The Diagnostic Difficulties of Bilateral Macronodular Adrenal Hyperplasia

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INTRODUCTION

- Bilateral Macronodular Adrenal Hyperplasia (BMAH) refers to bilateral adrenal gland enlargement featuring large (> 1cm) cortical nodules and increased cortisol production
- Historically BMAH has been deemed a rare cause of classic Cushing's syndrome (CS), but it is now considered as more heterogeneous disease with a wide spectrum of clinical, hormonal, and radiographic presentations
- While some patients with BMAH present with classic CS, most are asymptomatic and may have only subtle biochemical evidence of cortisol dysregulation
- Definitive diagnosis is made by histopathology, but a presumptive clinical diagnosis can be rendered based on clinical, radiographic, and biochemical findings
- Here we present a patient with bilateral adrenal nodules and indeterminate evaluation for cortisol excess who is suspected to have BMAH

CASE SUMMARY

- A 56-year-old women with a history of hypertension was referred for evaluation of bilateral adrenal masses
- Recent abdominal CT (fig. 1) demonstrated bilateral nodular adrenal enlargement including a 3.7 cm right adrenal nodule and 1.9 cm left adrenal nodule, both with radiographic features suggestive of benign adenomas
- Her prior imaging was reviewed:
  - 20 years prior to evaluation, abdominal MRI demonstrated a 2.8 cm right adrenal nodule and normal left adrenal gland
  - 15 years prior to evaluation, chest CT demonstrated a 3.5 cm right adrenal nodule and 1.4 cm left adrenal nodule
- Apart from hypertension, she had no symptoms or signs of Cushing's syndrome including moon face, facial plethora, cervicodorsal fat pad, central adiposity, violaceous abdominal striae, proximal muscle weakness, and acanthosis nigricans. She had no history of diabetes, dyslipidemia, or osteoporosis. She denied taking exogenous glucocorticoids.
- Biochemical evaluation (fig. 2) excluded pheochromocytoma, primary hyperaldosteronism, adrenal hyperandrogenism, and non-classic congenital adrenal hyperplasia.

CASE SUMMARY, CONTINUED

- Evaluation for cortisol excess (fig. 2) included several steps:
  - Two overnight 1 mg dexamethasone suppression tests (DSTs) were performed; on both occasions the 8am serum cortisol level failed to suppress, but the concomitant dexamethasone level was below the expected range, raising the question of whether rapid dexamethasone metabolism was causing false-positive results.
  - Two 24-hour urine free cortisol levels were checked; the first was normal but the second sample appeared to be under-collected based on the simultaneously-measured urine creatinine.
  - An initial late night salivary cortisol level was found to be quite elevated, but further questioning revealed this may have been due to recent use of nasal steroid spray. Two subsequent tests were normal.
  - Serum ACTH (remote from DSTs) was found to be suppressed.
  - Put together, these findings were felt to be indeterminate and could not exclude the possibility of subclinical hypercortisolism.
- Given the benign appearance of the nodules and the patient's desire to avoid surgery, continued surveillance was enacted.

IMAGING AND LABORATORY RESULTS

Figure 1:
CT Abdomen showing bilateral adrenal nodules

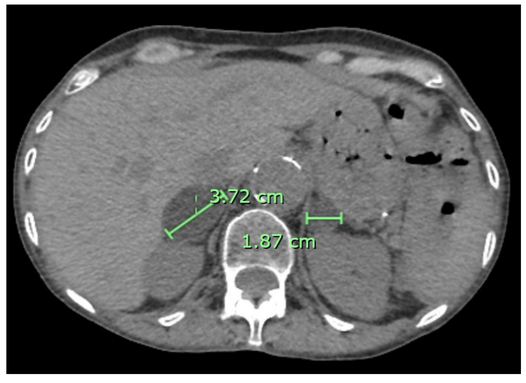

Figure 2:
Biochemical Evaluation

Test	Reference Range	Initial Testing	Subsequent Testing	
Plasma Free Metanephrine	< 0.50 nmol/L	< 0.20		
Plasma Free Normetanephrine	< 0.90 nmol/L	0.27		
Aldosterone	< 21.0 ng/dL	9.6		
Plasma Renin Activity	0.6-3.0 ng/mL/h	< 0.6		
DHEA-Sulfate	9.7 – 159.0 mcg/dL	27.0		
17-Hydroxyprogesterone	< 51 ng/dL	< 40		
8AM cortisol (1 mg DST)	< 1.8 ug/dL	9.8 (H)	13.2 (H)	
Dexamethasone (1 mg DST)	180-550 ng/dL	163 (L)	44 (L)	
24 Hour Urine Free Cortisol	3.5-45 mcg/24 h	13	8.1	
24 Hour Urine Creatinine	11-20 mg/Kg/24hr	12.6	5.3 (L)	
Late Night Salivary Cortisol	< 100 ng/dL	946 (H)	< 50	< 50
ACTH	7.2-63 pg/mL	< 5.0 (L)		

DISCUSSION

- The underlying cause and pathophysiology of BMAH is incompletely understood, and its true prevalence is unknown
- The incidence of BMAH increases with age and there seems to be a female predominance; hypertension and/or diabetes mellitus are frequently present
- Most cases of BMAH appear to be sporadic, but there are also well-documented familial cases with autosomal dominant transmission patterns
- Three potential mechanisms have been implicated in the pathophysiology of BMAH:
  - Inactivating mutations of the *ARMC5* tumor suppressor gene
  - Aberrant adrenal expression of g-protein coupled hormone receptors (GPCRs)
  - Intra-adrenal (paracrine) production of ACTH and/or ligand(s) for aberrant receptors
- In some patients with BMAH, excess cortisol production is driven by expression of aberrant GPCRs such as those for gastrointestinal peptide (GIP); LH/hCG, vasopressin, angiotensin, serotonin, and glucagon; in rare cases this can result in discrete patterns of CS, such as food-induced CS (via GIP receptors) and pregnancy or menopause-induced CS (via LH/hCG receptors).
- Treatment of BMAH is individualized based on the degree of cortisol excess, comorbid illnesses, type of receptor aberrancy, and potential genetic cause
- Some patients may only require medication to block aberrant receptors (if identified), while others require partial or bilateral adrenalectomy.

KEY POINTS

- It is important to consider BMAH in the differential diagnosis of bilateral large adrenal nodules, as the associated hypercortisolism may result in increased morbidity and mortality
- Given its protean manifestations, a high degree of clinical suspicion is required to recognize BMAH
- As our case illustrates, it can be challenging to make a clinical diagnosis of BMAH as most patients have no Cushingoid features and may have only subtle biochemical evidence of cortisol dysregulation. This challenge is compounded by the inherent pitfalls encountered in the biochemical workup for CS, as also seen in our case.

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