THE MULTIFARIOUS CUSHING'S – LESSONS FROM A CASE SERIES

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Abstract

Endogenous Cushing's syndrome is rare, with an incidence of 0.7–2.4 per a million people a year. Clinical presentation of Cushing syndrome can be pleomorphic, and establishing diagnosis can be difficult. Early recognition and rapid control of hypercortisolaemia are necessary to decrease morbidity and mortality in these patients.

We report a series of 6 endogenous Cushing's syndromes of different etiologies (4 Cushing's disease and 2 adrenal Cushing's syndrome) assessed in our endocrine department over a decade (2009-2019). In order to highlight the diversity of clinical forms, diagnostic tools and specific management of this condition we labelled each case suggestively: the typical Cushing's disease, the Pseudo Cushing's, the elusive Cushing's disease, the mild autonomous cortisol hypersecretion, Cushing's syndrome in pregnancy and Cushing's disease with thromboembolism. We discussed their particularities which were revelatory for the diagnosis, such as dermatologic, cardiovascular, musculoskeletal, neuropsychiatric, or reproductive signs, reviewing literature for each manifestation. We also discuss the commonalities and differences in laboratory and imagistic findings. Therapeutic approach can also differ with respect to the particular condition of each patient and the multiple choices of therapy will be reviewed.

Key words: Cushing's syndrome, Cushing's disease.

INTRODUCTION

Cushing's syndrome (CS) is largely used as a generic term for all disorders which manifest with glucocorticoid excess, while there are more specific terms for different types of lesions. Endogenous CS is rare, with an incidence of 0.7–2.4 per a million people a year. It is classified as ACTH dependent or ACTH independent CS. The most frequent ACTH dependent is Cushing's disease (CD) due to a corticotroph pituitary

adenoma is 5 to 6 times more frequent than adrenal CS caused by adrenal tumors (AT) or adrenal hyperplasia. CD affects mostly women (3-15:1) between 20 and 40 years old (1).

A population-based study in Denmark reported the incidence of adrenal adenoma as 0.6 and adrenal carcinoma as 0.2 per million per year (2). In 1.3 to 8.7 percent of adults AT are discovered incidentally. Over 99 % of adrenal incidentalomas do not have symptomatic adrenal disease at presentation (2), but some could have subclinical CS.

Ectopic corticotropin (ACTH) syndrome is probably an underestimated cause of CS, as it is often not diagnosed. Around 1% of patients with small cell lung cancer have been shown to harbour an ectopic ACTH syndrome while this carcinoma causes half of all cases of the ectopic Cushing's (3).

Clinical presentation of CS can be pleomorphic, and establishing the diagnosis can be difficult. Early recognition and rapid control of hypercortisolaemia is necessary to decrease morbidity and mortality in these patients.

MATERIAL AND METHODS

Case series

We report a series of 6 endogenous CS of different etiologies (4CD and 2 AT) assessed in our endocrine department over a decade (2009-2019), in order to highlight the diversity of clinical forms of CS which may delay diagnosis. While the most common features of CS are central obesity and hypertension, these may very well be part of a pure metabolic syndrome. Therefore additional features may be revelatory of CS such as dermatologic, cardiovascular, musculoskeletal, neuropsychiatric, or reproductive. Patients have given written consent for pictures publication. Hormonal

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assessment was performed by electrochemiluminescence immunoassay (ECLIA) for adrenocorticotrophic hormone (ACTH), plasma cortisol on a Cobas e601 automated analyser. Chemiluminescence immunoassay (CLIA) on an Access2 Immunoassay System or DxI 600 Beckmann Coulter was used for urinary free cortisol,

Estradiol (E2), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), dehydroepiandrosterone sulphate (DHEAS). Thyroid function tests (thyroid stimulating hormone - TSH, free thyroxine-FT4, triiodothyronine-T3) were performed also by CLIA on an Architect 2000i Abbot automated analyzer. Diagnosis of CS was based on demonstrating non-suppressible hypercortisolism by a low dose dexamethasone suppression test (LDST) and/or an altered night

Figure 1. Case 1. Typical features of CD: central adiposity, slim limbs, hirsutism and facial acne.

salivary/plasma cortisol. CD was diagnosed on the basis of ACTH dependent hypercortisolism and cortisol suppression failure at LDST in the presence of a pituitary adenoma >6 mm.

Case 1. The typical CD

A 38 years old female was referred to our endocrine unit for decreased muscle strength, irritability, bloating, irregular menstrual cycle started 4 months before and progressive weight gain (about 6 kg over the last 5 years). At presentation she had a body mass index (BMI) of 27.8 kg/m² with central adiposity, a round face, hirsutism and facial acne, very thin skin with no striae, slim limbs, high blood pressure of 165/90mmHg with no treatment (Fig. 1).

Biochemical testing was consistent with CD (Table 1).

MRI of the pituitary revealed a left sided pituitary microadenoma of 9/7.5/5.5 mm, prominent to the left cavernous sinus (Fig. 2). Transsphenoidal pituitary adenectomy was successfully performed within 2 weeks from diagnosis, followed by adrenal insufficiency which requires corticosteroid cover until hypothalamic-pituitary-adrenal (HPA) axis recovery. At 3 months follow-up she was still under steroid cover.

Case 2. The Pseudo Cushing's

A 46-year old female with a history of CD diagnosed at age 20 with a pituitary microadenoma, treated at that time by conventional fractionated radiotherapy only, was referred to our endocrine unit for

Table 1. Hormonal assessment at presentation

Test	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6
Cortisol 8-9 am (4.82-19.5 mcg/dL)	22	12.2	25.80	25.3	51.25 (4)	18.51
ACTH (3-66pg/mL)	70	37	78	1	< 5 (4)	131.70
24h Urinary free cortisol (21-111 µg/24h)	951	55	1068.25	681	-	53
Midnight salivary cortisol <0.4 µg/dL	0.69	0.05	2.59	-	-	0.57
Midnight Plasma Cortisol µg/ dL	-	-	-	-	57.00 (4)	15.45
LDST <1. 8 µg/ dL	15.4	0.4	21.54	20	45.96 * (4)	14.16
DHEAS (70-495 mcg/dL)	203.10	-	-	49	-	-
Thrombocytes (150-400 x10³)	395 x10 ³	254 x10 ³	263 x10 ³	72 x10³	261 x10 ³	276 x10 ³
FSH 3-20mUI/mL	2.8	13	-	-	-	-
E2 49-291pg/mL	33	241	-	-	-	-
PRL 3-36 ng/mL for women, 2.64-13.13ng/m for men	9.61	9.8	-	-	-	39.26
TSH 0.5-5mUI/L	0.775	3	0.01	1.18	0.85	0.672
FT4 9-19 pmol/L	-	-	9	16	8.2	15.2
T3 80-200 ng/dL	-	-	71	108	124	

*based on a high dexamethasone suppression test (4).

extreme obesity, increased fatigability, poorly controlled diabetes mellitus, suspected of persistent CD.

At presentation, the patient was obese with a BMI of 40.2kg/m², round face with plethora, white abdominal striae, high blood pressure and a history of type 2 diabetes mellitus diagnosed 5years before, currently insulin treated in basal-bolus regimen; menstrual history revealed secondary amenorrhea since the age of 17, due to subtotal hysterectomy. Psychiatric evaluation revealed major depression. Biochemical testing revealed hyperglycemia and a high HbA1C value (8.75%) and hormonal screening showed a normal pituitary function (Table 1).

The contrast enhanced computer tomography imaging of the pituitary revealed an empty sella aspect. Antidepressive treatment improved compliance to weight loss programme aimed to control diabetes.

Case 3. The elusive CD

A 56-year old woman presented in an endocrine outpatient clinic for fatigue, weight loss, restlessness. She was obese with a BMI of 51 kg/m², hypertensive and had a medium nontender goiter (Fig. 3).

Laboratory tests revealed hyperglycemia, suppressed TSH (<0.03mUI/L) on two separate occasions, normal fT4 and T3. Thyroid ultrasound unveiled multinodular goiter. A diagnosis of grade 3 obesity, multinodular goiter with subclinical

hyperthyroidism was made and patient was commenced on thiamazole and referred to our endocrine unit.

Three weeks later she presented with a BMI of 47kg/m², facial plethora, purpura on her breasts and bruised easily at venepuncture sites. Full blood count showed neutrophilia with lymphocytopenia, normal platelets. Thyroid function tests revealed suppressed TSH (0.0164 mUI/L) with low fT4 and low radioiodine uptake in the thyroid. Adrenal function tests showed ACTH dependent CS (Table 1).

Contrast enhanced pituitary MRI revealed a left sided pituitary microadenoma of 7.5/7 mm, consistent with CD. Transsphenoidal pituitary adenomectomy excised a corticotroph adenoma of 1/1/0.6 cm, acidophilic, immunohistochemistry positive for ACTH and a Ki67 index of 1%.

Figure 2. Coronal pituitary MRI of case 1: left sided pituitary microadenoma of 9/7.5/5.5 mm, prominent to the left cavernous sinus.

Figure 3. Case 3. The Elusive CD presented with grade 3 obesity BMI of 51 kg/m², facial plethora, purpura on the breasts.

Postoperative biochemical remission of Cushing's required temporary cortisone cover. HPA axis recovered after 2 months postoperatively, when serum ACTH was normal, midnight plasma cortisol 1.44 mcg/dL and urinary free cortisol remain in low-normal range. Thyroid function tests also returned to normal.

Thyroidectomy was performed 3 months later to reveal a multinodular goiter with a papillary microcarcinoma 0.8/0.7 cm on the left lobe with minimal extrathyroidal extension, pT1a pNx, no lymphovascular extension identified, residual tumor present R1. Patient received a dose of 50 mCi 131I and LT4 therapy. Tyreoglobulin dropped to 0.04ng/mL (normal 0.9 - 54 / ng/mL), and no signs of local disease were present at 2 years postoperatively when the patient was still in remission of CD, with a BMI of 40kg/m² and her blood glucose was controlled by nutritional therapy only.

Case 4. Mild autonomous cortisol hypersecretion

This is a 44 years old man, a professional soldier known with high blood pressure since the age of 25 and thrombocytopenia, who complained of decreased muscle strength and abdominal adiposity. An abdominal CT scan revealed a right adrenal mass of 31/33/31mm with moderate iodophilia and reduction to 50 % of contrast load at 10 min after injection of contrast agent (Fig. 4).

At presentation he had a plethoric face, a BMI of 30.5kg/m², lumbar and limb ecchymosis; his BP was 150/90mmHg on treatment with sartan/calcium channel blocker.

The biochemical testing documented autonomous cortisol secretion (Table 1).

Figure 4. Abdominal CT scan of case 4: incidentally discovered right adrenal mass of 31/33/31mm.

Laparoscopic right adrenalectomy was performed. The pathology report showed adrenocortical adenoma - large cells with finely granulated eosinophilic cytoplasm, central nuclei with minimal pleomorphism, very low mitotic activity (2/50HPF), no atypical mitosis. The immunohistochemistry was positive for VIM; Keratin Pan; Inhibin, Melan A, negative for Calretinin; CrA; Ki67<1%; Weiss score 0.

Post-operative reassessment of HPA axis revealed adrenal insufficiency which was persistent 9 months postoperatively, requiring steroid cover, then HPA axis recovered within 12 months. Within 6 months the patient had lost 15 kg and normalized blood pressure. The hematologic consult reported blood smear count mild thrombocytopenia, idiopathic. At 4 yrs follow-up he remained normotensive and overweight, with a BMI of 27 kg/m².

Case 5. CS in pregnancy

This 33 years old pregnant woman was previously reported in detail as an outstanding case of CS (4).

She was first referred to endocrinology in the third trimester of gestation with a history of purple abdominal striae, weight gain and facial rounding since the 12th week of pregnancy which were overlooked as pregnancy-related hypercortisolism. In the second trimester of gestation she had been diagnosed with hypertension and one month later with gestational diabetes mellitus. On admission at 30 weeks of gestation the patient had central adiposity, a BMI of 30.17 kg/m², purple striae on her abdomen and thighs, high blood pressure, and a gravid uterus with upper limit 10 cm above umbilicus.

Adrenal function tests revealed suppressed ACTH and increased midnight plasma cortisol consistent with adrenal CS, confirmed by a 3.65/2.97 cm right adrenal mass seen at ultrasonography. At 34 week of gestation cesarean section was performed due to intrauterine growth retardation and a healthy male infant was delivered. The baby's weight at birth was 2250 g and length 43.5 cm. Postpartum retesting of the mother confirmed CS. Right adrenalectomy was performed at 6 weeks from giving birth. A 4.5cm adrenal adenoma was removed, consisting of hyperplasia of zona fasciculata and zona reticularis, without vascular or capsular invasion, or any atypical cells. Postoperatively the patient became adrenal insufficient and commenced on prednisone for the next 6 months, then recovered (4). She remained well 10 years postoperatively and her boy developed normally.

Case 6. CD with Thromboembolism

This is the case of a 73 years old man with a history of deep vein thrombosis and pulmonary thromboembolism 2 years before presentation, hypertension and type 2 DM, poorly controlled on insulin in basal-bolus regimen, who was incidentally discovered with a pituitary macroadenoma. The CT scan of the brain had been performed as screening for a syncopal episode 1 month before presentation.

At presentation he had a BMI of 26.4kg/m², plethoric face and controlled hypertension, had monocular vision due to posttraumatic optic atrophy on the right side and shrinkage of temporal superior visual field on the left. Hormonal testing for pituitary hormones revealed CD based on lack of cortisol suppression on LDST and the loss of circadian rhythm of cortisol, though the levels of free urinary cortisol were normal, possibly explained by that midnight and 8 am cortisol are similar and not very high (Table 1).

Pituitary MRI revealed an intrasellar mass of 26/15/21 mm, with suprasellar extension in contact with both carotid arteries and displacing the optic chiasm. Transsphenoidal adenomectomy excised a 20/15/5 mm mixt pituitary adenoma with atypical cells, suspected of atypical adenoma. Immunohistochemistry was not available. At 6 weeks postoperatively the biochemical testing showed normal ACTH (54.02 pg/mL) and morning plasma cortisol (15.01 µg/dL), normal UFC (29.02 µg/24 h), suppressed plasma cortisol at LDST (1.35 µg/dL), high PRL levels (23.63 ng/mL) and low testosterone (1.46ng/mL), suppressed TSH while on 50 µg of levothyroxine postoperatively. Prednisone and levothyroxine were stopped and treatment with cabergoline 2mg/week was initiated, but soon was dropped due to dizziness.

At 4 months postoperatively the pituitary scan revealed a residual tumor of 10/5/8 mm on the right anterior side, in contact with the optic chiasm and with the right internal carotid artery. Hormonal assessment revealed normal ACTH (53.97 pg/mL) and morning plasma cortisol (10.09, µg /dL) normal UFC (27.37 µg/24 h), normal midnight salivary cortisol (0.16 µg/dL), thyroid function tests returned to normal, high PRL 23.29 ng/mL, testosterone low 1.57 ng/mL. Given the fact that despite residual tumor the patient was eucortisolemic and that surgical reintervention was denied by the patient, while radiotherapy was hazardous in the context of optic chiasm proximity, a decision of close observation had been made. The patient remained eucortisolemic at 6 months, 1 and 2 years postoperatively, with left visual field normalization,

diabetes well controlled by metformin and glimepiride. However an acute coronary syndrome has occurred with transitory ST elevation (V1-V3) and hypotension, requiring coronarography which was refused by the patient. Despite this, he remained stable 30 months since presentation.

DISCUSSION

Cortisol excess in CD or CS has a large spectrum of manifestations from subclinical to overt syndrome, depending on the duration and amplitude of secretion. While obesity, hypertension, and glucose intolerance are the most common features of CS, these are more often encountered in individuals with metabolic syndrome without adrenal hyperfunction. In adults, signs and symptoms more specific of hypercortisolism include facial plethora, proximal muscle weakness with limb wasting, increased fat in the abdomen, face and supraclavicular fat pads, wide purplish striae, easy bruising (5).

All of our cases reported here, irrespective of the cause of Cushing syndrome had progressive central obesity and hypertension.

The degree of fat accumulation in Cushing's syndrome is variable. As shown in case 4 and 6, patients who diet and exercise rigorously may have little or no weight gain, however facial rounding, or central weight redistribution are usually present. The cause of abdominal fat accumulation may be cortisol-induced downregulation of adenosine monophosphate-activated protein kinase (AMPK), which controls lipid and carbohydrate metabolism (6).

The distinction between physiologic hypercortisolism as seen in severe obesity, major depressive disorder, poorly controlled diabetes mellitus or pregnancy and the pathologic secretion in CS/CD is not always easy, as illustrated by case 2, 3 and 5.

The psychiatric literature suggests that as many as 80% of patients with major depressive disorders have minimal increased cortisol secretion (7). Even in the presence of pseudocushingoid features in major depression, the diurnal rhythm of ACTH and cortisol secretion is usually preserved, as shown in case 2. Their abnormal cortisol secretion presumably results from HPA axis hyperactivity and disappears after remission of depression (7).

Normal pregnancy is associated with a hypertonic HPA axis and also an increased production of cortisol-binding globulin (CBG) and lack of suppression of serum cortisol after dexamethasone

(8). In addition, the placenta produces ACTH and corticotropin-releasing hormone (CRH). Thus, the biochemical diagnosis of CS during pregnancy is more challenging than in the nonpregnant state (8). Even though serum and salivary cortisol concentrations and urinary cortisol excretion are increased in pregnant women, the bedtime nadir of serum cortisol is maintained (9) which is an important diagnostic clue of CS in pregnancy. The loss of cortisol circadian rhythm illustrated in case 5, along with the suppressed ACTH supported the diagnoses of adrenal CS.

Classical CS/CD has a high prevalence (up to 75%) of anovulation as cortisol excess induces attenuation of pulsatile LH secretion indicating gonadotropin failure in the majority of women with CS (10), as we noticed in case 1, and women with untreated CS rarely become pregnant. However, there are over 220 reported cases of CD/CS diagnosed in pregnancy, mostly with important maternal and fetal complications (11). In pregnant women the prevalence of ACTH-independent cases is higher than in nonpregnant individuals. Of the reported cases, around 55 percent were ACTH-independent CS, while in nonpregnant women adrenal adenomas account for only approximately 15 percent of cases. Most of the rest cases in pregnancy were CD or bilateral adrenal hyperplasia. Ectopic ACTH syndrome has also been reported in seven pregnancies (11).

In occasional cases, pregnancy appears to induce CS. In a small number of patients, CS remits completely postpartum while in some cases CS reoccurs during multiple pregnancies (12). Possible explanations include placental CRH production, ectopic expression of receptors for human chorionic gonadotropin (hCG) in the adrenal cortex and estrogen-dependent nodular adrenal hyperplasia (12).

As reported in case 3, cortisol excess also affects thyroid function. TSH synthesis and release are inhibited by high doses of glucocorticoids, although basal levels are usually normal in CD/CS, as seen in cases 1, 4, 5, 6. Sometimes total and free T3 concentrations may be low because glucocorticoid excess decreases the conversion of T4 to T3. Despite these alterations, signs of hypothyroidism are not obvious and it is unusual for hypercortisolism in CD to suppress TSH to “thyrotoxic” level. In case 3, TSH suppression led to thyroid investigation and unveiled a thyroid carcinoma, which was therefore cured. A future use of glucocorticoid induced TSH suppression may improve diagnostic accuracy in CS (13).

None of the screening tests for CD/CS have

ideal sensitivity or specificity. For example, in one study of 369 overweight and obese patients with two additional features of CS, the specificity of these tests ranged from 84 percent to 96 percent (14).

As a result, the choice of test should be individualized to minimize false positive results. In our case series the first step in the evaluation was to determine whether the hypercortisolism was ACTH-dependent or ACTH-independent by measuring morning plasma ACTH. Second line evaluation was to assess midnight nadir of plasma or salivary cortisol and thirdly to test cortisol suppression by dexamethasone. CRH is not available in our country and inferior petrosal sinus sampling could not be performed in CD cases. However, in ACTH dependent cases, cortisol suppression failure at LDST in the presence of a pituitary adenoma >6 mm were pretty accurate in making the diagnosis of CD, as resulted postoperatively.

Patients with biochemical evidence of autonomous cortisol secretion, but without ‘specific’ clinical signs of CS, in which ACTH is suppressed (<5pg/mL) or low (5-20pg/mL) might be affected by hypertension, glucose intolerance/type 2 diabetes, obesity, dyslipidemia and osteoporosis due to this low grade autonomous cortisol excess (15-17).

The current guidelines indicate a surgical approach in a patient with autonomous cortisol secretion with a post-dexamethasone cortisol >5 µg/dL and in the presence of at least two of the above comorbidities potentially related to cortisol excess, if at least one is poorly controlled by medical measures (18, 19). Case 4 illustrates adrenal tumor with autonomous cortisol secretion associated with hypertension and obesity in which the adrenalectomy normalized weight and blood pressure.

As shown in case 6 a higher risk of venous thromboembolism (VTE) has been reported in most studies of patients with CS. The risk is possibly due to glucocorticoid-induced rise of plasmatic clotting factors, especially factor VIII, IX and von Willebrand factor, along with the decrease in fibrinolytic activity.

In a systematic review of 15 studies, a risk of 1.9 - 2.5% was reported for non surgical-related VTE, whereas risk of postoperative VTE varied between 0 and 5.6% (20). Pulmonary thromboembolism was considered the cause of death in 0-1.9% of CS patients and occurs mainly within 3 months of surgery(20). Another review showed that non surgical-related VTE risk in inpatients is highly variable and dependent on multiple individual factors: age >70 years, malignancy, acute infection, etc. Cumulative risks of deep vein

thrombosis and of pulmonary embolism in a high- risk population may increase up to 11% (21).

However in the perioperative setting, the odds of VTE in patients undergoing pituitary surgery or adrenalectomy seems lower than in patients undergoing orthopedic surgery for hip fracture (21). Thromboprophylaxis with low-molecular weight heparin / low-dose heparin / fondaparinux should be individualized in patients with CD/CS undergoing transsphenoidal or adrenal surgery taking into account the bleeding risk, especially in patients with increased risk of bleeding conditions (as thrombocytopenia in case 4) or those undergoing neurological surgery (20-22).

First line treatment in CD is transsphenoidal pituitary adenomectomy, with 60-80% remission rate, whereas in adrenal CS is adrenalectomy. 20-40 % of patients will need at some point a second line treatment with one or more drugs in order to decrease hypercortisolism (23, 24).

Remission after transsphenoidal surgery has been defined as morning serum cortisol < 5 µg/dL (<138 nmol/L) or UFC < 28–56 nmol/d (<10–20 µg/d) measured within the first week of operation (25). However, in patients with mild CD their postop morning cortisol and UFC may be normal, as they may not have suppressed corticotropes. In these patients, remission is documented by normal diurnal rhythm of plasma/salivary cortisol. In patients with normal cortisol after resection, as seen in case 6, or in those with early recovery of the HPA axis (within 6 months) as seen in case 3, CD is more likely to recur. Recurrence rate is estimated 15–66% within 5–10 years of initially successful surgery (25). Glucocorticoid replacement is required until the HPA axis recovers after successful surgery. This is expected to occur in 6–12 months after resecting corticotroph tumors in adults and around 18 months after unilateral adrenalectomy (25). We prefer using hydrocortisone for glucocorticoid replacement in doses of 20-25 mg/day in 3 doses, with the first dose at awakening (as in cases 1 and 3), but prednisone 5 mg/day was used in cases 4 and 5 as oral hydrocortisone was not available at the time. As indicated in the guidelines we would assess HPA axis recovery with a morning plasma cortisol (before dosing) every 3 months. If cortisol levels are < 5 µg/dL (138 nmol/L) the patient remains on glucocorticoids until retested in 3–6 months (25). An ACTH stimulation test will be performed if morning plasma cortisol > 7.4 µg/dL (200 nmol/L) (25). Once the baseline or stimulated

level of cortisol is > 18 µg/dL (500 nmol/L) the patient should stop corticosteroids and will be tested for normal diurnal rhythm of cortisol levels and LDST, in order to distinguish between HPA axis recovery and CS/CD recurrence.

After unsuccessful surgery or recurrence, medical therapy or bilateral adrenalectomy is needed in order to normalize cortisolemia. It is not clear whether there is any benefit in treating patients with eucortisolism, or a mild early recurrence if they are asymptomatic (25), as seen in case 6. Pasireotide is the first choice pituitary directed therapy approved for CD after unsuccessful surgery, however case 6 has not fulfill the hypercortisolism criteria for pasireotide indication.

Cabergoline could be a second line therapy in CD as dopamine receptor 2 is expressed in approximately 80% of corticotroph adenomas. However, cabergoline is of limited and variable value (26), and should be tried either in combination or if contraindications to or lack of other medications are present. At doses of 1.5–5 mg/week a response is expected to be around 30–50% in patients with mild or moderate disease (24). Cabergoline is only advantageous for CD in pregnancy where therapeutic options are otherwise limited (27, 28). However, the most experience in CS in pregnancy is with metyrapone, which is generally well tolerated, but hypertension and preeclampsia have been reported. Surgery should be avoided in the first 3 months of pregnancy, but in the second trimester can be successful (29), while in the third trimester laparoscopic adrenalectomy can also be performed up to 29 weeks of pregnancy. Mild Cushing's syndrome should be treated conservatively, baby delivery should be done as soon as possible, followed by treatment for CS as we did in case 5, while severe Cushing's syndrome, when diagnosed in the 1st trimester of pregnancy, should be followed by termination of pregnancy and specific treatment (8).

Steroidogenesis inhibitors alone or in combination have also proved efficacious in treating CS/CD. Pasireotide alone or in combination with cabergoline, and ketoconazole or mitotane plus metyrapone, and ketoconazole could minimize side effects while maximizing efficacy (23).

In selected cases of aggressive CD caused by macroadenomas, temozolomide can be used either alone, or in combination therapy with pasireotide, expecting a partial or complete response in usually around 80% of patients within 2 months of therapy (24).

Mifepristone, a glucocorticoid and progesterone

receptor antagonist, reported improvement in CS clinical manifestations in 87% of subjects in SEISMIC trial (23).

Radiation treatment for CD is usually a third choice treatment when surgery and medical therapy failed to control hypercortisolism. Stereotactic radiosurgery (20Gy) is preferred for microadenomas that are not in the proximity of the optic chiasm, while fractionated radiotherapy (42-45 Gy) is used in the other cases. When the location of pituitary tumor is not known, entire sella must be irradiated. The efficacy of stereotactic radiosurgery in normalizing cortisol levels is between 55-85% that can be raised up to 85-100% with adjuvant medical therapy (30). When conventional megavoltage radiation is used as primary therapy, as it was in case 2 from our series, the success rate in cortisol normalization drops to 15-35 % in adults, as opposed to 80% in children. The response in adults treated with conventional fractionated radiotherapy is higher when used as secondary therapy after transsphenoidal surgery. Also normalization of cortisol appears sooner after radiosurgery (7-33 months) than after fractionated radiotherapy (18-42 months) (30). Side effects of both types of irradiation include hypopituitarism and a possible increase in cerebrovascular morbidity and mortality.

In conclusion, Cushing's syndrome has a plethora of manifestations that can sometimes be misleading. This case series highlights some specific aspects of CS that can be valuable tools in assisting its diagnosis and therapy. Management of CS needs a pluridisciplinary approach to deliver the best individualized treatment choice for each patient for optimal control of hypercortisolism and management of comorbidities.

Conflict of interest

The authors declare that they have no conflict of interest.

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