Case Report

Endogenous Cushing’s syndrome and Graves’ disease in a patient with history of steroid intake- A diagnostic dilemma.

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Abstract:-
Objective: To report a case of simultaneous occurrence of Graves’ disease and Cushing’s syndrome in a patient who had unusually low serum cortisol levels.

Case report: A 34 year male presented with generalised weakness, proximal myopathy and low backache on a background history of prolonged steroid intake. On examination he had facial puffiness with plethora, petechiae, ankle edema and bilateral posterior subcapsular cataract. Bone mineral density revealed severe osteoporosis. A provisional diagnosis of iatrogenic Cushing’s syndrome was considered at this stage. However as he was off steroids for the last six months, a possibility of endogenous Cushing’s was also kept in mind. Investigations revealed an elevated 24 hour urinary free cortisol on two occasions but an unusually low basal serum cortisol level. The serum cortisol level was suppressed to 2 µg/dl after a low dose dexamethasone suppression test (LDDST), thus leading to confusion in the diagnosis of endogenous Cushing’s syndrome. He was also found to have Graves’ disease on further evaluation and started on methimazole. Four weeks later he was euthyroid and a repeat basal cortisol at this time was characteristically elevated with a serum cortisol post LDDST of 12 µg/dl, clearly suggesting a diagnosis of endogenous Cushing’s syndrome.

Conclusion: There have been very few reports of the simultaneous occurrence of Graves’ disease and Cushing’s syndrome in the same patient. The coexistence of Graves’ disease and Cushing’s syndrome poses a diagnostic dilemma because of the
effects of thyroid hormone on cortisol metabolism and cortisol binding globulin (CBG) and vice versa.

**Introduction:**
There have been very few reports of the simultaneous occurrence of Graves’ disease and Cushing’s syndrome in the same patient.¹ The coexistence of Graves’ disease and Cushing’s syndrome poses a diagnostic and therapeutic dilemma because of the effects of thyroid hormone on cortisol metabolism and cortisol binding globulin (CBG) and vice versa. The effects of hypercortisolism on thyroid hormone metabolism and thyroid autoimmunity. In addition, if there is a history of long standing steroid intake in such a patient, the interpretation of investigations becomes still more challenging.

In hyperthyroidism, serum CBG levels are decreased and return to normal after an euthyroid state is achieved.²,³ The reduced CBG in turn may lead to a falsely low serum cortisol levels posing a diagnostic challenge in the evaluation of Cushing’s syndrome. Also in hyperthyroidism the adrenocorticotropic hormone (ACTH) levels may be increased due to accelerated cortisol metabolism further complicating the interpretation of the values.

Similarly in Cushing’s syndrome, hypercortisolism as a result of its immunosuppressive action may lead to remission of Graves’ disease with relapse after correction of hypercortisolism. Hypercortisolism also leads to suppression of TSH and decreased tri-iodo thyronine (T3) as a result of inhibition of deiodinase 2. Serum thyroid binding globulin (TBG) is also reduced in hypercortisolism leading to lower levels of thyroid hormones.⁴

Hence we present a case report of a patient who had a long history of steroid intake, certain features suggestive of iatrogenic Cushing’s but with laboratory evidence of endogenous Cushing’s syndrome with a diagnosis of Graves’ disease on subsequent evaluation, for the rarity of its presentation and for the diagnostic challenge it posed.

**Case report:**
A 34 year old male apparently well in January 2012 started taking dexamethasone 1.0 mg orally daily by self medication for weight gain as he was losing weight. He continued taking these tablets for 15 months during which he gained his lost weight, but along with that he also developed facial puffiness. After discontinuation of steroid intake, over a period of few months he also developed generalised weakness, bodyache, proximal myopathy and low backache. There was no history of abdominal striae or ecchymosis. There was no history of headache/vomiting/visual symptoms/abdominal mass/abdominal pain.

He presented to us with these complaints along with exacerbation of backache in November 2013. On examination he was of moderate build with a BMI of 19.1 kg/m². He had a resting pulse rate of 106 per minute. His blood pressure was 110/70 mm Hg with no postural fall. General physical examination revealed facial puffiness with plethora, petechiae over his upper limbs, tinea corporis over the chest, abdominal obesity, (fig.1) onychomycosis of both feet and ankle edema. Thyroid gland was normally palpable. Ophthalmologic examination revealed posterior
subcapsular cataract in both eyes but fundus and visual fields were normal. Musculoskeletal examination revealed thoracic kyphosis (fig. 2) and tenderness over lumbar spine with proximal myopathy in lower limbs. There were no other signs of Cushing’s syndrome.

Since the patient had predominance of skeletal symptoms and subcapsular cataract with a history of prolonged steroid intake, a provisional diagnosis of iatrogenic Cushing’s syndrome with secondary adrenal insufficiency was made.

The morning serum cortisol was 4.4 µg/dl. The midnight serum cortisol was also done as there were certain subtle features of endogenous hypercortisolism and it was found to be 5.4 µg/dl. In view of the altered diurnal rhythm further tests to rule out endogenous Cushing’s were done. The low dose dexamethasone suppression test (LDDST) revealed a serum cortisol of 2.0 µg/dl. 24 hour urinary free cortisol (UFC) was elevated on two occasions (3168 µg/day and 2570 µg/day) suggesting a diagnosis of endogenous Cushing’s syndrome. However, though two of the screening tests were positive, the diagnosis of endogenous Cushing’s was still in doubt as he had a low morning cortisol and an equivocal midnight cortisol.

Routine evaluation also revealed a TSH of 0.23 mIU/L (0.4-4.0). The T3 and T4 levels were 2.45 nmol/l (1.2-2.75) and 194 nmol/l (58-168) respectively. Anti TPO antibodies were negative. USG thyroid revealed a mildly enlarged thyroid gland with increased vascularity. A thyroid uptake scan revealed diffusely increased uptake in both lobes suggestive of Graves’ disease.

The spine radiographs showed osteopenia with height reduction in D7 and L1 vertebra. (Fig. 3) DEXA scan revealed a T score of -5.0 at spine and – 3.4 at hip. Other relevant investigations revealed impaired glucose tolerance, normal liver and renal function tests.

Meanwhile, he was started on Methimazole 5 mg tablets twice daily for hyperthyroidism. After four weeks patient was clinically and biochemically euthyroid. A repeat 8 am cortisol at this time was 23.6 µg/dL and the midnight serum cortisol was 8.2 µg/dL. The serum cortisol after a repeat post LDDST was 12 µg/dL, unequivocally suggesting the diagnosis of endogenous Cushing’s syndrome. (table 1)
Table 1. Investigations of adrenal axis

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Values at presentation</th>
<th>Values (after euthyroidism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S cortisol (8 am)</td>
<td>4.16 µg/dL</td>
<td>23.6 µg/dL</td>
</tr>
<tr>
<td>S cortisol (midnight)</td>
<td>4.76 µg/dL</td>
<td>8.2 µg/dL</td>
</tr>
<tr>
<td>LDDST</td>
<td>2.0 µg/dL</td>
<td>12 µg/dL</td>
</tr>
<tr>
<td>24 Hour UFC (day1)</td>
<td>3168 µg/day</td>
<td>2890 µg/day</td>
</tr>
<tr>
<td>24 Hour UFC (day2)</td>
<td>2570 µg/day</td>
<td>3035 µg/day</td>
</tr>
<tr>
<td>Serum ACTH</td>
<td>11.9 pg/mL (10-46)</td>
<td>-</td>
</tr>
</tbody>
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Since two of the screening tests were positive for Cushing’s syndrome, further work up for localizing the source of hypercortisolism were done. The serum ACTH was 11.9 pg/mL (10-46). MRI brain revealed a normal pituitary and CT adrenals with contrast revealed normal adrenals. A CECT Thorax was also done to look for any ectopic source but did not identify any source.

In view of definite hypercortisolism but with an unidentified source, and as IPSS is not available in our centre, a repeat imaging six months later was planned. He was started on ketoconazole 600 mg per day and gradually increased to 1200 mg a day. After 3 months of medical therapy, his 24-hour UFC was reduced by more than 50% and the patient is presently being followed up.

Discussion:
A very few case reports of the coexistence of Cushing’s syndrome and Graves disease in a same patient have been reported. One such case has been reported by Krienes of a 56 year old female who presented with disease and was simultaneously diagnosed to have Cushing’s syndrome. This patient had unusually low serum cortisol levels (2 - 7 µg/dl) despite the increased urinary cortisol levels. Because of this discrepancy the plasma CBG was estimated and found to be low (20 versus normal value of 35±4 mg/l). After achieving euthyroidism, the morning serum cortisol levels had risen to 21 µg/dl. Lambert had earlier reported in 1964, a case of simultaneous occurrence of the two disorders in a patient, but in contrast to the previous case, the plasma cortisol levels in this patient were more characteristic of Cushing’s syndrome (29-42 µg/dl).

Our case was similar to the case reported by Kreines, as he had simultaneous occurrence of Graves disease and Cushing’s syndrome with an unusually low serum cortisol levels. However, in addition our patient had a history of steroid intake for a long duration with signs of iatrogenic Cushing’s, further complicating the interpretation of low cortisol levels. The patient had elevated 24 hour UFC but with an unexpectedly low serum cortisol levels posing a difficulty in distinguishing iatrogenic cushing’s from endogenous cushing’s. However once the patient was
euthyroid after treatment of hyperthyroidism, his morning serum cortisol levels increased from 4.16 μg/dL to 23.6 μg/dL and his midnight serum cortisol increased from 4.76 μg/dL to 8.2 μg/dL suggesting a diagnosis of endogenous Cushing’s.

The explanation for the low cortisol levels when the patient was hyperthyroid could be due to the reduction of CBG. This would have been supported by the demonstration of a low plasma CBG but unfortunately it was not estimated. However, the fact that there was a significant increase in serum cortisol levels after achieving euthyroidism suggests that the low cortisol levels was in fact due to the low CBG as a result of hyperthyroidism. Previous studies have demonstrated that in thyrotoxicosis, serum CBG levels are reduced and return to normal after induction of the euthyroid state.2,3 Reduction in cortisol levels and reserves in thyrotoxic patients and its normalization after euthyroidism5–7 could be due to variation related to CBG.

In the present patient it may be suggested from the history that Graves’ disease developed before Cushing’s syndrome as the patient had an unexplained weight loss. We must also keep in mind the possibility that the abnormalities of cortisol metabolism could entirely be due to those attributable to disease alone, wherein increased cortisol production, excretion, conjugation, degradation and responsiveness to administered ACTH and even increased circulating ACTH all have been described. The presence of some physical findings of Cushing’s syndrome and the increased levels of cortisol after the achievement of euthyroidism make it clear, however, that Cushing's syndrome was truly present.

Also it is interesting to observe that other than the initial weight loss, this patient did not have obvious symptoms of Graves’ disease and that hyperthyroidism was diagnosed incidentally on biochemical evaluation. Hypercortisolism because of its immunosuppressive action might have lead to suppression of the Graves’ disease.

**Conclusion:**
This case highlights the importance of considering a possibility of endogenous Cushings syndrome even when there is a long standing history of steroid intake. Also it emphasizes that the clinician should be aware of the interaction of hyperthyroidism on cortisol metabolism and the effect of hypercortisolism on thyroid metabolism and thyroid autoimmunity. In a patient who has endogenous Cushing’s syndrome but with unusually low serum cortisol levels, one should carefully look for evidence of hyperthyroidism.

**References:**

Figure legends:
Figure 1: Facial puffiness with plethora
Figure 2: Kyphosis with abdominal obesity
Figure 3: Generalized osteopenia with D7 vertebral collapse