Abstract

Objective: Ectopic ACTH syndrome (EAS) occurs in about 5–10% of all patients with ACTH-dependent hypercortisolism with most of them caused by intrathoracic neoplasms. It may be associated with overt malignancies or with occult and indolent tumors. We assessed the accuracy of dynamic tests, inferior petrosal sinus sampling (IPSS) using desmopressin, and imaging in the work-up diagnosis of EAS.

Design and subjects: Tumor markers, imaging, and outcome data from 25 patients (13F/12M) aged 18–72 years. High dexamethasone suppression test (HDDST), desmopressin test, GHRP-6 test, corticotropin-releasing hormone (CRH) test, IPSS, computed tomography (CT), magnetic resonance imaging (MRI), and 111In-pentetreotide scintigraphy were revised.

Results: In 5 out of 20 patients HDDST was positive. In 13 patients who underwent desmopressin test, ACTH- and cortisol-positive responses were seen in six and five patients respectively. GHRP-6 test was positive in two out of three cases. Two patients underwent CRH test with negative response. In the seven patients submitted to IPSS using desmopressin in six of them, none had ACTH gradients. CT was positive in 15 out of 21 patients and MRI in 8 out of 17 cases. 111In-pentetreotide scintigraphy was positive in three out of five patients. Fourteen patients had intrathoracic tumors, five had pheochromocytomas, three had pancreatic tumors, one had a glomic tumor, and had three occult tumors. Six out of 11 patients with metastasis died and 3 others without metastasis died.

Conclusions: IPSS with desmopressin was helpful for differential diagnosis. Patients initially harboring occult carcinoids may also exhibit severe hypercortisolism and those harboring tymic carcinoids had poor prognoses when compared with bronchial carcinoids and pheochromocytomas.
Subjects and methods

From 1975 to 2005, 363 cases of ACTH-dependent Cushing’s syndrome were studied at the Division of Endocrinology and Metabolism, Hospital das Clinicas, University of Sao Paulo Medical School (FMUSP), with 25 cases being diagnosed as Cushing’s syndrome due to EAS (Table 1). An informed consent form was obtained from either the patients or a close relative and the study was approved by the Ethical and Research Committees of the institutions.

Diagnosis of ectopic ACTH syndrome

Diagnosis of hypercortisolism was made by measurements of 17-hydroxycorticosteroid (17OHCs) excretion (11), urinary cortisol, midnight serum and salivary cortisol (12), and low dose dexamethasone suppression test (13). For ACTH-dependent differential diagnosis, patients underwent HDDST (8 mg) (14–16), desmopressin test (17, 18), corticotropin-releasing hormone (CRH) test (19–23), growth hormone releasing peptide (GHRP)-6 test (24, 25), and IPSS (26–28) with desmopressin stimulus indicated when magnetic resonance imaging (MRI) was negative for a pituitary lesion. IPSS was performed by collecting blood samples simultaneously from the inferior petrosal sinuses and a peripheral vein before and 3, 5, and 10 min after 10 μg of IV desmopressin (DDAVP, Ferring Pharmaceuticals, Limhamn, Sweden) (29). Imaging studies were done with computed tomography (CT) and MRI scans. Some patients with initial occult tumors underwent [131I] metaiodobenzylguanidina (30) or scintigraphy with [111In] DTPA-peptide (31–33). Tumor markers, such as calcitonin, gastrin, carcinoembryonic antigen (CEA), α-fetoprotein, β-human chorionic gonadotropin (βHCG), and 5-hydroxyindolacetic acid (5-HIAA), were also measured.

Hormonal assays

ACTH was measured by RIA and IRMAs. Serum and urinary cortisol were measured by IRMAs. Calcitonin, gastrin, CEA, βHCG, and α-fetoprotein were measured by commercial assays. Urinary 17OHCs was measured by colorimetric method (11).

Hormonal detection by immunohistochemistry

Immunohistochemical detection of hormones according to the clinical context in each case is depicted in Table 2.

Table 1: Clinical, biochemical, and hormonal data of patients with ectopic ACTH syndrome.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>History months</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>K (mEq/l)</th>
<th>UC (mcg/24h)</th>
<th>HDSST (8 mg)</th>
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IGT, impaired glucose tolerance; K, potassium (RV: 3.5–5.0 mEq/l); UC, urinary cortisol (RV: 30–300 mcg/24 h; conversion factor: 0.2202); HDDST, high-dose (8 mg) dexamethasone suppression test (positive: serum cortisol suppression >50%); ACTH, adrenocorticotropic hormone (RV: <60 pg/ml; SI: <13 pmol/l; conversion factor: 0.2202); serum cortisol (RV: 7–31 μg/dl; SI: 193–855 nmol/l; conversion factor: 2.759); desmopressin test (positive: peak to baseline value: ACTH >35% and cortisol >20%) (19); +, positive; –, negative; nd, not done; na, not available.
Briefly, the reactions were performed in 4 μm sections from formalin-fixed paraffin-embedded samples. Whenever specified 'hier', pre-treatment for epitope retrieval was performed in citrate buffer (pH 6.0) for 3 min in a pressure cooker. The following antibodies were used: calcitonin-polyclonal, Dako (A576), 1/3200; neuron-specific enolase-cloned 8/18, Dako M869, 1/500; synaptophysin, clone SY38, Dako M776, 1/100 (hier); ACTH-polyclonal, Dako (A571), 1/100,000; chromogranin, clone-DAK A2, Dako M69, 1/500 (hier); CD56-cloned NCL-CD56-1B6, Novocastra, 1/100 (hier); TTF-1-cloned NCL-TTF-1, Novocastra, 1/300 (hier); Gastrin-polyclonal, Dako A568, 1/6000; Glucagon-polyclonal Dako A565, 1/2400. All incubations with primary antibodies were performed at 37 °C for 8 h (overnight). Signal amplification was achieved through LSAB + Systems DAKOCYTOMATION (Santa Barbara, CA, USA), according to the manufacturer's specification, with incubations of secondary antibody and avidin–biotin complex for 30 min each at 37 °C. Positive and negative controls were run in parallel to sections from the study case.

Results

Patients’ ages ranged from 18 to 72 years, with 13 females and 12 males. Symptoms duration lasted from 3 to 132 months. All patients presented clinical signs of hypercortisolism with intense weakness due to proximal myopathy, 24 presented arterial hypertension, 16 presented diabetes mellitus, 2 presented abnormal fasting glycemia, and 12 presented hyperpigmentation. Seven patients presented a severe psychotic picture.

Hypokalemia was present in 16 cases, 14 of which had potassium levels < 3 mEq/l. All cases presented absence of cortisol circadian rhythm with high urinary levels. Considering the upper limit of normal values for the assay (RIA or IRMA), plasma ACTH concentrations were increased in 18 patients and normal in 6 (4 of them with a diagnosis of pheochromocytoma, 1 with a lung carcinoid, and 1 with occult ACTH secretion syndrome). Patient #10 died during the work-up diagnosis and necropsy revealed a lung carcinoid with a positive immunohistochemistry for ACTH. Patient #7 presented a history of gastric ulcers produced by a pancreatic carcinoma. This patient died during the immediate postoperative period, and presented a huge bilateral adrenal hyperplasia.

Concerning overnight HDDST, we observed that 5 out of 20 patients presented cortisol suppression (decrease in serum cortisol levels > 50% in relation to baseline levels). Only two cases underwent the human CRH test, with no increment in plasma ACTH and serum cortisol levels.
Of the 13 patients who underwent desmopressin test, we observed a positive plasma ACTH response in 6, and serum cortisol in 5 of them. One of the patients with the absence of response to desmopressin and CRH tests presented a broad increment in plasma ACTH and serum cortisol after the administration of GHRP-6, a GH secretagog, which is also a potent ACTH secretagog in normal individuals and patients with Cushing’s disease (24). The molecular analysis of lung carcinoid tumor identified a higher mRNA expression of GHSR-1a receptor, thus establishing a correlation between the presence of the receptor and the in vivo response to the releasing peptide.

Due to the absence of an MRI lesion compatible with pituitary adenoma, 7 out of our 25 patients underwent IPSS and the highest central to peripheral ACTH gradients varied from 1.11 to 1.95, which is compatible with non-pituitary ACTH production (Table 3).

We also evaluated calcitonin, βHCG, α-fetoprotein, CEA, and gastrin in our patients and observed increased levels of calcitonin in three cases, with one of them harboring a thyroid medullary carcinoma (MEN 2), CEA in six cases (in one extremely high), gastrin in seven cases (in four only modestly), α-fetoprotein in one case, and a case with slightly elevated levels of βHCG.

Androgen concentrations were evaluated in 18 patients. We observed an increase in the androstenedione levels in 14 and DHEA-sulfate in 5 patients. Serum testosterone levels were high in seven female and low in five male patients.

CT scan was positive in 15 out of the 21 cases and MRI was positive in 8 out of the 17 cases. It is noteworthy that in one of our patients, a lung carcinoid tumor was eventually detected by CT 11 years after the bilateral adrenalectomy. One of the patients presented a pituitary image compatible with a microadenoma at MRI, which was not found during the transsphenoidal surgery (false-positive). After pituitary transsphenoidal surgery, an IPSS showed no central to peripheral ACTH gradient. In our series of ACTH-producing ectopic tumors, 14 patients had intrathoracic tumors, 5 had pheochromocytomas (1 bilateral case), 3 had pancreatic tumors, 1 had a glomic tumor (cervical), and 2 patients had persistent occult tumors. Immunohistochemistry for cromogranin A, which is the best marker of neuroendocrine tumors was negative in 5 out of the 22 cases. In 8 out of the 22 patients submitted to tumor removal, although immunohistochemistry did not show ACTH in the tumoral cells, a substantial postoperative drop in ACTH and cortisol was observed.

Five patients initially categorized as harboring ectopic ACTH-producing tumors underwent 111In-pentetreotide scintigraphy, of which two were true-positive for lung carcinoid tumor and one for glomic tumor, all surgically confirmed. However, with a stricter retrospective re-evaluation, these three patients already presented tumor image at CT. In patient #25, whose 111In-pentetreotide scintigraphy showed an anomalous tracer concentration in the cervical region, CT and ultrasonography evaluation did not disclose the presence of tumor (Table 2). In patient #22, fluorodeoxyglucose (FDG)-positron emission tomography (PET) was performed revealing the presence of infectious pulmonary lesions in preclinical phase (pneumocystosis).

### Treatment

Once the localization diagnosis of ACTH-secreting tumor source was accomplished, surgical removal of these lesions was the treatment of choice. However, during the localization diagnosis period, even in occult cases, given the severity of the case, clinical treatment was necessary with cortisol synthesis blockers, ketoconazole being the most often used due to its efficacy (34). An example of such efficacy was the normalization of urinary cortisol values, which were very high in patient #24.

Another therapeutic alternative was the use of octreotide, as ectopic ACTH-producing tumors can

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**Table 3** IPSS with desmopressin data of patients with ectopic ACTH syndrome.

<table>
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<tr>
<th>Patient no.</th>
<th>ACTH (pg/ml)</th>
<th>IPS</th>
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<th>Pathology</th>
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<td>Basal Peak</td>
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</table>

IPS, inferior petrosal sinus; PER, periphery; CEN:PER, central to peripheral ACTH gradient; *GHRP-6 stimulation; ACTH: pg/ml (pmol/l; multiply by 0.2202).
express receptors for somatostatin and thus, respond to the administration of this polypeptide (35). Although performed in only three cases, the acute test with 50 μg of octreotide s.c. to evaluate the ACTH response had a good predictive value for a long-term clinical response to octreotide (36). As observed in Fig. 1, patients #22 and #23 presented response to the acute octreotide test, with a significant decrease in plasma ACTH concentration. The administration of octreotide at doses of 300–600 μg s.c./day resulted in normalization of ACTH and cortisol concentrations in three patients, one of whom did not undergo the acute test with octreotide. The patients with bilateral pheochromocytoma and those with disseminated disease or harboring occult tumors were submitted to bilateral adrenalectomy. In one patient harboring an occult tumor, a small lung carcinoid was detected 11 years after adrenalectomy. None of these patients developed Nelson’s syndrome in the follow-up.

**Evolution**

Overall, patients harboring pheochromocytomas and lung carcinoids seem to have better prognosis than those with thymic carcinoids. Out of our 25 patients, 11 presented metastases and 6 of them died. Patient #1 with a bilateral pheochromocytoma (MEN 2) died due to medullary carcinoma. Of the patients without metastases, only patient #10 died, due to postoperative meningitis after a transsphenoidal pituitary surgery. It should be emphasized that there could have been more deaths as we lost the follow-up in some patients. Patient #20, without metastases, presented a local tumor recurrence 24 months later, and died at the time of reoperation. Patient #23, who had presented an unusual cyclic Cushing’s syndrome, died due to an acute myeloid leukemia after chemotherapy for the lung carcinoid tumor. Patient #24, with a glomic tumor, was submitted to radiotherapy and cured, and the three cases of occult syndrome were submitted to bilateral adrenalectomy (Table 2). A survival curve could not be calculated because of the loss of some follow-ups.

**Discussion**

In patients with clinical findings suggestive of Cushing’s syndrome and ACTH-dependent hypercortisolism, the diagnostic challenge is to differentiate an occult ectopic ACTH-producing tumor from an ACTH-producing pituitary microadenoma.

At diagnosis, 64% of affected patients presented hypokalemia which is quite similar to literature data, rarely seen in patients with Cushing’s disease and highly suggestive of EAS. The more intense hypokalemia in EAS can be explained by the mineralocorticoid effect of cortisol, which in EAS tends to be higher than in Cushing’s disease and also because the activity of 11-hydroxysteroid dehydrogenase type 2, for reasons yet to be clarified, is decreased in patients with ectopic secretion of ACTH (9, 10).

There have been several reports of ectopic ACTH-producing tumors in literature, most of them of neuroendocrine origin. About 45% are small-cell lung carcinomas (SCLC), 15% thymic carcinoid tumors, 10% bronchial carcinoids, 10% pancreatic islet cell tumors, 5% other carcinoid tumors, 2% pheochromocytomas, and 1% ovarian adenocarcinomas (37–42). A miscellany of non-amine precursor uptake and decarboxylation cell tumors, such as squamous cell carcinomas, adenocarcinomas, and hepatomas can also produce EAS.

In corticotrophic pituitary adenomas, plasma ACTH concentrations are at the upper limit of normality or slightly elevated (50–210 pg/ml), whereas in EAS, these are usually higher (> 200 pg/ml), although in some cases they overlap those found in Cushing’s disease (16). In our series, 6 out of 24 (25%) cases exhibited normal plasma ACTH levels, 4 of them harboring pheochromocytomas and those with high plasma ACTH levels ranged from 87 to 1453 pg/ml. Thus, in our patients harboring pheochromocytomas, plasma ACTH levels were lower when compared with the other tumors. It is reasonable to accept that due to the close relationship between tumor and adrenal cortex, small amounts of ACTH could lead to cortisol hypersecretion. However, there is no clear complete explanation for the latter findings. The paper by Beuschlein et al. (7) stated that in 67% of the patients harboring pheochromocytomas, plasma ACTH levels were higher than 200 pg/ml. We could not establish a comparison with the last published series by Isidori et al. (43) where there was only one patient harboring a pheochromocytoma and in the paper by Ilias et al. (44), plasma ACTH levels were not individualized according to the type of tumor.

HDDST suppresses the morning cortisol secretion > 50% of the basal value in around 80% of Cushing’s disease cases, with 12% of false-negative results. Usually, in EAS, there is no cortisol suppression, although 20% of small carcinoid tumors can be suppressible (45). When data from the literature were analyzed, the sensitivity of the suppression test with 8 mg of oral dexamethasone varied from 65 to 100%,
and the specificity from 60 to 100% (22). It is considered that the accuracy of this test is lower than the pre-test probability of Cushing’s disease in the population (45). Some controversies regarding the HDDST are due to the different suppression criteria utilized (16, 46). Considering the criterion of 50% suppression, in our series, 5 out of 20 (25%) cases had a positive response to HDDST. This high false-positive rate could be explained by the small number of cases and also by the fact that four of them were lung carcinoid tumors which can be suppressible.

Classically, patients with ectopic ACTH secretion do not respond to CRH stimulation test (1.0 μg/kg IV) (47), although rare cases of Cushing’s disease might not respond either. An ACTH increase >35% and cortisol >20% above baseline levels is considered a specific response to ovine CRH stimulation test for Cushing’s disease (19). With the use of human CRH, the cutoff line for a specific response is an increase in plasma ACTH >105% and serum cortisol >14% (20). An ACTH increase >100% is highly suggestive of Cushing’s disease, as an ACTH elevation >100% rarely occurs after CRH stimulation in ectopic ACTH secretion syndrome. CRH serum cortisol response can be considered more specific when compared with ACTH response because non-intact ACTH molecules exhibit less biological activity. However, the complete discrimination between ACTH secretion in Cushing’s disease and the ectopic ACTH secretion by non-pituitary tumors is not always achieved by the CRH test only, since 8–10% of pituitary adenomas do not respond to the test and around 20% of patients with EAS can exhibit response to CRH (19, 20, 23). CRH peptide is not available in our institution; thus, the CRH test was performed only in two cases.

Therefore, desmopressin test was used as an alternative to CRH testing in the differential diagnosis of ACTH-dependent Cushing’s syndrome (17). A positive response to desmopressin (increment of 35 and 20% above baseline ACTH and cortisol levels respectively) (19) would be compatible with Cushing’s disease, although patients with carcinoids might present a positive response to this peptide administration due to V1b receptor expression which can be quite similar to pituitary corticotroph expression (48). In our data (not published) experience, 16% of patients with Cushing’s disease do not respond to the desmopressin test. Due to the small number of cases submitted to CRH test, accuracy of both tests could not be compared. However, data from the literature show that the diagnostic value of desmopressin test for differential diagnosis is more limited than CRH test (18). Concerning GHRP-6, it became available only recently in our institution and for that reason, GHRP-6 test was done in only three patients. Thus, in our experience with EAS, 5 out of 20 (25%) cases had a positive response to HDDST and 6 out of 13 (46%), and 5 out of 13 (38%) cases exhibited positive responses to desmopressin test for ACTH and cortisol respectively.

IPSS is considered the ‘gold standard’ method for the differential diagnosis of ACTH-dependent Cushing’s syndrome. A baseline ACTH gradient between the inferior and the peripheral petrosal sinuses >2, and after stimulation with CRH/desmopressin >3, would indicate a pituitary source of ACTH secretion (26, 28, 29).

Data gathered from literature with 838 cases (726 with Cushing’s disease and 112 with EAS) showed 41 false-negative and 7 false-positive cases with a sensitivity and specificity of 94% for ruling out Cushing’s disease (49). False-positive results in IPSS can be caused by periodic hormonogenesis in ectopic tumors as has been reported by Yamamoto (50) in two patients harboring ACTH-secreting bronchial carcinoids or also by CRH-producing ectopic tumors which are already reported (51, 52).

IPSS is still restricted to some centers, demanding experienced professionals since it is an invasive procedure susceptible to complications. It should be stressed that in cases of central to peripheral ACTH gradient not reaching the threshold for pituitary disease, CRH response may provide improved diagnostic accuracy and transsphenoidal pituitary approach considered as has been reported recently (53). The incidence of severe complications secondary to IPSS, such as stroke and perforation of the atrial wall is around 0.2%, whereas hematomas and transitory arrhythmias can occur in 20% of the cases (27, 28). Since none of the dynamic non-invasive tests provide 100% accuracy, 7 out of our 25 cases were submitted to IPSS.

We have extensive experience with desmopressin and its use in IPSS for differential diagnosis of ACTH-dependent Cushing’s syndrome. In order to amplify central to peripheral ACTH gradient, six patients underwent IPSS with desmopressin and one with GHRP-6 administration (Table 3). There was no false-positive for Cushing’s disease with this diagnostic approach and in five cases with an initially occult EAS, tumors were found and surgically removed. In the other three patients, EAS remained occult and due to its severity they were submitted to bilateral adrenalectomy. As mentioned previously, in one of these three cases with an occult EAS, a bronchial carcinoid tumor was found after 11 years of imaging evaluation. After surgical removal of the tumor, plasma ACTH dropped from 590 to 17 pg/ml.

Regarding imaging evaluation, CT, MRI, and scintigraphy with radioisotopes can be utilized for the localization diagnosis. Tumors >1 cm are detectable by CT and MRI, being usually visualized in plain thorax X-rays. The great challenge for the imaging methods are the bronchial carcinoids, which are commonly small tumors (on an average 1 cm) and difficult to visualize, especially in hilar region. The use of CT with 5 mm cuts allows the detection of many of these tumors.
although around 30–40% of them are undetectable (54). Chest MRI seems to be more sensitive than CT to detect thymic and bronchial carcinoids because it differentiates small hilar nodules from vessels (55).

In our series, CT was positive in 15 out of 21 cases and MRI in 8 out of 17 cases and the latter was unable to identify any case not identified by CT. Both scans failed to localize the tumor in 5 out of 25 (20%) of our patients, which is a better result when compared with other published series (33). In patients with occult ectopic tumors, functional imaging methods with radioisotopes were utilized.

Among these methods, positron emission tomography (PET) has been used in oncology and whole body scintigraphy with [18F-]fluorodeoxyglucose (FDG) is presently the most broadly used method to identify occult tumors, although it has little accuracy (31). In only one of our cases, FDG-PET was performed, showing a preclinical lung inflammatory process diagnosed as pneumocystosis. In a recent study, FDG-PET scan did not detect occult tumors not detected by conventional CT/MR imaging (31).

Another method that is broadly utilized in the detection of occult ectopic tumors is the scintigraphy with somatostatin analog (111In-pentetreotide scintigraphy). The use of this scintigraphic method in 18 patients with ectopic ACTH-secreting tumors did not detect the presence of tumor when CT/MRI results were negative. In this series of 18 patients, 40 111In-pentetreotide scintigraphies were performed, resulting in 6 false-negative and 8 false-positive results. The authors concluded that although the method can be useful in selected cases, it does not present a higher sensitivity than the conventional methods using CT and MRI (33). However, in a meta-analysis of 14 papers, 111In-pentetreotide scintigraphy identified some occult tumors not identified by conventional CT/MRI scans (56). Although there is some debate about its usefulness, in our five cases in which CT/MRI failed to localize ectopic ACTH secretion, somatostatin receptor scintigraphies using 111In-pentetreotide were true-positive in four out of five cases. One of our cases showed an anomalous tracer concentration in the cervical region but CT and ultrasonography failed to disclose the presence of local tumor. Finally, it is noteworthy that the use of scintigraphy with 123I-metaiodobenzylguanidine (123I-MIBG), a drug with great affinity for chromaffin tissues, has a lower sensitivity than the two previously reported methods (30).

The measurement of tumor markers (calcitonin, CEA, gastrin, βHCG, α-fetoprotein, 5-HIAA), must be routinely carried out in ACTH-dependent Cushing’s syndrome, as its presence favors the diagnosis of ectopic ACTH secretion. In our series, 18 (72%) out of 25 patients had elevated levels of tumor markers. Different from other series in which calcitonin was the most commonly elevated tumor marker, in our series, gastrin was the most elevated tumor marker being elevated in 7 (28%) out of 25 cases including 2 cases with gastrinomas. It should be mentioned that in the paper by Isidori et al. (43), gastrin and calcitonin levels were both equally elevated in 11 patients. The association of ectopic ACTH secretion and gastrin is not uncommon in pancreatic tumors (57). In our series, calcitonin levels were elevated in only three cases including one with a medullary carcinoma (MEN 2A). CEA levels were elevated in six of them, α-fetoprotein in two, and a small increase in βHCG were observed in a patient with a bronchial carcinoid.

Concerning survival, in our experience, all cases with thymic carcinoids had poor prognosis. Patients harboring pheochromocytomas, bronchial carcinoids, and those cases without local or lymph node metastases seemed to have better prognosis when compared with those with local or spread metastases. Similar to the last extensive published series, patients harboring SCLC, medullary thyroid carcinomas, and pancreatic tumors had poor prognosis when compared with bronchial carcinoids (43, 44). In our cases, those initially occult had better prognosis even when they presented severe hypercortisolism.

Regarding treatment, once the tumor is localized surgical removal is the treatment of choice. However, while waiting for localization diagnosis in severely affected cases, patients should receive clinical treatment with cortisol synthesis blockers, the most often used being ketoconazole, octreotide, or both.

EAS still remains one of the most challenging issues in endocrinology especially in those occult cases. Concerning clinical findings, there is a broad spectrum of severity which can be similar to Cushing’s disease. The endocrine non-invasive dynamic testing and IPSS leads to correct diagnosis in the majority of cases, and conventional or functional imaging studies help to correctly localize these tumors, but a considerable proportion of cases remain occult.

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