Case Report

Unravelling the Mystery in a Case of Persistent ACTH-independent Cushing's Syndrome

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Abstract

Introduction: We present a rare variety of adrenocorticotrophic hormone (ACTH)-independent Cushing's syndrome known as primary pigmented nodular adrenocortical disease (PPNAD). Clinical Picture: The patient initially underwent unilateral adrenalectomy for what was thought to be a left adrenal adenoma. Outcome: Partial resolution of symptoms and demonstrable persistent hypercortisolism after surgery prompted further evaluation with findings leading to the diagnosis of Carney complex. A review of the adrenal histology was consistent with PPNAD. Conclusion: This entity of PPNAD, which has rarely been reported in Asians, forms part of the Carney complex. The diagnosis may not be simple and straightforward, as illustrated in this patient.

Ann Acad Med Singapore 2006;35:892-6

Key words: Adrenocortical hyperfunction, Cushing's syndrome, Nodular adrenocortical disease

Case Report

A Malaysian Chinese male patient, CMO, first presented at the age of 22 years with a 2-week history of severe spontaneous low backache with no prior trauma or back injury. A lumbar spine X-ray showing marked osteopenia and compression fracture of the first lumbar vertebra led to findings of osteoporosis confirmed on the dual energy bone densitometry with T scores of –3.93 and –3.70 in the hip and spine respectively.

Further questioning revealed significant central abdominal weight gain over the preceding 6 months. There was also proximal weakness of the lower limbs with the onset of the backache. He also noticed spontaneous easy bruisability. There had been no headache, visual disturbance, hip pain or peptic ulcer pain. The patient was the shortest amongst his family of 8 siblings, with no known family history except a sister with hearing impairment. He had no history of diabetes mellitus or hypertension. He did not drink alcohol and did not have a history of long-term steroid use.

Clinical features suggestive of Cushing's syndrome were found on examination, including centripetal fat distribution with abdominal striae, proximal myopathy and skin atrophy with spontaneous bruises. He also had rounded facies with acne, plethora and a prominent dorsocervical hump with supraclavicular fat pads. Blood pressure readings were mildly elevated in the range of 140 to 150/90 to 100 mm Hg. There was no visual field defect. He had normal secondary sexual characteristics and was clinically euthyroid.

The 24-hour urinary free cortisol and 17 hydroxy-corticosteroids were elevated at 2.7 (NR, 0.22 to 1.05) umol/day and 74.1 (NR, 17 to 55) umol/day, respectively, with adequate total urine volume collection of 1700 mL. The baseline 8 am cortisol level was 742.2 (NR, 193.2 to 579.6) nmol/L and there was failure of suppression with the 1 mg overnight dexamethasone suppression test, with a post-suppression cortisol level of 656.1 nmol/L. Both the low-dose and high-dose (Liddle's 2-day 8mg) dexamethasone suppression tests also failed to show suppression, with post-suppression cortisol levels of 650.5 nmol/L and 778.5 nmol/L, respectively, which confirmed Cushing's syndrome and suggested a non-pituitary source. The baseline adrenocorticotrophic hormone (ACTH) level of 11.5 ng/L (10 to 40) was consistent with that in ACTH-independent Cushing's syndrome. Endocrine evaluation for other secondary causes of osteoporosis revealed normal calcium profiles, thyroid function, gonadotrophin-stimulated responsiveness and testosterone levels. A

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Table 1. Sequential Bone Densitometry Results Before and After Initial Unilateral Adrenalectomy

Date	Hip T-score	Hip BMD (g/cm^2)	Spine (L2-4) T-score	Spine (L2-4) BMD (g/cm^2)
16/3/1993 (before left adrenalectomy)	-3.93	0.627	-3.7	0.610
27/1/1996 (after left adrenalectomy)	-1.95	0.651	-3.69	0.623
26/7/1999	-4.46	0.565	-3.18	0.679
14/9/2002	-2.90	0.536	-3.50	0.597
1/6/2005 (after right contralateral adrenalectomy)	-2.40	0.693	-2.50	0.710
15/11/2006	-2.30	0.702	-1.80	0.787

computed tomography (CT) scan of the adrenals reported a 1-cm left adrenal adenoma. A left adrenalectomy was subsequently performed with findings of an open haemorrhagic cyst measuring 4 x 2 x 2 cm with an adjacent compressed adrenal gland. The discrepancy between the imaging nodule size and the operative size of the cyst was postulated to be due to a subsequent haemorrhage within the nodule. The microscopic histological description was that of nodular hyperplasia, which did not concur with the radiological finding of an adenoma.

In the 6 months following adrenalectomy, there was resolution in his clinical features with less facial rounding and plethora (Fig. 1). His weight decreased from 51 to 49.7 kg within 2 months and the central adiposity decreased. However, surprisingly, he had not required any postoperative steroid supplementation. The backache also persisted. The overnight 1 mg dexamethasone test, when repeated, showed failure of suppression with a post-suppression cortisol level of 304.1 nmol/L, as were the low-dose and high-dose dexamethasone suppression tests with post-suppression cortisol levels of 412 nmol/L and 477 nmol/L respectively. The repeat 24-hour urinary cortisol was still elevated at 1.02 mmol/day, further indicating a persistent hypercortisolic state. The ACTH level was low at 9.5 ng/L, as would be expected in ACTH-independent Cushing's syndrome. A repeat CT scan of the adrenals showed a bulky and nodular right adrenal gland. The initial histology of adrenal nodular hyperplasia, in the absence of clinical pituitary disease and probable bilateral adrenal disease, pointed towards primary pigmented nodular adrenocortical disease. Clinical features of Carney complex, in which primary pigmented nodular adrenocortical disease (PPNAD) forms an important feature, were sought and a subtle left conjunctival pigment naevus (Fig. 2) was found. This had been noted by the patient in the preceding few years only. Clinically, he had no testicular mass or heart murmurs. A transthoracic echocardiogram did not reveal any intracardiac tumours or myxomas. The histology of the left adrenal gland was reviewed with the pathologist and was consistent with PPNAD (Fig. 3). A CT scan of the pituitary gland was done to evaluate for pituitary co-existent macroadenomas and this was normal [The CT was chosen in preference to our recommended magnetic resonance imaging (MRI) for cost considerations]. Measurements of serum insulin like growth factor I and growth hormones were within normal limits. The patient had initially declined contralateral adrenalectomy. His sequential bone densitometry results (Table 1), which did not show any significant improvement, led to his final consent to surgery, which was performed successfully in March 2003. He remains well currently on glucocorticoid and mineralocorticoid replacement. His blood pressure was within normal acceptable limits after surgery. His family members have, however, declined screening.

Discussion

Cushing's syndrome may be evident clinically and biochemically but PPNAD as a cause of ACTH-independent Cushing's syndrome may be difficult to diagnose, as illustrated in this patient. Firstly, adrenal imaging can be normal or there may only be minor or minimal adrenal nodularity that cannot always be distinguished from normal glands. Indeed, it is not uncommon that the adrenal nodularity may resemble an adrenal adenoma, as in this case (Fig. 4). Radiologically, the adrenal glands are of normal size in half of the cases.[1] The classical radiological appearance on the CT scan characteristic of PPNAD is described as a "string of beads" appearance, with multiple small adrenal nodules and intervening segments of atrophic adrenal cortex. It had been noted that beyond the age of 18 years, unilateral 2-cm to 3-cm adrenal macronodules are common in PPNAD, making it difficult to distinguish from ACTH-dependent adrenal adenomatous hyperplasia.

Secondly, most hyperplasias described histologically are not specific and are nondescript. Adrenal hyperplasia secondary to capsular microvasculopathy is not uncommon in those patients with hypertension. In patients with Cushing's syndrome with hypertension, adrenal hyperplasia would not have been unexpected except for 3 reasons in this patient. The patient does not have long-standing hypertension with proven target organ involvement to account for the adrenal hyperplasia. The histology of adrenal hyperplasia was not expected nor congruent with the original clinical suspicion of an "adrenal adenoma". Lastly, typical adrenal hyperplasias do not have cortical cellular pigmentation as seen in this patient's histology (Fig. 3). In view of these reasons, a review of the histological specimen was undertaken, which confirmed findings

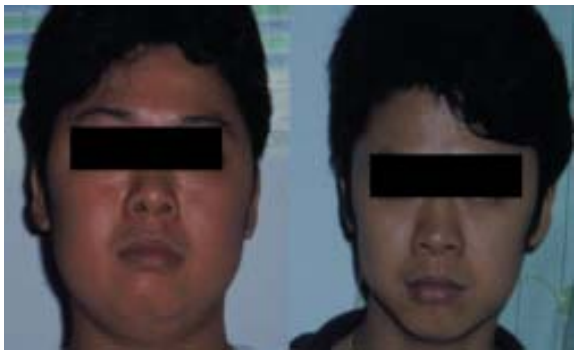

Fig. 1. Clinical appearance of the patient before and after initial unilateral adrenalectomy. The facial phlethora and rounding have reduced significantly.

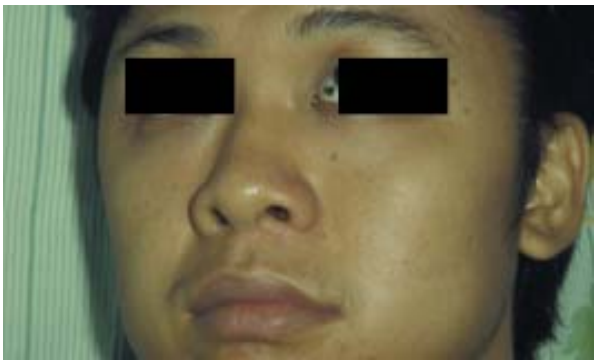

Fig. 2. Left conjunctival naevus found in Carney complex.

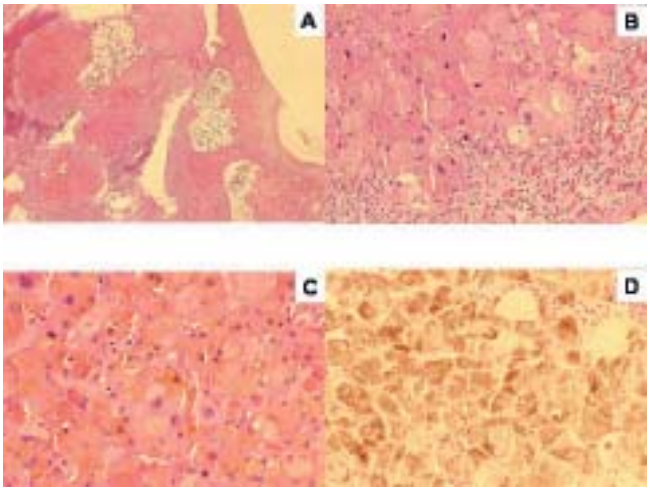

Fig. 3 (A) Lowe-power view showing multiple corticomedullary micronodules comprising mainly lipid-depleted, compact cells (H&E, x40). (B) Close-up view displaying a typical micronodule abutting against the deep cortex without encapsulation, consisting of markedly enlarged cortical cells with abundant, eosinophilic (lipid-depleted) cytoplasm, sometimes disclosing enlarged, hyperchromatic nuclei (H&E, x200). (C) Some nodules, in addition, contain prominently nucleolated cells and cells with discernible, yellowish intracytoplasmic lipofuscin pigment (H&E, x400), which are (D) argentaffin by the Masson-Fontana reaction (Masson-Fontana, x200).

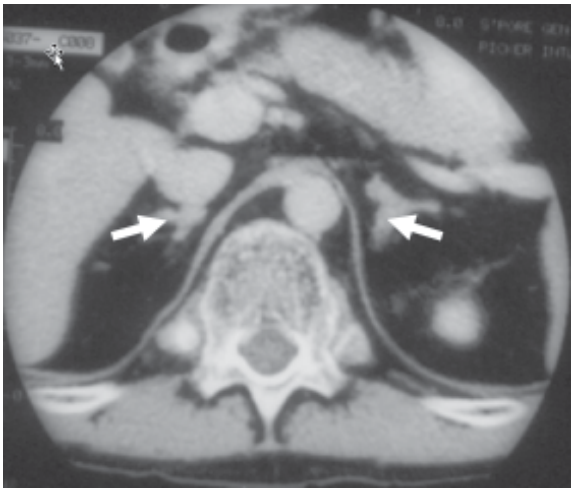

Fig. 4. CT scans of the adrenals showing the adrenal nodularity (arrow).

consistent with PPNAD. The finding of adrenal nodular hyperplasia also favoured bilateral adrenal involvement rather than unilateral adrenal disease, which prompted a revision of the initial diagnosis of an "adrenal adenoma".

Adrenal nodular hyperplasia describes adrenal glands containing 1 or more prominent yellow nodules from 0.5 cm onwards, often measuring 2.0 to 2.5 cm in diameter. These nodules are almost always bilateral.[2] On the other hand, in PPNAD, the characteristic macroscopic findings usually described include small brown-black nodules separated by an atrophic adrenal cortex. The cut surface is yellow, often with small brown foci. Histologically, the nodules consist of clear lipid-laden zona fasciculata-type cells corresponding to the yellow areas on gross examination, while the brown foci consist of compact lipid-sparse zona-reticularis type cells.[2] The large cortical cells with eosinophilic cytoplasm rich in lipofuscin pigment and large hyperchromatic nuclei are classical.[3] There is also loss of normal zonation. Lipofuscin and possibly neuromelanin in the cell cytoplasm account for the dark colour.

There were a few important points to suggest bilateral adrenal disease rather than a unilateral adrenal adenoma. The histology gave the first clue. Post-adrenalectomy, although the patient had resolution of his clinical symptoms in terms of his weight and physical appearance, it was unusual that he did not require any postoperative steroid supplement. The question of a possible concurrent adrenal disease with persistent hypercortisolism was raised. When the repeat endocrine evaluation with a 24-hour urinary free cortisol was still high with non-suppression of the overnight, the low-dose and high-dose dexamethasone suppression tests, it was reaffirmed that biochemically, he still had Cushing's syndrome.

Piecing together all the data available, the diagnosis of PPNAD was put across. This entity of PPNAD represents

a rare ACTH-independent adrenal form of Cushing's syndrome. Our patient had clinically evident Cushing's syndrome, which exists in about 84% of patients with PPNAD. Approximately 10% have a paucity of symptoms and are diagnosed late; this group represents latent PPNAD. The remaining 6% of patients have only biochemical evidence of Cushing's syndrome.[4,5] One interesting feature in the latent form of PPNAD was that hypercortisolism usually progresses slowly and sometimes periodically. The clinical and laboratory features can be normal during the non-hyperscretory periods.[6] The symptoms and signs of Cushing's syndrome in PPNAD may be insidious. There may be paucity of usual classical cardinal stigmata and features like myasthenia and osteoporosis may be more prevalent instead. Indeed, it was the evaluation of osteoporosis in this young man, which led to the diagnosis of Cushing's syndrome. The problem of osteoporosis remains an important consideration when it comes to the management issue. ACTH levels are usually low normal or undetectable and adrenal glucocorticoid production is not suppressed by high-dose dexamethasone.[3]

PPNAD forms part of a wider clinical spectrum of an autosomal dominant multiple endocrine neoplasia syndrome known as Carney complex, which was first reported and described in 1985 as "a complex of myxomas, spotty pigmentation and endocrine overactivity" by Carney and colleagues.[4] The main diagnostic criteria were recently reviewed and summarised by Stratakis et al.[7] The main features comprise spotty skin pigmentation, myxomas (cardiac, breast, cutaneous and mucosal) and endocrine manifestations, typically Cushing's syndrome with PPNAD, and occasionally acromegaly due to growth hormone-producing pituitary adenoma. Thyroid carcinomas, testicular neoplasms (large cell calcifying sertoli cell tumours) and psammomatous melanotic schwannomas are other features. Rarer but described associated features include blue naevi, multiple breast ductal adenomas and osteochondromyxomas. To make a diagnosis of Carney complex, at least 2 of the above features must be present or one of these features and a supplementary criteria of either an affected first-degree relative or presence of an inactivating mutation in the involved PRKAR1A (protein kinase A type 1-alpha regulatory subunit) gene must be met. Linkage studies had identified 2 genetic loci at chromosome 2p16[3] and 17q23-24.[8] Although the clinical features are in keeping with the best-fit diagnosis of Carney complex, the absence of strict fulfillment of the criteria for diagnosis of Carney complex is noted.

Dermatological manifestations associated with Carney complex are varied. Our patient had a subtle left conjunctival naevus, which further helped to support the diagnosis of Carney complex. Conjunctival lentigines are of special and particular importance due to their strong correlation with Carney complex. The presence of pigmented lesions of the caruncle or conjunctival semilunar fold occurs in 7 of 27 patients described by Kennedy et al.[9] Such pigmentation had been described to occur on mucosae as well.

The abnormal skin spotty pigmentation, being the most common clinical manifestation of Carney complex, ranged from lentigines, cafe-au-lait spots, blue and other naevi to depigmented lesions.[4] These abnormal pigmentations, which may exist from birth, usually do not assume usual characteristics until the peripubertal period.

Other features in the Carney's complex were the presence of myxomas, notably cardiac myxomas. Our patient had a normal cardiac echocardiogram. Clinical examination did not reveal any suspicious testicular mass as large-cell calcifying sertoli cell testicular tumors (LCCSCT) are common associations. Endocrine manifestations such as growth hormone pituitary tumour had been described. The patient had normal CT of the pituitary gland as well as a normal GH and IGF-I. He did not have features suggestive of acromegaly.

The persistence of autonomous adrenocortical hyperfunction may have long-term implications in terms of morbidity over the course of decades to come; hence, the management of PPNAD involves bilateral adrenalectomy. In this young patient, an additional consideration was the concern of worsening osteoporosis in ensuing years if total adrenalectomy was not performed. We could follow from his trends of densitometry that his osteoporosis did not improve significantly at the spine after his first adrenalectomy. The particular concern of Nelson syndrome was considered but this phenomenon had not been described to occur after bilateral adrenalectomy in patients with Carney complex. In the series by Carney and Young,[10] 48 out of the 88 cases (65% of the patients) were cured of Cushing's syndrome after bilateral adrenalectomy.

The third issue relates to family screening since the mutation in the involved PRKAR1A gene can be found in Carney complex. As the family members had declined screening and had not given consent for genetic testing, there were difficulties for further evaluation with respect to this. None in the family of 8 siblings had any known endocrinological problem. One sister had hearing impairment, raising the question as to whether this may have been due to a schwannoma.

Our patient illustrates the diagnostic difficulties involved in PPNAD. The high index of suspicion arose from the discrepant radiologic and histological findings. Resolution of clinical Cushing's despite persistent biochemical hypercortisolism following unilateral adrenalectomy added to the diagnostic difficulty but also helped clinch the final

diagnosis. The varied presentations of PPNAD were recognised. It must also be highlighted that in PPNAD, there may be overrepresentation of less common features such as that of osteoporosis compared to the garden variety Cushing's syndrome.

Acknowledgements

The authors would like to gratefully acknowledge and thank Dr Aidan Carney and Prof William Young of the Mayo Clinic, Rochester, Minnesota, USA for their kind assistance in the pathological slide review and clinical discussions related to the case.

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