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Glucocorticoid resistance syndrome: let's give it a thought

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Abstract

Background: Generalized glucocorticoid resistance syndrome has a tremendously heterogenous and very broad clinical spectrum. This syndrome is caused by loss of glucocorticoid receptor (GR) function due to mutation leading impairment in GR signalling. It presents with hypercortisolism, hypertension, enlarged adrenal glands but no Cushingoid features. Extensive endocrinologic investigations and genetic analysis can determine this disease and help in managing the sequalae of this syndrome. We report this case after looking into its rarity and presentation which would give an insight about this disease.

Case presentation: A 26-year-old female presented with, hirsutism, acne, deep voice (which was patients main concern), hypercortisolism, raised testosterone, without features of Cushing's. On examination she was normotensive, hirsutism and poorly developed breast with ambiguous genitalia. On investigation, she was found to have left adrenal mass, hypercortisolism and had resistance to dexamethasone suppression test. She underwent left open adrenalectomy followed by continued medication with dexamethasone.

Conclusion: This syndrome should be considered as a differential diagnosis in patients with hypercortisolism but without any features of Cushing's syndrome. It is a difficult diagnosis for a urologist, endocrinologist help should be sought for better outcomes and adherence on long-term hormonal treatment.

Keywords: Glucocorticoid, Dexamethasone resistance, Adrenal mass, Ambiguous genitalia

1 Background

In recognition of Professor George P. Chrousos' extensive and ground-breaking research work in this field, it has been proposed that the term "Chrousos Syndrome" is used in place of "Primary Generalized Familial or Sporadic Glucocorticoid Resistance" [1]. The first patient presenting with glucocorticoid resistance syndrome was described in 1976, in whom high blood pressure was incidentally found in association with hypokalemia and high urinary free cortisol reaching 30–40 times the normal reference values [2].

Glucocorticoids (GC) such as cortisol regulate multiple physiological functions, notably those involved in development, metabolism, inflammatory processes and stress, and exert their effects upon binding to the glucocorticoid receptor (GR, encoded by NR3C1 gene in humans). Generalized glucocorticoid resistance syndrome, due to GR loss-of-function mutations, may be related to the impairment of one of the GC signalling steps. To date, 31 NR3C1 loss-of-function mutations have been reported in patients presenting with various clinical signs such as hypertension, adrenal hyperplasia, hirsutism or metabolic disorders associated with biological hypercortisolism but without Cushing syndrome signs and no negative regulatory feedback loop on the hypothalamic–pituitary–adrenal axis. The main signs at presentation are very variable from resistant hypertension, bilateral adrenal hyperplasia likely related to increased ACTH levels but not exclusively, hirsutism to isolated renin–angiotensin–aldosterone system abnormalities in a context of 11βHSD2 deficiency [3].

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2 Case presentation

26-year-old female patient child of a consanguious marriage came with complaints of excessive facial hair growth since last 10 years, poor development of breasts and occasional episodes of headache since last 10 years. She was diagnosed to have hypertension and was taking tablet amlodipine 5 mg (not regularly). She had history of tuberculosis at age of 14, took antitubercular medications for 9 months. At 15 years of age patient had an episode of myalgia and weakness of all 4 limbs (Sudden onset Quadriparesis). She was diagnosed to have renal potassium loss as her trans-tubular potassium gradient was 14, Serum Potassium—1.9 mmol/l, Urine potassium—27.8 mEq/l, Plasma osmolality—315 mOsm/l, Urine osmolality—350 mOsm/l. Her echocardiogram showed U waves, ST segment depression with T-wave inversion and Q-T prolongation. Patient was started on oral potassium supplements and was still on Syrup K-sol.

2.1 Clinical findings

She was moderately built and nourished, Blood pressure—130/70 mm/hg, Pulse—72 beats/minute. She had hirustism, acne, deep voice and no cushingoid features. Poorly developed breast with normal nipple and areola. Clitoromegaly (+2.5 cm), poorly developed vaginal openings with fusion of the lower part of labia (Fig. 1). Systemic examination was unremarkable.

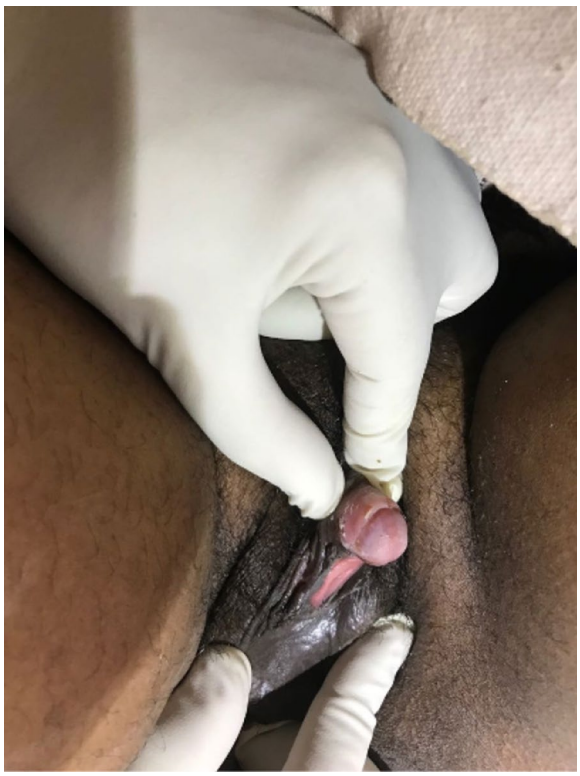

Fig. 1 Ambigous gentalia

2.2 Diagnostic assessment

Upon reviewing her earlier reports over the years. Sequence as follows:

In 2006: Ultrasound Abdomen was normal, her biochemistry: 2007: Serum Cortisol: > 63.44 ug/dl (6.2–19.4). Karyotype: 46 XX; Normal female karyotype (Fig. 2).

In 2010: Serum Cortisol 44.72 ug/dl (6.2–19.4), Serum Testosterone: 121.46 ng/dl (14–76), Serum Androstenidione: 9.87 ng/ml (0.3–3.3), Serum Prolactin: 17.17 ng/ml (2.8–29.2), Serum DHEAS: 248 ug/dl (145–395), Serum ACTH: 980 pg/ml (0–46), Serum 17 alpha OH progesterone: 10.89 (0.2–1.3), Serum Estradiol: 98 pg/ml, Serum FSH: 4.94 IU/L, Serum LH: 6.41 IU/L. CT Scan abdomen and pelvis revealed left adrenal gland to be enlarged and measured approximately 5 cm in anteroposterior and 1 cm in thickness. Right adrenal gland was normal. MIBG scan was normal.

She came to us in 2017 with all the above reports and was again investigated by us after consultation with endocrinologist.

Her biochemistry profile: Serum Cortisol: > 75 ug/dl (3.09–16.66), 24 h Urine Cortisol: 3025.88 (20.9–297), Serum ACTH: 668 pg/ml (7.9–600), Serum Testosterone: 121.46 ng/dl (14–76), Serum Aldosterone: 25.46 ng/dl (25–315), Serum Renin Activity: 2.14 ng/ml/h (0.06–4.69), 24 h urine metanephrine: 225 (normal) and Resistance to Dexamethasone suppression test. Ultrasound abdomen suggested an enlarged left adrenal gland measuring $87 \times 80 \times 60$ mm in size which appeared heterogenous, solid and echogenic and shows few hypodense components in it. MRI Abdomen with contrast showed a well-defined heterogenous mass seen in the left suprarenal region mass of size $72 \times 70 \times 45$ mm. It appeared to invade the superior pole of left kidney and mass was reaching medially upto the tail of pancreas and superiorly till the inferior surface of the spleen. Suggestive of neoplastic etiology of adrenal gland? Adrenal Cortical Carcinoma (Fig. 3). MRI pituitary protocol and visual acuity test was normal.

2.3 Therapeutic intervention

With all the above reports and after endocrinologist opinion. She was put on Tab. Dexamethasone 1 mg once daily pre operatively. Perioperative Inj. Hydrocortisone 100 mg 8 hourly she underwent left open adrenalectomy which was uneventful (Figs. 4, 5). Her postoperative recovery was unremarkable and was discharged on Tab. Dexamethasone 5 mg once daily.

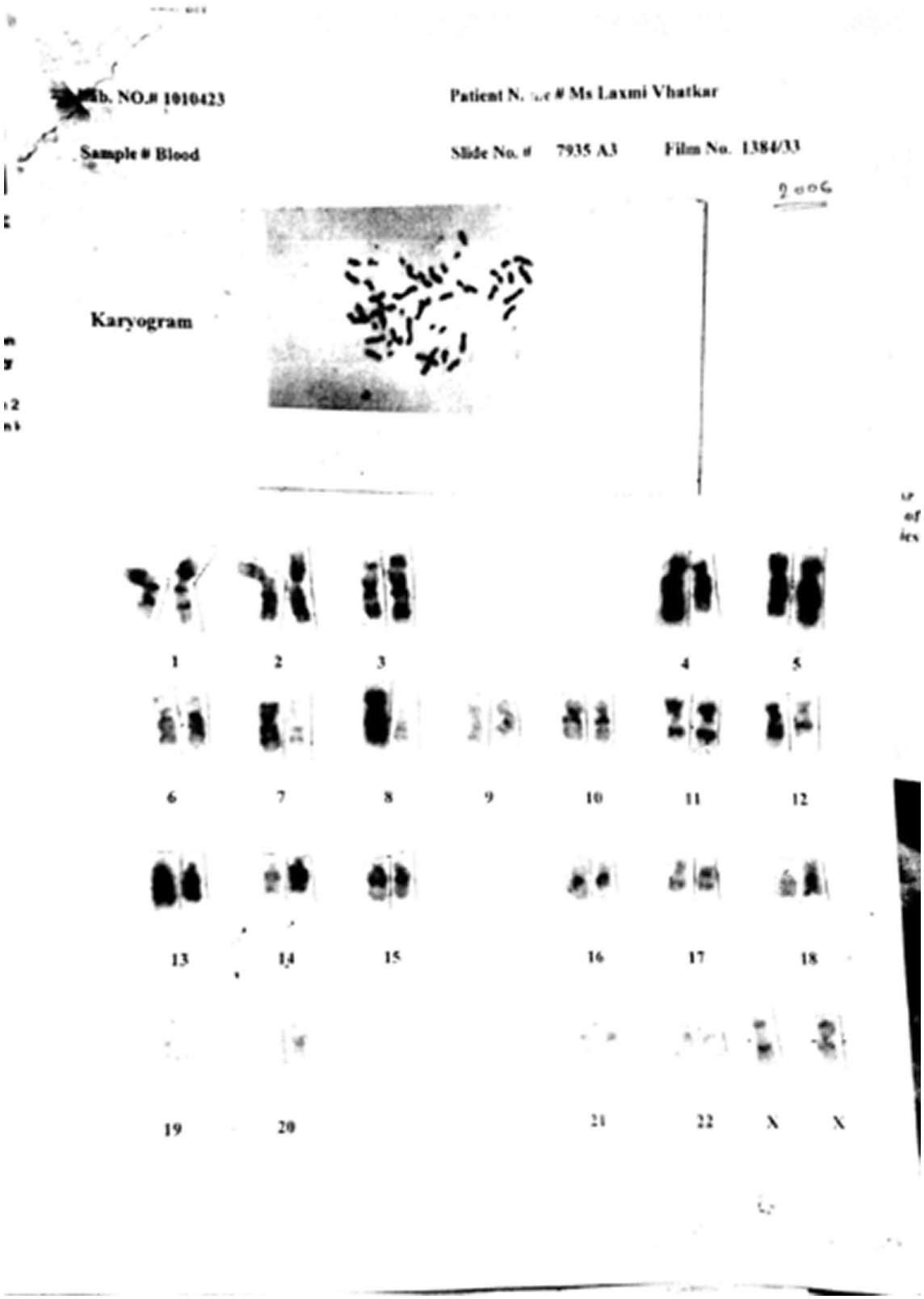

Fig. 2 Karyotype

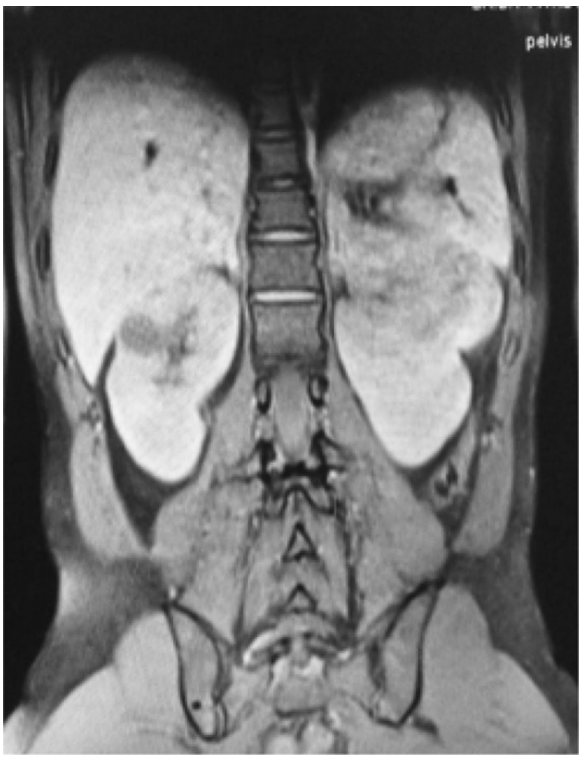

Fig. 3 MRI abdomen with left adrenal mass

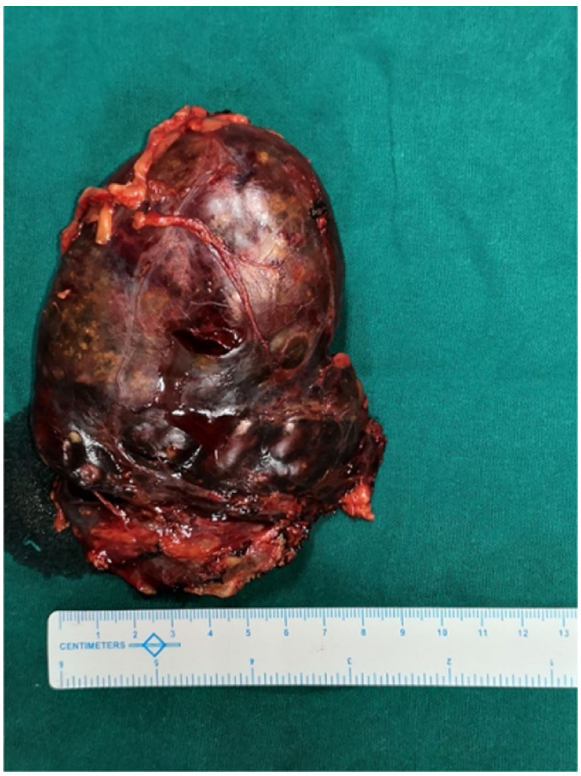

Fig. 5 Excised specimen

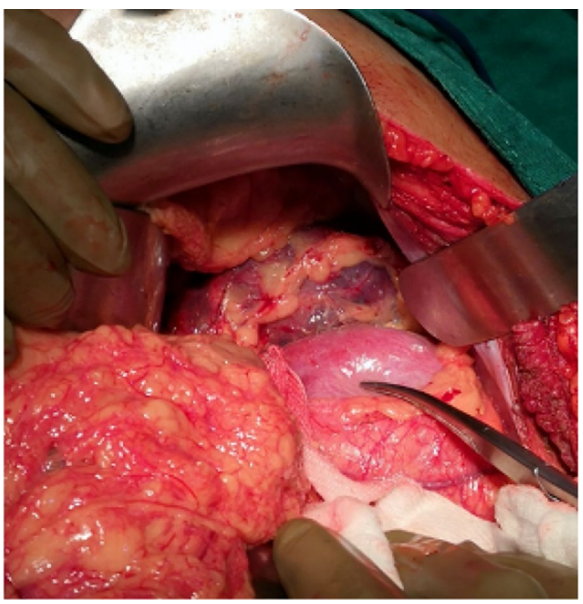

Fig. 4 Intraoperative left adrenal mass

2.4 Follow-up and outcomes

Her histopathological report suggested adrenal neoplasm composed of mature fat cells mixed with sheets of hematopoietic cells (Marrow elements). Suggestive of adrenal myelolipoma.

Her follow-up biochemistry: Serum Cortisol: > 75 ug/dl → 61.77(3.09 – 16.66), Serum ACTH: 668 pg/ml → 302 (7.9–600), Serum Testosterone: 121.46 ng/dl → 44.5 (14–76).

She is still on tablet Dexamethasone 5 mg once daily.

3 Discussion

Generalized glucocorticoid resistance syndrome is defined by an absence of overt Cushing's syndrome signs (no skin weakness, muscle atrophy, or osteoporosis), associated with biological hypercortisolism consisting of high urinary free cortisol (UFC) and an absence of negative feedback loop of cortisol on HPA, defined as 8-AM cortisol level > 50 nmol/L after overnight 1 mg dexamethasone suppression test (DST) [4].

Differential diagnosis of generalized glucocorticoid resistance includes: (1) mild forms of Cushing's disease, in which hypercortisolism is accompanied by normal or mildly elevated ACTH concentrations; (2) pseudo-Cushing's states, such as generalized anxiety disorder and melancholic depression; (3) conditions associated with elevated serum concentrations of corticosteroid-binding globulin, such as normal pregnancy and estrogen

treatment; (4) essential hypertension, hyperaldosteronism, and other causes of mineralocorticoid-induced hypertension; and (5) other causes of hyperandrogenism or virilization, such as idiopathic hirsutism, polycystic ovarian syndrome, and congenital adrenal hyperplasia (CAH).

The aim of treatment is to suppress the excess secretion of ACTH, thereby suppressing the increased production of adrenal steroids with mineralocorticoid and androgenic activity. Treatment involves administration of high doses of mineralocorticoid-sparing synthetic glucocorticoids, such as dexamethasone (1–3 mg/d). Long-term dexamethasone treatment should be carefully titrated according to the clinical manifestations and biochemical profile of the affected subjects [5].

If one suspects Chrousos syndrome in clinical practice, a detailed personal and family history should be obtained, meanwhile physical examination should include an assessment for signs of mineralocorticoid and/or androgen excess. Suspected patients should then undergo a detailed endocrinologic evaluation with particular emphasis on the measurement of serum cortisol concentrations and determination of the 24-h urinary free cortisol (UFC) excretion on 2 or 3 consecutive days. Diagnosis of Chrousos syndrome is confirmed by sequencing of the coding region of the NR3C1 gene. Endocrinologist evaluation and subsequent treatment should be sought for in these cases.

3.1 Patients perspective

She was happy that her adrenal mass was excised and her disease was diagnosed and treatment was started. She was advised for clitoroplasty and may need vaginoplasty for which patient has to still follow-up.

Abbreviations

ACTH: Adrenocorticotropic hormone; DHEAS: Dehydroepiandrosterone-sulphate; FSH: Follicle stimulation hormone; LH: Luteinizing hormone; MRI: Magnetic resonance imaging; CT: Computed tomography; MIBG: Metaiodobenzylguandine.; HPA: Hypothalamus-pitiutary-adrenal; BHSD: Hydroxysteroid dehydrogenase.

Authors' contributions

SS:Operating surgeon, Drafting Report. RR: Assisting surgeon, DraftingReport. VS: Conception, Interpretation of data. VSv: Conception,Interpretation of data. AM: Proof Reading. SM: Proof Reading. DM:Proof reading. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval has been waved and obtained from the ethicalcommittee of Dr D.Y Patil Medical University Pune 411018. India. Consent to Participate was taken from the patient.

Consent for publication

A written informed consent for publication was obtainedfrom the patient.

Competing interests

The authors declare thatthey have no competing interests.

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