Primary pigmented nodular adreno-cortical disease

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Abstract

Cushing's syndrome can cause significant morbidity; effective treatment requires integrated clinical, biochemical, and radiological assessments to reach an accurate diagnosis. Primary pigmented nodular adreno-cortical disease (PPNAD) is an uncommon cause of ACTH-independent Cushing's. Diagnosis can be challenging, in particular where the radiological findings are normal or suggestive of a unilateral process. The condition is very commonly associated with Carney complex and referral for evaluation by a clinical genetics team is essential. The pathological features have been well documented, and there are specific findings which should prompt consideration of a hereditary aetiology.

Keywords adrenal hyperplasia; carney complex; cushing's syndrome

Case report

An adult presented with the symptoms and signs of Cushing's Syndrome and was found to have hypercortisolaemia resistant to dexamethasone suppression. CT imaging of the adrenal glands demonstrated the presence of unilateral nodularity and laparoscopic adrenalectomy was performed. On macroscopic assessment, the adrenal was found to contain several pigmented subcapsular nodules. Histology showed these nodules to be comprised of cells with abundant granular eosinophilic cytoplasm with granular brown pigment (Figure 1). Similar nodules were identified in extra-adrenal fat (Figure 2). The pigment granules stained with PAS but not with Masson-Fontana, Ziehl-Neelsen, Sudan Black, or Perl's Prussian blue. Immunohistochemistry showed that the cells expressed melan A, inhibin, and synaptophysin. A pathological diagnosis of PPNAD was made. The reporting pathologist recommended referral to the clinical genetics service.

Discussion

Cushing's Syndrome, first described by Harvey W. Cushing in 1932, arises from an excess of glucocorticoids, which may be endogenous or exogenous in origin.[1] Cushing's syndrome causes a range of symptoms and signs including weight gain, muscle weakness, hair loss, skin fragility, abdominal striae, and easy bruising. It is associated with various complications including diabetes mellitus, hypertension, risk of fracture, impaired wound healing, and psychiatric disturbances.[1] Of the endogenous cases of Cushing's syndrome, around 80% are ACTH-dependent and 20% ACTH-independent.[1] These may be distinguished by dexamethasone suppression testing, with resistance to suppression observed in ACTH-independent cases.[1] The majority of cases of ACTH-independent Cushing's are due to adrenal lesions such as adenomas, or, less commonly, adrenocortical carcinomas.[1] Bilateral adrenal hyperplasia accounts for less than 5% of ACTH-independent cases and are sub-classified as macro- or micro-nodular based on a size threshold of 1 cm.[2] Primary pigmented nodular adreno-cortical disease (PPNAD) is an uncommon, but important, entity within the category of bilateral adrenal hyperplasia.[2] Interpretation of preoperative findings in patients with PPNAD can be challenging. In addition to biochemical evaluation, radiology is required usually with MRI of the pituitary gland (expected to be normal) and CT of the adrenals, the findings of which can be variable and confounding — in particular the presence of normal or unilateral adrenal changes does not exclude a diagnosis of PPNAD.[3] The differential diagnosis for adrenal enlargement is shown in Table 1.

The term PPNAD was first coined in 1984 by Shenoy et al., based on a retrospective review of 4 cases at the Mayo Clinic in Rochester.[4] These cases were subsequently revisited in 2014 by Carney et al.[5] They reported a comprehensive macroscopic, microscopic,

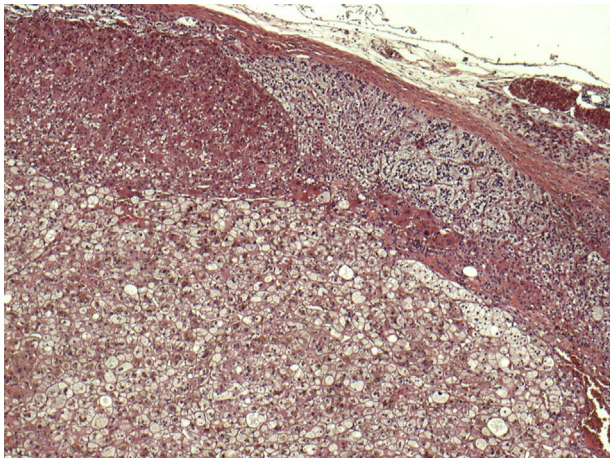

Figure 1 Adrenal gland H&E section, low power view demonstrating a nodule composed of polygonal cells with granular eosinophilic cytoplasm and cytoplasmic lipochrome pigment.

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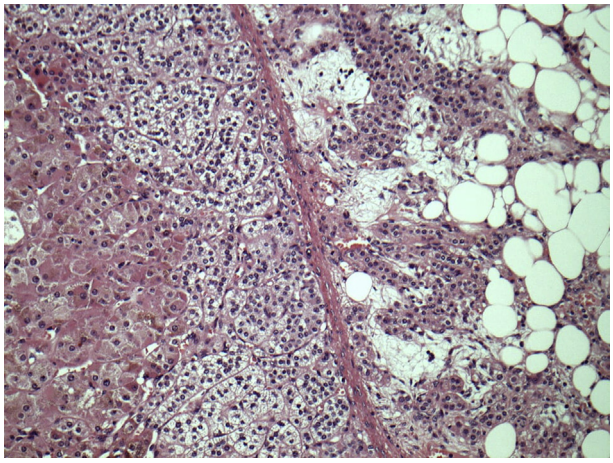

Figure 2 Adrenal gland H&E section, high power view demonstrating extra adrenal extension.

Differential diagnosis for adrenal enlargement

1. Neoplasms
   a) Adenoma
   b) Adrenocortical carcinoma
   c) Pheochromocytoma
   d) Metastasis, most commonly from the lung
   e) Other neoplasms such as neuroblastoma, ganglioneuroma, myelolipoma, lymphoma, haemangioma, haemangiosarcoma, lymphangiosarcoma, teratoma
2. Adrenocortical hyperplasia
3. Granulomatous processes
   a) Tuberculosis
   b) Histoplasmosis
4. Cystic lesions
   a) Epithelial
   b) Endothelial
   c) Pseudocysts
   d) Parasitic
5. Haemorrhage or haematoma
6. Abscess

Table 1

and immunohistochemical characterisation of the adrenals in the series. They found that the adrenals together weighed between around 5 and 9 grams.[5] The glands showed dark pigmentation of the external surface and grossly evident multi-nodularity.[5] Microscopy demonstrated unencapsulated nodules composed of circumscribed aggregates of large, polygonal cells with eosinophilic-granular to clear-vacuolated cytoplasm. Occasional cells showed features such as binucleation, larger more bizarre nuclei, and rare mitotic activity.[5] Cortical atrophy was observed between the nodules.[5] Cytoplasmic lipochrome pigment was often present and usually positive for PAS, Ziehl-Neelsen, and Masson Fontana.[5] Cytoplasmic reactivity was variably seen with immunohistochemistry to inhibin A, synaptophysin, melan A, and Ki-67.[5] Extra-adrenal extension has been noted in several instances of hereditary bilateral adrenal hyperplasia and its presence should specifically raise suspicion of a germline disorder.[5]

PPAND is associated with Carney complex in a large majority, >90%, of cases.[6] This is an autosomal dominant condition comprising myxomas of the heart and skin, mucocutaneous lentiginosis, psammomatous melanotic schwannomas, and endocrine pathologies (namely, PPNAD).[7] The condition is caused by mutations on *PRKAR1A*, a tumour-suppressor gene found on chromosome 17, which encodes a regulatory subunit of protein kinase A.[8]

Bilateral laparoscopic adrenalectomy is the favoured treatment for PPNAD with demonstrable Cushing's syndrome. Following this, the patient will require life-long hormone replacement with both glucocorticoid and mineralocorticoid. Consideration should also be given to excluding the presence of co-existent cardiac and thyroid diseases. Additionally, a referral to clinical genetics should be considered in all cases.[6] ◆

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Practice points

- PPNAD is an uncommon cause of ACTH-independent Cushing's syndrome which is a biochemical diagnosis based on elevated plasma cortisol resistant to the dexamethasone suppression test.
- PPNAD affects both adrenals but counter-intuitively can present with unilateral, or even normal, findings on imaging, making interpretation of pre-operative findings particularly challenging.
- The vast majority of cases of PPNAD are associated with the Carney complex which is most commonly due to mutations in *PRKAR1A* on chromosome 17.
- Usual treatment involves laparoscopic bilateral adrenalectomy followed by long-term hormone replacement, screening for associated conditions, and referral to clinical genetics.

Self-assessment

(1) Which of the following biochemical or radiological features is not seen in PPNAD?
   a. Elevated plasma ATCH
   b. Elevated plasma cortisol
   c. Resistance to dexamethasone-suppression
   d. Unilateral adrenal enlargement
   e. Pituitary enlargement on MRI

(2) Which of the following histological features should cause the pathologist to consider a germline aetiology in an adrenal lesion:
   a. Adjacent cortical atrophy
   b. Eosinophilic granular cytoplasm
   c. Extra-adrenal extension
   d. Necrosis
   e. Mitotic activity

(3) What percentage of cases of PPNAD are associated with Carney Complex
   a. 0–20%
   b. 20–40%
   c. 40–60%
   d. 60–80%
   e. >80%

Correct answers – 1:e, 2:c, 3:e.