Pathological thyroid uptake in Cushing’s syndrome: An unexpected finding
Captación patológica tiroidea en síndrome de Cushing: un hallazgo inesperado

To the Editor:

Imaging tests indicated for the characterization of adrenal lesions include computed tomography (CT) scan and magnetic resonance imaging (MRI). Size, homogeneity, and lipid contents, as measured by Hounsfield units (HU), help distinguish benign from malignant lesions. There are however instances with indeterminate radiographic characteristics. Some studies support the use of positron emission tomography (PET) with 18-fluorodeoxyglucose (18F-FDG) to assess these lesions.

However, what is used in principle to establish a diagnosis can become a tool for the diagnosis of unsuspected conditions.

We report a 34-year-old female patient with an unremarkable personal history except for carbohydrate intolerance. She was referred to the endocrinology clinic for abnormal thyroid function test results including free T4 levels of 0.79 ng/dL (0.9-1.7) and TSH levels of 0.84 µg/mL (0.27-4.5), which were not confirmed by repeat testing (free T4 1.14 ng/dL, TSH 0.64). The patient reported an increase in body hair, mainly in the limbs, over the previous two years and a weight gain of 16 kg in one year. She reported no hematoma, alopecia, or menstrual cycle changes.

Physical examination revealed blood pressure of 130-70 mmHg, heart rate of 74 bpm, moon face, and trunk obesity. Weight: 90.5 kg; height: 165.5 cm; BMI: 33.5 kg/m²; waist circumference: 123 cm; and increased interscapular fat. Hirsutism, particularly in the face, was prominent (17 points on the Ferriman-Gallwey scale). Neck palpation found no goiter, thyroid nodules, or adenopathies. The examination was otherwise normal.

Cushing’s syndrome was suspected, and laboratory tests were performed with the following results: basal cortisol: 18.8 µg/dL (6.2-19.4); free cortisol in 24-h urine: 158 µg/24 h (22.2-128.5); plasma cortisol after dexamethasone 1 mg: 19.48 µg/dL; cortisol after dexamethasone 0.5 mg every 6 h for 2 days: 16 µg/dL; cortisol at 23 h: 12.75 µg/dL; cortisol after strong suppression with dexamethasone 8 mg: 14.48 µg/dL; ACTH: < 5 pg/mL; androstenedione: 1.5 (0.2-3.1 ng/mL), DHEA-S: < 15 (35-430 µg/dL).

Based on the diagnosis of a non ACTH-dependent Cushing’s syndrome of adrenal origin, abdominal MRI was performed (Fig. 1). The image showed a left adrenal mass 3 cm in size with no signal loss in the opposite phase, which could not therefore be confirmed as being an adenoma. An abdominal CT scan showed the same lesion with indeterminate radiographic characteristics. Malignancy could not therefore be ruled out. An additional imaging test, a PET/CT with 18F-FDG (Fig. 2), was thus requested. This showed the left adrenal nodule with a maximum standard uptake value (SUV) of 2.66, lower than SUV in the liver (3.4), and benign metabolic criteria. At neck level, a mild intensity deposit was seen in the left thyroid lobe with a maximum SUV of 2.76 (lower than maximum SUV in mediastinum), suggesting malignancy. Thyroid ultrasound examination confirmed a
but little morphological information. When combined with information about the functional characteristics of lesions, thyroid lobe.

perithyroid soft tissues. An ablation dose of $^{131}$I (150 mCi) size, with no nodal involvement and focal extension to a stage pt3 papillary thyroid carcinoma, 1 x 0.9 x 0.9 cm in complete removal of the central neck lymph nodes revealed hospital discharge. Subsequent total thyroidectomy with Hydrocortisone was administered perioperatively and at control. She reports an improvement of hirsutism and a significant weight loss with normalization of carbohydrate control. Although uncommon, there are suspected, but the nature of such a lesion could not be caused of Graves-Basedow disease, a diffuse, symmetrical FDG metabolic increase may be seen. A more heterogeneous uptake is usually identified in multinodular goiter. Incidental focal uptake occurs in 1%-4% of PET/CT studies in oncological patients with no thyroid disease. This may represent autonomous hyperfunctioning nodules or benign tumors such as Hürthle cell adenoma and follicular adenoma. It is however important to rule out primary malignant disease because it has been found in a non negligible percentage of these uptakes (from 14% to 63% depending on the series).

Adrenal glands do not take up FDG under normal conditions. Malignant lesions show an increased uptake, but this may also occur in glands with benign conditions. There are studies supporting the value of $^{18}$F-FDG PET/CT for differentiating malignant and benign adrenal lesions in patients with no history of neoplasm. In the Tenenbaum et al. study, using the SUV index only, the predictive value of $^{18}$F-FDG was good, but the authors recognized that it was imperfect. Using a cut-off point of 3.4 they achieved a 100% sensitivity for an accurate diagnosis of all malignant lesions, although specificity for differentiating adenoma from carcinoma was only 70%. Thus, a negative or fainter uptake in PET/CT is highly predictive of a benign lesion and may help prevent surgery or delay it if necessary. If surgery is indicated, PET/CT may help in the selection of a less invasive surgical approach.

On the other hand, mild diffuse and homogeneous uptake may be seen in the thyroid gland (although it is absent in most cases). In chronic thyroiditis of Graves-Basedow disease, a diffuse, symmetrical FDG metabolic increase may be seen. A more heterogeneous uptake is usually identified in multinodular goiter. Incidental focal uptake occurs in 1%-4% of PET/CT studies in oncological patients with no thyroid disease. This may represent autonomous hyperfunctioning nodules or benign tumors such as Hürthle cell adenoma and follicular adenoma. It is however important to rule out primary malignant disease because it has been found in a non negligible percentage of these uptakes (from 14% to 63% depending on the series).

The studies so far conducted have not been able to conclude what uptake index is most helpful for discriminating benign from malignant thyroid lesions, but agreement exists as to the usefulness of studying all thyroid focal lesions found in PET/CT because of the high probability of a malignant lesion.

To conclude, the performance of PET/CT was helpful both in arriving at a more precise definition of the adrenal mass causing Cushing’s syndrome, and in identifying a malignant subcentimetric thyroid lesion which would otherwise have been overlooked, and so changed the therapeutic approach to the patient.

Figure 2 PET/CT with $^{18}$F-FDG. Mild intensity deposit in left thyroid lobe.

1-cm hypoehogenic lesion, and FNA suggested papillary carcinoma.

Left laparoscopic adrenalectomy was performed, followed by pathologic examination of the adrenal adenoma. Hydrocortisone was administered perioperatively and at hospital discharge. Subsequent total thyroidectomy with complete removal of the central neck lymph nodes revealed a stage pt3 papillary thyroid carcinoma, 1 x 0.9 x 0.9 cm in size, with no nodal involvement and focal extension to perithyroid soft tissues. An ablation dose of $^{131}$I (150 mCi) was administered, and at the time of writing there is no trace of the disease. The patient is on replacement therapy with hydroaltesone and levothyroxine with good hormone control. She reports an improvement of hirsutism and a significant weight loss with normalization of carbohydrate metabolism.

Small (< 4 cm) homogeneous adrenal masses with smooth, rounded contours suggest a benign condition, particularly if they have a density lower than 10 HUs and show fast contrast elimination in CT, or are isointense with the liver in T1 and T2 in MRI. Irregular, heterogeneous lesions with calcification and > 4 cm in size suggest malignancy, especially if they also have a density higher than 20 HUs in CT and show irregular contrast uptake and delayed contrast elimination. Hypointensity as compared to liver in T1 and high density in T2 in MRI suggest a malignant lesion. However, diagnosis is not always easy, and the radiologist’s report sometimes states: “adrenal lesion with indeterminate characteristics” or “malignancy cannot be ruled out”. In the reported case, a Cushing’s syndrome secondary to adenoma was suspected, but the nature of such a lesion could not be distinguished because, although uncommon, there are adrenal carcinomas which cause hormone overproduction, and the final radiographic diagnosis had both therapeutic and prognostic implications. A PET/CT with $^{18}$F-FDG was therefore performed. This procedure provides metabolic information about the functional characteristics of lesions, but little morphological information. When combined with CT, PET/CT allows for the merging and correlating of anatomical and functional images.

References

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Pituitary apoplexy due to macroadenoma bleeding

Apoplejía hipofisaria por sangrado de macroadenoma

A 54-year-old male attended the emergency room for sudden bifrontal headache, nausea, and vomiting. Nine years previously, he had experienced a similar condition associated with diplopia and had been diagnosed a non-secretory pituitary macroadenoma (Fig. 1 A-B) with secondary panhypopituitarism (tSH 0.026 mcU/mL, t4 0.54 ng/dL, basal prolactin 1.88 ng/mL, FSH 1.01 mIU/mL, LH < 0.5 mIU/mL, ACTH < 10 pg/mL, cortisol < 1 µg/dL, GH < 0.3 ng/mL). The patient had refused any therapeutic intervention other than hormone replacement therapy.

Physical examination revealed partial paresis of the right third cranial nerve with no campimetric or visual acuity deficits. Both CT and MRI of the head showed a 2.6 x 2.3 cm pituitary adenoma which had increased in size since the previous examination, extending to the chiasm without compressing it and had recent intratumoral bleeding (Fig. 2 A-B). Based on a diagnosis of pituitary apoplexy (PA) due to macroadenoma bleeding, transsphenoidal hypophysectomy with evacuation of intratumoral hematoma was performed with no complications. The postoperative course was uneventful, with complete neurological recovery.

PA is an uncommon complication in the course of pituitary tumors. It is caused by a sudden expansion of the pituitary gland secondary to an ischemic or hemorrhagic infarction which almost invariably occurs in the presence of a pituitary adenoma. The true incidence of PA is difficult to establish because pituitary tumor bleeding is often asymptomatic. The reported data suggest that up to 25.7% of pituitary tumors exhibit some degree of surgically documented bleeding. However, PA occurs as a syndrome in 0.6%-21% of the cases. In addition, a vast majority of them occur in non-functioning adenomas (77% in the Semple et al series). The rapid growth of sellar contents compresses both adjacent structures and pituitary vascularization and causes sudden headache, vomiting, disorders, oculomotor nerve palsy, meningism, impaired consciousness, and hypopituitarism. PA spontaneously occurs in 60%-80% of previously asymptomatic patients. However, it has been reported as being associated with a number of triggering factors such as head trauma, arterial hypotension or hypertension, a history of irradiation, heart...
surgery, anticoagulation, bromocriptine administration, and pituitary dynamic tests. Diagnosis is mainly based on clinical signs, and pituitary MRI is the imaging test of choice.

The optimal treatment for this condition is controversial. There is general agreement that initial management should consist of the monitoring of water and electrolyte balance, strict clinical control, and the correction of hormone deficiencies, as well as the administration of glucocorticoids at supraphysiological doses. Once clinical status is stabilized, surgical decompression of sellar contents through a transcranial or transsphenoidal approach could be indicated, but the need or urgency of this procedure has not been fully established. If severe neuro-ophtalmological damage (chiasm compression, impaired consciousness, or focal neurological signs) or progressive clinical impairment occur despite conservative treatment, surgical decompression is indicated. Conservative treatment should be adequate for patients with no headache and ophthalmoplegia. Controversy also exists as to the optimal timing of surgery. The most representative studies reported in the literature suggest that the best visual prognosis and recovery of pituitary function are achieved with early (within 7-8 days of the start of symptoms), but not necessarily urgent, surgical decompression of sellar contents. An exception should be made for patients with sudden, severe visual impairment, for whom urgent surgical decompression is recommended. Most patients who experience PA have transient or permanent pituitary insufficiency, and up to 80% of patients require hormone replacement therapy at least once. Prognosis will depend on the degree of initial involvement and delay in treatment. In the past PA had a high mortality rate, but it is currently associated with a significant improvement in survival rates as a consequence of a greater understanding of the condition at both the clinical and the therapeutic level and also due to the development of new imaging techniques.

References


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Plasmapheresis as treatment for severe hypertriglyceridemia

To the Editor:

Severe hypertriglyceridemia (HTG) is defined as plasma triglyceride levels higher than 1,000 mg/dL. Hypertriglyceridemia may be primary, such as familial HTG, or secondary to other causes such as chronic alcohol consumption. The most serious complication of HTG is acute pancreatitis. While under normal conditions the mainstays of HTG treatment include diet, exercise, and lipid lowering drugs, severe HTG requires a treatment which is highly effective in the short term because of the risk of pancreatitis. Plasmapheresis is the treatment that meets these requirements. The case of a patient with severe HTG who required plasmapheresis is reported below.

This was a 28-year-old male patient who was admitted to the endocrinology department for hyperglycemic decompensation without ketosis. The patient had been diagnosed two years before with type 2 diabetes mellitus (DM) for which he was receiving treatment with metformin and vildagliptin with an irregular compliance. He had smoked a pack of cigarettes daily since the age of 16, but denied alcohol consumption. There was no other personal history of interest or family history of diabetes or other significant diseases. The patient had lost 30 kg in weight since DM was diagnosed, and in the previous 5 months had shown cardinal clinical signs of diabetes. He therefore consulted his primary care physician, who referred him to the endocrinology outpatient clinic after receiving the following laboratory test results: total cholesterol 174 mg/dL, triglycerides 128 mg/dL, HDL 52 mg/dL, LDL 96 mg/dL, and HbA1c 14%.

As noted above, HTG may have a primary or a secondary cause. Primary HTG is caused by genetic disorders such as lipoprotein lipase (LPL) and apolipoprotein lipase (Apo) C-II deficiency, familial HTG and others. There are multiple secondary causes, including DM, obesity, alcohol consumption, and drugs, and other less common causes such as amyloidosis and glycogenesis. Intake of food with high saturated fat contents, hormone treatments (steroids, estrogens), pregnancy, and intercurrent diseases may act as factors triggering acute pancreatitis in these patients.

Drug treatment for severe HTG should be prescribed at diagnosis. Fibrates decrease triglyceride levels by 40%-60% and increase HDL levels, and are therefore considered the first choice drugs. Omega 3 acids and nicotinic acid decrease triglyceride levels by 45% and 30%-50% respectively. They decrease chylomicron production and stimulate fatty acid oxidation. Response to these treatments is slow, and they are therefore not helpful in patients with severe HTG. In these patients, the first measure should be absolute diet, which causes a rapid decrease in chylomicrons and triglyceride levels. Insulin and heparin may also be used in severe HTG. Insulin activates LPL and accelerates chylomicron degradation, while heparin stimulates LPL entry into the bloodstream. Clinical studies have shown that both agents may decrease triglyceride levels alone or in combination. Many authors prefer insulin to heparin even in non-diabetic patients because the effect of heparin may be transient, as LPL levels increase in the bloodstream but LPL deposits decrease, with a resulting final LPL deficiency. These treatments may achieve a decrease in triglyceride levels, but not as rapidly as with plasmapheresis.

Plasmapheresis is an extracorporeal clearance technique designed to remove from blood circulation harmful high molecular weight substances such as autoantibodies, immune complexes, cryoglobulins, endotoxins, and cholesterol-containing lipoproteins. To be removable by plasmapheresis, the substance should have a molecular weight greater than 15,000 kDa and not be filtered by more simple clearance procedures such as hemofiltration. It should also have a long half life, so that
extracorporeal elimination is much faster than endogenous elimination\(^5\).

Plasmapheresis was first reported as treatment for severe HTG by Betteridge et al in 1978. Since then, several similar reports have been published\(^6-7\). Yeh et al\(^6\) and Lennertz et al\(^7\) showed that a single plasmapheresis session could decrease triglyceride levels by 70%.

Controversy exists about the technical details of apheresis (plasma exchange versus dual membrane apheresis), but there is a trend towards performing it using plasma exchange\(^5\) and adequate fluid replacement (fresh frozen plasma or albumin), although no studies comparing these two approaches are available.

On the other hand, there are studies which show that mortality and morbidity due to complications of severe HTG decrease when plasmapheresis is performed without delay\(^8-9\). However, plasmapheresis is an expensive treatment and is not available at all hospitals. Current clinical guidelines for the use of therapeutic apheresis in clinical practice, issued in 2007, recommend the use of plasmapheresis in acute pancreatitis secondary to HTG at evidence category level C\(^10\).

Conflict of interest

The authors state that they have no conflict of interest.

References


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