Reminder of important clinical lesson

Crossing the other side of the algorithm: a challenging case of adrenal Cushing's syndrome

Imelda Digna Soberano Antonio, Mark Anthony Santiago Sandoval, Frances Lina Lantion-Ang

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines

Correspondence to Dr Imelda Digna Soberano Antonio, imeemd777@yahoo.com**Summary**

The diagnosis of endogenous Cushing's syndrome and its aetiology involved documenting the hypercortisolism and then determining whether that hypercortisolism is adrenocorticotrophic hormone-dependent (ACTH-dependent) or not. Hence, following the algorithm, an undetected ACTH level points to an adrenal Cushing's while a detectable or elevated ACTH level points to either a pituitary or ectopic Cushing's syndrome. The authors present a case of florid adrenal Cushing's syndrome initially presenting with a normal ACTH level, which led to the investigation for an ACTH-secreting tumour. Adding to the confusion, a MRI done showed an intrasellar focus. Knowledge of how ACTH-dependent (versus ACTH-independent) Cushing's syndrome manifests clinically, supported by results of repeat laboratory tests, led to the true diagnosis. This case illustrates that a detectable ACTH does not rule out an adrenal Cushing's syndrome nor does a positive pituitary imaging confirm Cushing's disease.

BACKGROUND

Basing on the current algorithm for diagnosing and differentiating the aetiology of Cushing's syndrome, this case is important because the laboratory results were misleading and more suggestive of another aetiology. Initially, despite the collaboration of a neurologist, neurosurgeon, radiologist and an endocrinologist, there was misdiagnosis at initial presentation regarding the aetiology. Serum adrenocorticotrophic hormone (ACTH) was misleading in this case as it narrowed the differential diagnosis to either a pituitary or an ectopic ACTH-secreting tumour. Adding to the confusion was the presence of a 2 mm focus on pituitary MRI and a 26% suppression of 8 a.m serum cortisol after an overnight 8 mg dexamethasone suppression test (DST), which seemed to strengthen a pituitary cause.

CASE PRESENTATION

A 19-year-old lean female, with no known comorbidity, started to gain weight. She developed moon facies, supraclavicular and dorsocervical fat pads, purple striae near the axilla and lower abdominal area, thinning of skin, and menstrual irregularity. A year later, she was rushed to a hospital when she had a seizure, manifested as upward rolling of the eyeballs, and tonic-clonic movement of all extremities. Assessment was Cushing's syndrome, with secondary seizure disorder. There were no investigations done. She was transferred to our institution where similar findings were noted- moon facies, central obesity, purple striae 2–3 cm wide, thin and smooth skin. Laboratory investigations confirmed the excess cortisol: 24 h urine free cortisol (604 µgm/24 h), which is greater than four times the upper limit of normal (NV=20–90 µgm/24 h), elevated 8 a.m serum cortisol at 1087 nmol/l (NV=154–638 nmol/l) after an overnight 1 mg dexamethasone suppression test. Her serum ACTH was detectable (10.4 pg/ml). At this point, an ACTH-secreting pituitary tumour was highly

entertained. MRI of the pituitary showed a 2 mm focus (figure 1). Other tests showed elevated fasting blood sugar, elevated triglycerides and LDL-cholesterol. Subcutaneous insulin, metformin and statin were started. Plan for transphenoidal excision was on the way when patient was lost to follow-up.

She resurfaced at the emergency room a year later, presenting with behavioural changes (ie, combativeness- biting herself and her father, shouting at people, interspersed with periods of depression). Her blood pressure was slightly elevated at 150/90 mm Hg. She had a body mass index of 30 kg/m². Physical findings still showed moon facies, supraclavicular and dorsocervical fat pads, with central obesity and fair thin skin, no hyperpigmentation at the skin creases and knuckles, no hirsutism (Ferriman-Gallwey score of 2), no acne, with large purple striae near the axilla and lateral abdominal area (figure 2), and atrophic lower extremities. There was no lateralising sign on neurologic examination.

INVESTIGATIONS

As was mentioned, initial investigation was toward documenting the hypercortisolism. Having confirmed the excessive cortisol, serum ACTH level was taken to determine the aetiology of cortisol excess. With the result showing a detectable/normal ACTH, investigation towards an ACTH-secreting pituitary tumour (being the more common) was carried out. Both the pituitary MRI and an overnight 8 mg DST supported the diagnosis, or so it was thought.

When patient presented again at the emergency room, review of her records were made. The result of the 8 mg dexamethasone suppression test showed a reduction of cortisol from 1197 to 891.2 nmol/l equivalent to a 26% reduction. This is not consistent with Cushing's disease which is expected to show a cortisol suppression of less than 50% of baseline value (sensitivity 90%, specificity 100%).¹

Since the ACTH level cannot differentiate pituitary from ectopic Cushing's syndrome, a referral to neurosurgery for inferior petrosal sinus sampling was considered. But at the same time, serious doubt began to be cast if this were truly an ACTH-dependent Cushing's syndrome. ACTH will

stimulate both the zona fasciculata (where cortisol is produced) and zona reticularis (where androgen is produced). The expected hyperpigmentation and hyperandrogenism accompanying a long-standing ACTH-secreting tumour were absent. Hence, a repeat ACTH was requested.

Cranial MRI (2/01/10)

Figure 1 MRI of the pituitary showing small 2 mm non-enhancing low attenuation lesion in the right intrasellar area.

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Figure 2 Patient prior to her illness (left) and with Cushing's syndrome before her surgery (right).

Figure 3 CT scan of the adrenal, showing a 2.4×1.9×2.8 cm adenoma on the right.

Figure 4 The excised right adrenal gland with the adenoma.

The result of the repeat (second determination of) ACTH was undetectable. And so was the third ACTH determination. This significantly changed the direction of management. Inferior petrosal sinus sampling was deferred and an adrenal CT scan was requested. CT image (figure 3) revealed a well-defined, homogenous, round mass arising from the right adrenal gland, measuring 2.4×1.9×2.8 cm. It is isodense to the liver and hypodense to the spleen, with an unenhanced Hounsfield Unit (HU) of 17. If the mass were less than 10 HU, a diagnosis of adrenal adenoma can be readily made. Since the mass exhibited more than 10 HU, CT with intravenously administered contrast material followed, and the washout calculated; benign lesions typically demonstrate more than 50% washout.² The mass exhibited mild uniform enhancement (HU=52), and fast washout with percentage washout 72.4%, consistent with an adrenal adenoma. The left adrenal gland is unremarkable. After ruling out pheochromocytoma with a normal

24 h urine metanephrine of 0.44 mg (normal value up to 1 mg/24 h), a laparoscopic adrenalectomy converted to open was subsequently carried out. Figure 4 showed the excised right adrenal with the adenoma.

OUTCOME AND FOLLOW-UP

Postadrenalectomy, the patient followed up at the outpatient department significantly improved. The result of the histopath showed adrenal adenoma (figure 5). Her blood sugar (98–112 mg/dl premeals) and blood pressure level were normal (90–110/60–70 mm Hg) off insulin and anti-hypertensive medication. At home and during her follow-up, her behaviour has improved significantly, being more conversant, with pleasant disposition and her mood not depressed. She was able to resume her usual activities.

She is maintained on prednisone 5 mg daily. An ACTH stimulation test will be done subsequently to determine sufficiency of the function of the remaining left adrenal prior to finally discontinuing prednisone.

DISCUSSION

The diagnosis of Cushing's syndrome can still be very confusing and challenging. It needs both expertise and a high degree of clinical knowledge. Once diagnosis is made, considerable expertise is still required to determine its aetiology while avoiding possible pitfalls and misdiagnosis.³

The clinical picture of Cushing's syndrome is significantly variable and depends on age, sex, severity, and duration or chronicity.⁴ With regard to age, Cushing's syndrome occurring in children will present with retarded linear growth, reflecting the effect of cortisol on epiphyseal closure. With regard to sex, decreased libido and erectile dysfunction are seen in males, while menstrual irregularity, hirsutism and alopecia in females.⁵ Likewise, purplish striae may not be seen in Cushing's syndrome with rapid onset.⁴

Figure 5 Histopath of the right adrenal gland and adenoma.

Features more specific of Cushing's syndrome include typical habitus (centripetal obesity) 97%, hirsutism 80%, broad violaceous cutaneous striae 67%, ecchymoses, 65%, proximal myopathy 62%.⁶ Other symptoms and signs such as hypertension, osteoporosis, obesity/weight gain, diabetes are non-specific and therefore, are less helpful in diagnosing the condition.⁶

Typical features of chronicity of Cushing's syndrome include thin, fragile skin, central obesity, hypertension, plethoric moon facies, purple striae and easy bruisability, glucose intolerance or diabetes mellitus, gonadal dysfunction, osteoporosis, proximal muscle weakness, signs of hyperandrogenism (acne, hirsutism), and psychological disturbances (depression, mania, psychoses).⁵⁻⁷ This patient clearly had evidence of chronic Cushing's syndrome- thin, fragile skin, central obesity, hypertension, moon facies, purple striae and easy bruisability, diabetes mellitus, gonadal dysfunction (amenorrhea), and psychological disturbances. Chronicity or an indolent course is generally seen in pituitary and adrenal Cushing's syndrome (except in cortisol-secreting adrenal carcinoma). Ectopic ACTH-secreting tumour usually runs a rapid course except for the ACTH-secreting carcinoid tumours which also run an indolent course.⁶

Seizure is a rare feature of Cushing's syndrome. Lodish *et al* reported a case of a 6-year-old girl with ACTH independent Cushing's syndrome secondary to bilateral adrenal hyperplasia. She presented with hypertension and seizures, and MRI shows changes consistent with posterior reversible encephalopathy syndrome.⁸ In our patient who also presented with seizure and hypertension 2 years prior during a previous admission at another hospital, it was not clear what the aetiology of her seizure was. Tests previously done were unavailable for review. However, her electrolytes, blood glucose level, acid-base status and brain imaging (MRI) done at our institution were normal and hence, unable to explain her previous seizure.

The clinical suspicion of Cushing's syndrome is confirmed by documenting the excess cortisol production-(1) elevated 24 h urine free cortisol, at least four times the upper limit of normal, (2) elevated 8 a.m serum cortisol

after an overnight 1 mg dexamethasone test and (3) elevated midnight salivary cortisol.⁹

The confirmation of elevated cortisol entails excluding other conditions that may cause similar elevation in cortisol (ie, pseudoCushing's state). These include liver disease, obesity, or depression.

The next step is to determine whether the Cushing's syndrome is ACTH-independent (suppressed ACTH level) or ACTH-dependent (normal or increased ACTH level), that is, whether the patient has primary adrenal disease or an ACTH-secreting tumour.

Because the ACTH level in this patient was normal, subsequent investigation was directed towards determining pituitary versus extrapituitary cause of Cushing's syndrome. But as it turned out the patient had adrenal Cushing's syndrome.

The issue raised by this case report is whether the diagnosis of ACTH-independent Cushing's syndrome can be excluded when ACTH is detectable/not suppressed below a reference range.

In a study by Klose *et al* on 34 patients with ACTH-dependent and 22 patients with ACTH-independent Cushing's syndrome, they found one patient with ACTH-independent (adrenal) Cushing's syndrome with one plasma ACTH measurement within but at low end of reference range. A second measurement of ACTH was below the reference range. It has been shown that a single plasma ACTH level at the lower end of the reference range does not exclude adrenal Cushing's, particularly if there is mild or occult disease.^{9 10} In a study by Invitti *et al*, plasma ACTH concentrations were detectable in 58% of patients with ACTH-independent Cushing's syndrome and fell within the normal range in 28%.¹¹ Our patient's case is interesting in that despite florid manifestation of Cushing's syndrome, her initial ACTH level was within normal. Only the second and third measurement of ACTH level done a year later in this patient showed undetectable level. Was the initial normal ACTH level just a laboratory error? Having ruled out error in transcribing result after verification with the laboratory personnel, a normal/detectable ACTH level is more plausible to be taken as such than an undetectable

ACTH level. ACTH in blood is considered highly unstable because of the proteolytic degradation,^{12–15} hence an error in ACTH assay is in not being able to detect it when it should really be detectable.

In such case where ACTH is normal, doing a peripheral corticotropin releasing hormone (CRH) test is recommended. The ACTH response to CRH should be blunted in adrenal Cushing's syndrome due to negative feedback and is usually exaggerated in Cushing's disease if the pituitary tumour expresses the CRH receptor.^{16 17}

Another source of confusion in this case is the suppression of 8 a.m cortisol after an overnight high-dose (8 mg) dexamethasone (DST). This test is used to differentiate pituitary from ectopic Cushing's syndrome based on the retained capacity of the pituitary adenoma to be suppressed by cortisol at a higher 'setting'. In adrenal Cushing's syndrome, there is lack of cortisol suppression after high-dose DST because cortisol secretion is autonomous and the ACTH secretion is already very low and cannot be further reduced.⁸ Our patient however showed a 26% reduction of cortisol from baseline at around the time when ACTH was detectable. How can this be explained in a patient with adrenal Cushing's syndrome? The available literature is not clear on this. But this could very well be a reflection of fluctuation in cortisol secretion in patients with Cushing's syndrome, rather than real suppression.^{16 18} Because microadenomas can be detected in up to 10–20% of individuals without known pituitary disease,¹⁹ a positive imaging study does not prove Cushing's disease as we also learnt from this patient. In the same manner, a negative imaging study does not rule out pituitary source.¹⁹ However, in patients with classic clinical presentation and dynamic biochemical study compatible with Cushing's disease, the presence of a focal lesion greater than 6 mm makes a definitive diagnosis, and no further evaluation is required.^{19 20}

The same imaging caveats hold for adrenal mass, which may be present in ~6% of adult/older subjects at autopsy.⁶ Hence, imaging studies should only be done and the result interpreted based on prior hormonal studies made. Cortical adenomas are very uncommon in individuals less than 30 years of age.⁶ Its presence in young patients, as in our patient, together with concordant hormonal finding is therefore indicative of adrenal Cushing's syndrome.

Learning points

- ▶ A normal ACTH does not rule out an adrenal Cushing's syndrome.
- ▶ The presence of a pituitary adenoma does not confirm Cushing's disease, especially when <6 mm and dynamic biochemical study is not consistent with Cushing's disease
- ▶ Suppression of 8 a.m cortisol with 8 mg high-dose dexamethasone can also be seen in adrenal Cushing's syndrome, especially at values <50%.
- ▶ The absence of hyperandrogenic manifestations suggested an ACTH-independent cause of Cushing's syndrome. Thus, it is prudent to repeat laboratory tests if the results are not compatible with the clinical presentation.

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