Primary Pigmented Nodular Adrenocortical Disease: a rare cause of Cushing’s syndrome

Catriona J Kyle, Marcus J Lyall, Roland H Stimson

Edinburgh Centre for Endocrinology and Diabetes, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom, EH16 4TJ.

Case Report

A 34-year-old lady presented with a 3 year history of central weight gain, hypertension and secondary amenorrhoea.

On examination, she was obese with a BMI of 33 kg/m² with a buffalo hump. There was evidence of generalised muscle weakness, mild hirsutism and violaceous striae over the abdomen.

Initial 24-hour urinary free cortisol (UFC) was raised (536 nmol/24hr) and subsequent overnight dexamethasone suppression test (DST) was elevated at 593 nmol/L.

Low and high dose DST confirmed the diagnosis of ACTH-independent Cushing’s syndrome with an unusual trend of increasing plasma cortisol levels compared with baseline. Adrenal imaging revealed 4 right adrenal nodules (7-11mm in size) and a normal left adrenal.

CT Report:

Right Adrenal: 4 nodules; 2 x 7mm, 9mm and 10mm respectively

Left Adrenal: Normal

Initial Investigations

<table>
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<th>Investigation</th>
<th>Day</th>
<th>Value</th>
<th>Reference Range</th>
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<tr>
<td>Dexamethasone 0.5mg QDS</td>
<td>Day 0</td>
<td>&lt;10 441</td>
<td>7-51 ng/L &lt;50 nmol/L &lt;100 nmol/24hrs</td>
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<td>408 212</td>
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<td>Cortisol UFC</td>
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<td>ACTH</td>
<td>Day 4</td>
<td>&lt;10 489 346</td>
<td>7-51 ng/L &lt;50 nmol/L &lt;100 nmol/24hrs</td>
</tr>
</tbody>
</table>

Treatment and Subsequent Investigations

Metyrapone was used to normalise UFC pre-operatively and she underwent right adrenalectomy.

Post-operatively, cortisol levels remained elevated with an undetectable ACTH.

Pathological examination of the excised adrenal revealed characteristics of primary pigmented nodular adrenocortical disease (PPNAD), a rare familial cause of Cushing’s syndrome.

Discussion

Primary Pigmented Nodular Adrenocortical Disease (PPNAD) is a form of micronodular adrenal hyperplasia causing ACTH-independent Cushing’s syndrome. PPNAD may be isolated or appear as part of the Carney Complex, characterised by myxomas, skin hyperpigmentation and endocrine over-activity.

Isolated PPNAD is an autosomal dominant inherited condition often associated with germline mutations in PRKAR1A and PDE. An important biochemical feature of PPNAD is a paradoxical rise in cortisol post high dose DST. This is thought to be mediated through a glucocorticoid receptor effect on the protein kinase A catalytic pathway.

Bilateral adrenalectomy is the treatment of choice. Diagnosis of this rare condition can be challenging as imaging may not always identify the bilateral micronodular changes. This case represents an extremely unusual cause of Cushing’s syndrome (<1% of all cases) and highlights the importance of considering rare diagnoses before referring for surgery.

References

4. Louiset E, Stratakis CA, Pernaudet V et al. The paradoxical increase in cortisol secretion induced by dexamethasone in primary pigmented nodular adrenocortical disease involves a glucocorticoid receptor-mediated effect of dexamethasone on protein kinase A catalytic subunits. J Clin Endocrinol Metab. 2009;94:2406-2413

Further Management

Since adrenalectomy, this patient has lost 2-3kg of weight, blood pressure has normalised and the buffalo hump has disappeared. There were no other features of Carney complex observed in this patient. The original CT scan was re-assessed and two further nodules were noted retrospectively in the left adrenal.

Subsequent investigations revealed ongoing suppressed ACTH and raised midnight salivary cortisol at 3.6 nmol/L. After overnight DST, plasma cortisol remains raised at 221 nmol/L. Left adrenalectomy is now planned.

Subsequent investigation of her mother (who complained of a 10-year history of weight gain and uncontrolled hypertension despite 3 agents) also confirmed ACTH-independent Cushing’s syndrome with an increase in UFC following high dose DST.

Genetic testing of these patients has failed to reveal the causative mutation thus far, although further testing of alternative candidates (e.g. PRKACA) is in progress.