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Ectopic Cushing's syndrome: Paradoxical effect of somatostatin analogs

Secreción ectópica de ACTH y respuesta paradójica a análogos de somatostatina

Ectopic ACTH secretion (EAS) is an uncommon cause of ACTH-dependent Cushing's syndrome. Previous large studies[1–3] concluded that two thirds of EAS tumors are located in the thorax and 8%–15% are located in the abdominal cavity. EAS tumors at other sites are less common; of note, up to 15% of tumors remain undetected. The adrenal glands are thus an extremely rare location.

Localization of these tumors can occasionally be difficult and may require extensive diagnostics test, therefore hypercortisolism normalization during this period is crucial. Adrenal steroidogenesis inhibitors as ketoconazole or metyrapone are preferred for their efficacy and safety. Somatostatin analogs (SSAs), have also been used to treat EAS with different results,[4–6] and in some cases a paradoxical increase in ACTH and cortisol after SSAs treatment has been reported.[7] In the present report, we describe a patient with adrenal EAS, who experienced a life-threatening worsening after conventional SSAs administration. We highlight the need to be aware of this rare presentation of EAS, and we remark the difficulties of EAS diagnosis and treatment.

A 48-year-old woman with newly diagnosed hypertension complained of amenorrhea, intense fatigue, muscular weakness and easy bruising, which had increased rapidly over the previous 3 months. Her past history was unremarkable except for recent treatment with enalapril. On examination the patient had normal body mass index, tanned skin with intense thinning with bruising, marked proximal limb muscle atrophy, and a mild moon face. She did not display buffalo hump, purple striae, or supraclavicular fat pads.

Laboratory findings revealed: 3-fold normal rate urinary free cortisol (UFC), (250 μg/day per two times; reference range 12.8–82.5 μg/day) and mild hypokalemia (3.3 mmol/l; reference range 3.50–5.10 mmol/l); lack of cortisol suppression after low-dose (1 mg) dexamethasone (19.67 μg/dl, reference value <1.8 μg/dl). Basal plasma cortisol was 29.56 μg/dl (reference range, 5.27–22.45 μg/dl), and ACTH was 47.83 pg/ml (reference range, 4.7–48.8 pg/ml). Therefore, ACTH-dependent Cushing Syndrome diagnosis was established. Pituitary-centered magnetic resonance imaging (MRI) showed no evidence of pituitary adenoma, and cortisol levels were virtually unchanged after 8-mg dexamethasone suppression test (from 18 to 20 μg/dl). The bilateral inferior petrosal sinus sampling (BIPSS) showed no significant central-to-periphery ACTH gradient, thus ruling out a pituitary origin of ACTH excess.

The results of neck, thorax, and abdomen 3-mm-sliced computed tomography (CT) scan and MRI were unremarkable. The somatostatin receptor scintigraphy (SSRS) and (PET)/CT localized only a slightly higher concentration of somatostatin receptors and glucose uptake in the left adrenal gland, compared with the right. As an ectopic source of ACTH located in the adrenal could be associated with pheochromocytoma and the patient had recent hypertensive state, we also performed urinary catecholamine determination, which was normal, and metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy, which showed increased uptake in the left adrenal.

As SSRS imaging was positive, a high-dose extended-release SSAs was initiated (lanreotide 120 mg) while waiting for ketoconazole provision; however, the patient's condition worsened and become life-threatening one week later, while UFC and ACTH raised up to 800 μg/day and 102 pg/ml respectively. Ketoconazole was started immediately (200 mg three times daily) in a ''block and replace'' regimen. The patient underwent surgery; her left adrenal gland and a contiguous lesion, not detected previously, were removed. Immunohistochemical study revealed heterogeneous but unequivocal ACTH positivity in the medullary area of the adrenal, but not in other areas. This was interpreted as pathological, based on ACTH negative staining in three additional adrenal glands analyzed as controls (Fig. 1A). The other resected lesion turned out to be an extra-adrenal, 2 × 1.5 cm ganglioneuroma; surprisingly, it had negative ACTH immunostaining (Fig. 1B). The patient's clinical condition has improved over the follow-up period and she was able to give up her hypertension pills. Her ACTH and urinary free cortisol levels remained normal at her latest control at ten

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Figure 1 (A1) Adrenal medulla of the present case, without morphological abnormalities (H&E, ×20); (A2) positive ACTH immunostain of the same histological area as A1; (A3) absolute negative ACTH stain in an adrenal control case. (B1) Extra-adrenal ganglioneuroma (H&E, ×20); (B2) ACTH immunostain, absolutely negative; (B3) NSE positive expression in neuronal component, according to the diagnosis.

months, but she still required cortisol replacement during stress.

EAS diagnosis is a challenge, and the patient's condition can be life-threatening during severe hypercortisolism. Despite clinical and biochemical evidence of ACTH-dependent Cushing's syndrome, up to 15% of tumors remain undetected.[1] BIPSS is considered the gold standard for differential diagnosis between EAS and Cushing disease.[2] An ectopic source of ACTH located in the adrenal gland occurs in less than 5% of cases, and is generally associated with pheochromocytoma or paraganglioma, not found in this case. We are no able to ensure that the high ^{123}I-MIBG uptake was from the adrenal medulla, or from the contiguous ganglioneuroma; nevertheless, it is important to note that ^{123}I-MIBG was associated with the highest percentage of false positives.[8] Likewise, the sensitivity of SSRS in EAS is known to be relatively low, ranging from 25% to 60%,[1,2,8] suggesting low receptor expression compared with other NETs. This could be an intrinsic characteristic of tumors causing EAS, though a functional mechanism involving selective downregulation of SSTR2 induced by elevated cortisol has also been advocated.[9,10] Moreover, SSRS has been reported to become positive after successful glucocorticoid-antagonizing therapy.[10] A recent systematic review[9] analyzed various nuclear medicine imaging techniques in ectopic Cushing's syndrome and concluded that ^{68}gallium-SSTR-PET/CT showed the highest SSTR5 affinity, and the highest sensitivity in EAS diagnoses. Unfortunately, this technique was not available in our center. Finally the same mechanism, selective downregulation of SSTR2, could be responsible for negative or paradoxical responses to traditional SSAs. Honestly, in this case we cannot completely rule out that the patient's deterioration merely was the natural course of the disease; however, we assume she had a paradoxical response on the basis of her dramatical worsening just after the SSAs administration, associated to an important rise in ACTH and UFC levels. In this sense, the use of the new SSAs pasireotide, with better SSTR5 affinity may be preferred for EAS treatment than, traditional SSAs: octreotide or lanreotide, which have mostly SSTR2 affinity.

In conclusion, EAS presents a major diagnostic challenge. Adrenal gland localization occurs in less than 5% of cases and is usually associated with ACTH-secreting pheochromocytoma, which was not found in our case. Surgery, if feasible, is the unique treatment option, with curative potential. To avoid the devastating effects of severe hypercortisolism, medical therapy must be initiated as soon as possible; Steroidogenesis inhibitors with fast and safe action must be the first medical treatment of choice. Others options like SSAs may have unpredictable responses.

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Patient consent

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Declaration of interest

The authors declare that they have no competing interests.

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Potential consequences in children of a testosterone gel used by their fathers☆

Posibles consecuencias en los niños del uso de gel de testosterona por sus padres

Testosterone replacement therapy has been used for male hypogonadism since 1930. In recent decades, gel preparations of this hormone have been preferred by many patients, since in most cases a daily application suffices to obtain stable physiological concentrations. It is important to warn about the side effects that result when the drug is transmitted to someone other than the patient for whom it has been prescribed. In this regard, it is advisable for the user to cover the application zone with clothing or to wash it before coming into contact with other people.[1]

We report two cases of children seen for the early development of sexual characteristics to different degrees, whose fathers had been receiving treatment with testosterone gel.

The first case was a two-year-old boy referred due to penile growth with frequent erections, pubarche, and exaggerated growth in stature in the previous few months. A physical examination revealed tallness for the age of the patient and the height of the parents, a muscled body, pubarche, enlarged penis (Tanner class III), and a rough and pigmented scrotum, but no change in testis volume. Laboratory tests showed a very high total testosterone level for his age, with suppressed LH and FSH, and no response of these hormones to leuprolide stimulation. The bone age was advanced by three years. His testosterone level normalized after gel exposure was discontinued, with a regression of the phenotypical changes. The boy had a normal growth rate and prepubertal testicular volume over the subsequent four years.

The second case was a 6-year-old boy seen due to the appearance of pubic hair and penile growth over the previous three months. The examination also revealed tallness and a testicle volume of 3 mL. Laboratory tests showed isolated total testosterone elevation with suppressed gonadotropins and no response to leuprolide. The bone age was advanced by 1.5 years. Three months after the suppression of exposure to the gel, the testicle volume had increased to 4 mL, indicating the start of puberty, with a high growth rate. The testosterone concentrations remained high, and an increase in gonadotropin levels was also noted, indicative of central activation. Hypothalamic-pituitary magnetic resonance imaging showed no abnormal findings, and treatment was started with monthly triptorelin.

In both cases, the fathers had undergone orchiectomy due to seminoma and were receiving replacement therapy with testosterone gel. The fathers were aware of the risk of transferring the gel to their partners, and followed the

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