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CASE REPORT

PITFALLS OF LONG-TERM HIRSUTISM AS CENTRAL FEATURE OF CUSHING'S DISEASE WITHOUT IDENTIFICATION OF A PITUITARY MASS ON A MENOPAUSAL WOMAN

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Summary

Introduction: Tumor-related hirsutism may be caused by an Adrenocorticotropin (ACTH) dependent Cushing's syndrome (CS) despite heterogeneous presentation.
Case report: A 57-year female, known with impaired glucose tolerance, was admitted for longtime progressive hirsutism and recently changed characteristics, in association with asthenia, headache, changes in mood, depression, sleep disturbances, weight gain. Specific laboratory test confirmed ACTH-dependent CS but no tumor mass was highlighted on pituitary Magenetic Resonance Imagery, neither was at abdominal, ovarian and thoracic Computed Tomography scan. Hormonal tests revealed high total testosterone for a postmenopausal woman and slightly elevated levels of 17-hydroxyprogesterone in addition to increased HOMA index, suggestive for insulin resistance. Since no underlying mass was identified, a conservative approach was initially offered to the patient: 400 mg daily ketoconazole alongside 1500 mg daily metformin, diet, exercise in order to weight loss. Further changes of the management are needed.
Conclusion: ACTH - dependent Cushing's syndrome is usually accompanied by hirsutism into larger frame of cardio-metabolic co-morbidities. Hirsutism features may change over time and this may be suggestive for an additive cause to otherwise idiopathic type. Another particular aspect is mild Cushing's disease without tumor imagery identification. Hypophysectomy under these circumstances is challenging and medical therapy should be tried first until a definitive therapeutically solution is done.
Abbreviations: mg = miligram, ACTH = Adrenocorticotropic Hormone, BMI = Body Mass Index, CS= Cushing's syndrome, CT = Computed Tomography, DHEA-S= Dehydroepiandrosterone Sulfate, DXM = dexamethasone, FT4 = Free Thyroxine, HAIRAN = Insulin-Resistant Acanthosis Nigricans, MRI = Magnetic Resonance Imaging, SHBG = Sex Hormone-Binding Globulin, TSH = Thyroid Stimulating Hormone

Résumé

Pièges de l'hirsutisme à long terme comme élément central de la maladie de Cushing, sans identification d'une masse hypophysaire chez une femme ménopausée

Introduction: L'hirsutisme lié à la tumeur peut être causée par un syndrome de Cushing (CS) dépendant de corticotrophine (ACTH) en dépit de la présentation hétérogène.
Présentation de cas: Une femme de 57 ans, connue avec une intolérance au glucose, a été admise pour hirsutisme progressif de longue durée et a récemment changé les caractéristiques, en association l'asthénie, des céphalées, des changements d'humeur, la dépression, les troubles du sommeil, le gain de poids. Les analyses de laboratoire spécifique ont confirmé l'ACTH dépendant de CS, mais aucune tumeur n'a été mise en évidence à l'imagerie de résonance magnétique de la glande pituitaire où à TC abdominale, ovarienne et thoracique. Les testes hormonaux ont montré un niveau élevé de la testostérone totale pour une femme en post-ménopause et des niveaux légèrement élevés de 17-hydroxy-progestérone en plus de l'augmentation de l'indice HOMA, suggestif pour la résistance à l'insuline. Vu qu'on n'a identifié aucune tumeur sous-jacente, une approche conservatrice a été initialement proposée à la patiente: 400 mg de kétoconazole par jour avec 1500 mg de metformine par jour, du régime alimentaire, de l'exercice pour perdre du poids. Des modifications utérieures de la gestion sont nécessaires.
Conclusion: Le syndrome de Cushing dépendant est généralement accompagné d'hirsutisme dans un cadre plus large de co-morbidités cardio-métabolique. Les traits de l'hirsutisme peuvent changer au fil du temps suggerant une cause additionelle au type idiopathique. Un autre aspect particulier est la maladie de Cushing légère sans identification imagistique de la tumeur. L'hypophysectomie dans ces circonstances est une défi et le traitement médical doit être premièrement essayé jusqu'à ce qu'une solution thérapeutique soit prise.

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Key words: hirsutism, Cushing's syndrome, insulin resistance, cortisol, testosterone

Mots clés: hirsutisme, syndrome de Cushing, résistance à l'insuline, cortisol, testostérone

Introduction

Apart from iatrogenic Cushing's syndrome (CS), pituitary dependent CS or Cushing's disease (CD) represents one of the most common cause of endogenous Cushing's syndrome leading to cortisol excess- related hirsutism. (1) Classical co-morbidities are: centripetal obesity, hypertension, impaired glucose tolerance, emotional lability, osteoporosis, menstrual and sexual dysfunction, etc. (1,2) Almost half of patients with CS have increased hair grow of the body. (2,3) Other causes of hirsutism are: polycystic ovary syndrome, hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) syndrome, congenital adrenal hyperplasia (classic and nonclassic), androgen-secreting tumors (ovarian, adrenal), hyperprolactinemia, drugs as danazol, etc. (4) Rapid progression of a hirsutism requires various assessments as: testosterone, DHEA-S (Dehydroepiandrosterone Sulfate), free/total testosterone, functionality of corticoid axes, etc. (5) The first-line treatment for CD is pituitary surgery followed by disease remission and improve of clinical signs but some cases do not have an adequate identification of a tumor, so hypophysectomy may be postponed until further imagery scans or if the clinical picture allows it while the patient is medically treated. (6)

Aim

This is a case report of a female with hirsutism for several years which became more severe in association with different metabolic anomalies that finally lead to the diagnosis of CD. The informed consent was signed by the subject who agreed to use the images below.

Case report

Medical history

This is a 57-year-old female, known with long-term history of un-investigated and un-treated hirsutism, associated with a recent increased grow rate and larger area of distribution. At the age of 32, she was investigated for infertility without relevant causes. She had no children, neither abortion. She entered menopause at age of 52. She is also known with menopausal osteopenia, Hashimoto thyroiditis, dyslipidemia, high blood pressure and impaired glucose tolerance. The medical family history includes: a sister with diabetes mellitus and father with ischemic coronary heart disease and high blood pressure.

Current assessment

On admission, clinical parameters are: Body Mass Index (BMI) of 38.2 kg/m^2, blood pressure of 150/90 mmHg, heart beat rate of 70/min. The main complaints are: hirsutism, asthenia, proximal muscle weakness, persistent headache, changes in mood, sleep disturbances, and weight gain. Physical examination revealed: a Ferriman Gallwey score of 18, moon face, buffalo hump. (fig. 1, 2)

*Laboratory tests showed high levels of morning plasma cortisol with loss of circadian rhythm, ACTH levels within the upper reference range and a very high testosterone levels. (table 1) Non suppression at DXM (Dexamethasone) 1 mg (milligram) overnight test was followed by 2 mg * 2 days DXM test confirming endogen CS. Inhibition at 8 mg * 2 days confirmed CD. Insulin resistance syndrome was confirmed by HOMA index of 3.5 (normal <2). Mild increase of 17-hydroxyprogesterone was detected (of 0.62 ng/mL, normal between 0.13 0.51 ng/mL) while gonade axes assays values suggestive of menopausal status.*

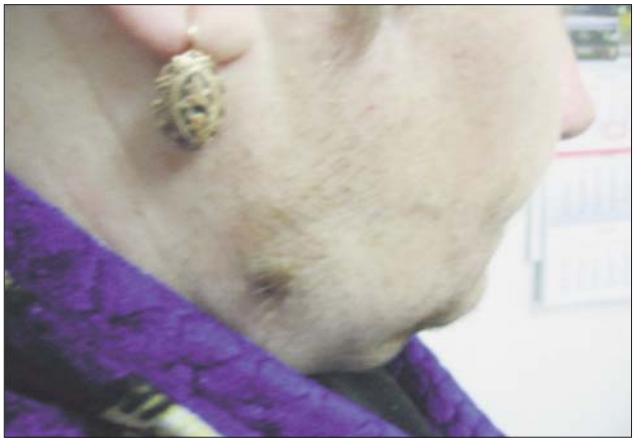

Figure 1 - Severe hirsustism on side burn, lower jaw and upper lip in a 57-year woman with Cushing's disease (Ferriman Gallwey score of 18)

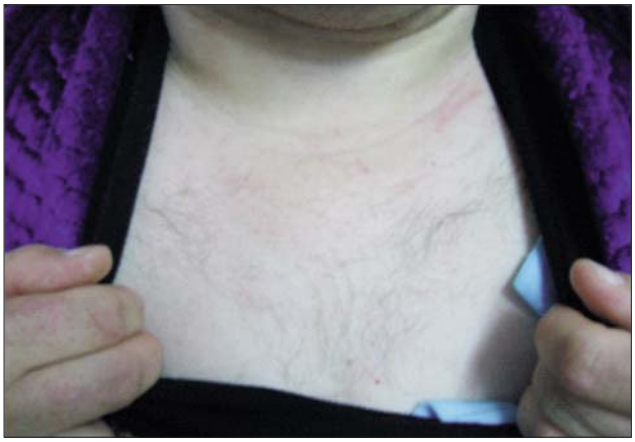

Figure 2 - Male pattern distribution of hairiness on chest in a postmenopausal woman of 57 years with Cushing's disease

Table 1 - Biochemical and hormonal profile of a 57-year old female with Cushing's disease-related hirsutism

Parameter	Patient's value	Normal Limits	Units
plasma cortisol (6 a.m.)	521	172-497	nmol/L
plasma cortisol (11 p.m.)	232	71.1-286	nmol/L
Plasma morning ACTH	41.2	< 46	pg/mL
24-h free urinary corisol	457	100-379	nmol/24-h
plasma morning cortisol*	376	< 50	nmol/L
plasma morning cortisol**	348	< 50	nmol/L
plasma morning cortisol**	257.2	#	nmol/L
serum total testosterone	6.1	0.2-0.75	ng/mL
serum sodium	141	136-145	mmol/L
serum potassium	3.5	3.7-5.4	mmo/L
Total cholesterol	224	< 200	mg/dL
Triglycerides	186	< 150	mg/dL
Fasting plasma glucose	107	60-99	mg/dL
Fasting plasma insulin	13.3	2.6-24.9	μUI/mL

ACTH = Adrenocorticotropic Hormone; 24-h = 24-hours; * after DXM 1mg overnight test; ** after DXM 2 day 2 mg suppression test; *** after DXM 2 day 8 mg suppression test; # > 50% of baseline plasma morning cortisol reduction is consistent with the diagnosis of Cushing's disease

Pituitary MRI (Magnetic Resonance Imagery) as well as adrenal CT (computed tomography) scan showed no tumor in association with the diagnosis of CD. Inferior petrosal sinus sampling test was not available. Complementary tests related to her medical records confirmed normal thyroid function (TSH of 1.24 μUI/mL, normal 0.4-4 μUI/mL, FT4 of 1.06 ng/dL, normal 0.89-1.76 ng/dL, under daily μg 50 of L-Thyroxine) with positive anti-thyreoglobulin antibodies (of 283.3 UI/mL, normal 70-225 ng/mL).

Therapy and further recommendations

Pituitary neurosurgery was postponed and medical treatment with 400 mg daily ketokonazole was offered to the patient in addition to metformin (500 mg three time per day), antihypertensive medications (atenolol 50 mg daily and indapamide 1.25 mg daily), vitamin D (0.5 μg daily Alpha-Calcidol), statin (atorvastatin 20 mg/day). Diet, exercise in order to weight loss was recommended in attempt to ameliorate hirsutism. Close endocrine and imagery check-up is recommended with a further definitive decision of pituitary or adrenal surgery depending on response to medical therapy, co-morbidities, imagery scan results, patient's options, etc.

Discussion

Mild signs of androgen excess may be found in CS, endogenous hypercortisolism being positively correlated with free androgen levels due to SHBG reduction. (1,2,3,4) Clinically aspects in CD- related hyperandrogenism are usually mild they are virtually absent in women with adrenal CS; generally the levels of androgens are not tight correlated with virilisation syndrome. (7,8) A rapidly progressive severe hirsutism is suggestive for corticoadrenal carcinoma. (9) We consider a particularity of this case a double hit etiology of hirsutism. The long-term history of hirsute appearance and infertility is less probable associated with CD through entire reproductive period of time, probably a polycystic ovaries syndrome or idiopathic type while recent changes of hirsutism features (within 2 years) in association with cardio-metabolic high risk parameters is caused by CD. Consistent with double hit theory, the levels of total testosterone levels were only slightly elevated (of 1.75 ng/mL, normal between 0.2 and 0.75 ng/mL) when she was first evaluated during her reproductive years, while, currently, an atypical high level of total testosterone for CD was confirmed. In addition to discussing differential diagnosis of hirsutism in this female subject, we mention that non classic adrenal hyperplasia might has been involved but currently the diagnosis is less probable due to 17-hydroxyprogesterone levels and normal adrenal aspect at imagery scans. (10,11,12). Insulin resistance itself which was also found in this patient is another possible cause of hirsutism but this is first connected with CS, rather than non-hypercorticism related metabolic syndrome. (13,14) Hirsutism can also occur in older women, beginning a few years before menopause, and continuing for a few years after menopause; this is caused by ovarian estrogen secretion which declines rapidly, whereas ovarian androgen production continues for a few years after menopause. (15) In this case, secondary amenorrhea was registered five years before CD was confirmed and high Follicle Stimulant Hormone showed that high androgens did not suppress the gonad axe. Pathology of the patient which is potentially linked with the etiology of hirsutism is hypothyroidism since it can indirectly affect serum free testosterone levels. (16) In addition, L-Thyroxine therapy may lead to hirsutism, causing a decrease in SHBG, transcortin, and estradiol levels, and an elevation in the level of DHEA-sulfate. (16) However, as pointed, an adequate thyroid substitution was offered to the patient. Another particular aspect in this case is the lack of suggestive imagery findings for CD which might not be so rare but it increases the difficulty of management. (17,18,19) Until choosing the definite line of therapy, the panel of drugs we choose for the

patient is expected to improve hipercorticism- related hirsutism and insulin resistance. The alternatives to pituitary surgery and/or irradiation are pasireotide, cabergoline, bilateral adrenalectomy, etc. (18,19,20)

Conclusion

ACTH - dependent Cushing's syndrome is usually accompanied by hirsutism into larger frame of cardio-metabolic co-morbidities. Hirsutism features may change over time and this may be suggestive for an additive cause to otherwise idiopathic type. Another particular aspect is mild Cushing's disease without tumor imagery identification. Hypophysectomy under these circumstances is challenging and medical therapy should be tried first until a definitive therapeutically solution is done.

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Conflict of interest: nothing to declare

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