and/or CRH-ACTH production (13, 18). This possibility cannot be excluded in our patient, because immunohistochemical determination of CRH within the tumor was not performed. In any case, the existence of the ectopic CRH-ACTH syndrome potentially reduces the reliability of inferior petrosal sinus sampling. In addition, this procedure may be less reliable in the presence of plexiform or hypoplastic inferior petrosal sinuses (24). The presence of a plexiform petrosal sinus led us to discount the absence of a C/P ACTH gradient in one patient, contributing to an incorrect diagnosis of Cushing's disease.

Even in the context of imaging, the differentiation between eutopic and ectopic (occult) ACTH syndromes may be difficult. Small bronchial carcinoids are sometimes undetected or identified late because of the inner location that makes them look like normal vessels. In the particular setting of ACTH-secreting bronchial carcinoids, the late recognition of the ectopic source of ACTH exposes the patient to unduly prolonged hypercortisolism or to adrenalectomy when medical therapy has limited efficacy. It is still debated whether chest MRI has an additional potential value with respect to CT in detecting bronchial carcinoids. This procedure was performed in only two patients of the present series, and it did not give additional information, but we cannot exclude that it might be useful in some cases (5, 25–27).

[^{111}In]PS has been proposed as a means to localize the source of ACTH in patients with a high suspicion of ectopic syndrome and negative results of common imaging techniques (28, 29). Bronchial carcinoids, as most of the neuroendocrine tumors, express somatostatin receptor subtype 2, which can be visualized by PS. In our experience the sensitivity of this procedure was 67%, similar to that reported by Torpy *et al.* (6) in four bronchial carcinoids, but lower than that reported by Krenning *et al.* (30) in a very large series of carcinoids with different sites of origin. This finding and the very low sensitivity of [^{111}In]PS reported by Tabarin *et al.* (5) in three bronchial carcinoids, might suggest that these tumors express somatostatin receptor subtype 2 less frequently than carcinoids originating at other sites, although the small size of the tumors might be another explanation. The specificity of PS is limited according to different reports (5, 6, 30); no false positive results were recorded in the present series.

As reported by Tabarin *et al.* (5), the present study confirms that the repetition of PS, even if performed in a drug-induced eucortisolemic state or several months after the first scintigraphic examination, is useless in patients with previous negative scintigraphic study.

When conventional imaging is negative, PS might help in localizing the tumor *a posteriori* by CT, focusing on a particular area. A surgical approach based exclusively on scintigraphic evidence of the tumor is not commonly accepted, taking into consideration the limits of specificity of this procedure.

In patients with positive PS tumors, the possibility to assess the complete removal of pathological tissue after surgery is of particular clinical relevance. In four of our patients surgical success was confirmed by the disappearance of tracer uptake as well as the parallel decrease in plasma ACTH. The persistence of both supranormal ACTH levels and tracer uptake was documented in the only patient with incomplete removal of pathological tissue due to the presence of multiple tumor foci.

In our experience the presence of multiple tumor foci and previous incomplete removal of tumor indicated the use of PS for intraoperative detection and removal of neuroendocrine tissue; to date limited data are available to suggest an extensive use of this procedure beyond this indication. The absence of correlation between tracer uptake by PS and the response to octreotide administration observed in the present study, already reported in the literature, suggests that the acute test cannot be used to select patients to submit to PS (31–33).

Although typically indolent, bronchial carcinoids are generally considered to be low grade malignancies, as shown by their ability to metastasize. Reportedly, the prevalence of node metastases in typical carcinoids ranges from 2.3–11%, lower than the range reported for atypical carcinoids (27–66%) (34, 35). In the present series, five of six tumors were typical; nonetheless, the prevalence of locoregional node metastases was 80%, and that of mediastinal nodes was 20%. This figure is higher than that reported for non-ACTH-secreting bronchial carcinoids and is comparable to those reported by Pass *et al.* (12) and Shrager *et al.* (13). This finding seems to confirm the evidence reported by Shrager *et al.* (13) of a much greater metastatic potential for ACTH-secreting than for hormonally quiescent typical carcinoids and supports the recommendation for routine, complete mediastinal lymph node dissection. Unlike nonsecreting tumors, in ACTH-secreting bronchial carcinoids, the ACTH concentration might be used as a marker of persistence of disease after surgery. In all of our patients ACTH clearly decreased postoperatively to low normal or normal values, but a correct cut-off point for the interpretation of a postoperative ACTH value cannot be easily set. In general, the persistence of mid to high normal ACTH values immediately after surgery in a hypercortisolemic patient might indicate residual disease, because in this setting normal corticotropes are suppressed. However, as in the case of Cushing's disease treated by pituitary microsurgery, a minority of cases show that this is not an absolute rule. As for ACTH-secreting bronchial carcinoids, in studies where post operative ACTH is measured, a decrease to normal values is considered a signal of removal of disease (12, 36–38). Undetectable postoperative ACTH values were reported only in a patient with ectopic ACTH syndrome due to retropancreatic carcinoid tumor who had been previously hypophysectomized (18). Another issue that should perhaps be taken into account is that four of our patients and others in the studies mentioned above had previously undergone bilateral adrenalectomy and were receiving replacement therapy with glucocorticoids (cortisone in all of our cases, two of whom had undergone adrenalectomy 8 and 9 yr before thoracic surgery); it is debatable whether in this setting one should expect ACTH suppression.

In conclusion, the present study shows that there is not a

single endocrine test or imaging procedure accurate enough to diagnose and localize small, occult, ectopic ACTH-secreting bronchial carcinoids. This suggests the opportunity of an extensive diagnostic approach. In our experience, plasma ACTH is a good marker of the presence or persistence of disease. ACTH-secreting bronchial carcinoids show a greater potential for node metastases than nonsecreting bronchial tumors; this is why a search for all diseased tissue is recommended; the use of an intraoperative γ counter to identify PS-positive tissue appears to be a promising procedure.

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