CASE REPORT

Subcentimeter Corticotroph Adenoma: an Evaluation of Diagnostic Elements

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ABSTRACT

Cushing's disease (CD) is an uncommon yet serious disorder, linked to increased morbidity and mortality. Diagnosis of these patients are complex, and emphasis should be placed on early detection for better management of these patients. The objective of this case report is to evaluate the diagnostic elements in the identification of a subcentimeter adrenocorticotrophic hormone (ACTH)-dependent pituitary adenoma. We report a case of a 26-year-old man who presented with extensive superficial fungal infection of the skin, unintentional weight gain, hypertension, dyslipidaemia as well as cushingoid appearance suspicious of hypercortisolism. Raised midnight plasma cortisol and 24-hour urinary cortisol levels warranted further investigation. Overnight and 48-hour low-dose dexamethasone suppression test (LDDST) were non-suppressed. Subsequent bilateral inferior petrosal sinus sampling (BIPSS) was not only efficient in differentiating pituitary from ectopic Cushing's syndrome (CS) but was shown to be superior to magnetic resonance imaging (MRI) in lateralisation of the pituitary adenoma.
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INTRODUCTION

Untreated hypercortisolism may lead to death owing to the amplified risk of cardiovascular complications, coagulopathy, infections, and psychiatric disturbances (1). Early diagnosis and intervention are imperative as the mortality associated with Cushing's syndrome (CS) is significantly related to time of exposure to excess cortisol (1). We report a case of a young man with clinical features of CS. The early diagnosis of Cushing's disease (CD) and effective lateralisation of his pituitary adenoma resulted in prompt surgery and reversal of his hypercortisolism.

CASE REPORT

A 26-year-old obese man presented with extensive tinea corporis and unintentional weight gain. Physical examination revealed hypertension and classical cushingoid features (moon facies, truncal obesity, and purple striae). A provisional diagnosis of CS was made.

Subsequent routine laboratory investigations (Table I) were unremarkable except for a deranged lipid profile. Thyroid and fertility hormones were normal however the midnight plasma cortisol was elevated at 742.1 nmol/L (RI: 94.9-462.4 nmol/L). An overnight dexamethasone suppression test (ODST) and a subsequent 48-hour low dose dexamethasone suppression test (LDDST) exhibited non-suppressed plasma cortisol levels, whilst 24-hour urine cortisol and random plasma adrenocorticotrophic hormone (ACTH) was also increased (Table II). Ultrasound abdomen did not show adrenal mass, but magnetic resonance imaging (MRI) brain revealed a micronodule (0.6 x 0.5 x 0.3 cm) at the midline of the pituitary gland.

He was then planned for bilateral inferior petrosal sinus sampling (BIPSS) to distinguish between ectopic ACTH syndrome and CD, as well as to determine the laterality of the pituitary adenoma. After cannulation of his femoral veins bilaterally, catheters were entered into the bilateral inferior petrosal sinuses (IPS). Evaluation of catheter positioning and anatomic irregularities was performed by retrograde venography. Blood samples were drawn simultaneously peripherally, as well as from the left and right petrosal sinus respectively at baseline (0 minutes) and at three-time points after 100μg corticotrophin releasing hormone (CRH) administration (2/5/10 minutes). Samples were assayed for prolactin and ACTH. The results of the BIPSS were consistent with CD and lateralisation of the pituitary tumour to the right side (Table III).

An endoscopic transsphenoidal adenomectomy was done. Interestingly, although the pre-operative MRI brain showed a centrally positioned pituitary adenoma,

Table I : Baseline laboratory investigations

Parameters	Parameter Value	Reference Interval
Haemoglobin (g/dL)	15.1	13.0-17.0
White cell count (10^9 /L)	13.8	13.0-17.0
Platelet (10^9 /L)	265	150-450
Urea (mmol/L)	3.7	1.4-4.3
Sodium (mmol/L)	143	134-146
Potassium (mmol/L)	4.3	3.7-5.9
Chloride (mmol/L)	102	98-113
Creatinine (µmol/L)	72	27-87
Total protein (g/L)	73	64-83
Albumin (g/L)	38	35-52
Globulin (g/L)	34	20-39
A/G ratio	1.1	1.1-2.5
ALP (IU/L)	89	40-130
ALT (IU/L)	31	<42
Total bilirubin (µmol/L)	10	2-17
Cholesterol (mmol/L)	5.6	<5.2
HDL cholesterol (mmol/L)	1.4	>1.6
LDL cholesterol (mmol/L)	3.6	<2.6
Triglycerides (mmol/L)	1.3	<1.2
Fasting glucose (mmol/l)	4.8	3-6.1
HbA1c (%)	5.2	≤ 6.5
FT4 (pmol/L)	12.1	12-22
TSH (mU/L)	1.19	0.27-4.2
FSH (IU/L)	5.1	1.5-12.4
LH (IU/L)	2.9	1.7-8.6
Testosterone (µmol/L)	5.9	8.6-29
GH (µg/L)	0.55	< 3

A/G ratio albumin globulin ratio, *ALP* alkaline phosphatase, *ALT* alanine transaminase, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *FT4* Free thyroxine, *TSH* thyroid stimulating hormone, *FSH* follicular stimulating hormone; *LH* lutenising hormone; *GH* growth hormone.

the intraoperative findings correlated with the BIPSS results showing a tumour margin arising from the right pituitary gland. A right partial hypophysectomy was done to fully remove the tumour.

DISCUSSION

How do we diagnose CS?

The Endocrine Society Clinical Practice Guidelines (CPG) 2008 endorses one of the following first-line examinations for diagnosis of CS (2):

1) ≥ 2 collections of 24-hour urinary free cortisol,
2) 2 collections of late-night salivary cortisol,
3) 1mg ODST, or 2mg 48-hour LDDST in certain populations.

Our patient was subjected to a single measurement of 24-hour urine cortisol and midnight plasma cortisol during his first visit. Midnight plasma cortisol was performed instead of salivary collection due to its unavailability in our setting. For urine free cortisol, at least two measurements are recommended due to its variability and low reproducibility (2); however, in this case, only a single measurement of 24-hour urine cortisol was completed as it was deemed too cumbersome for the patient. ODST was proceeded as the midnight plasma cortisol and single 24-hour urine cortisol results were insufficient to diagnose CS as per Endocrine Society CPG (2).

Although an initial ODST showed a non-suppressed

Table II : Laboratory investigations to confirm CS

Parameters	Parameter Value	Reference Interval
AM cortisol (nmol/L)	772.8	145.4- 619.4
24-hour urine cortisol (nmol/day)	867	57.7–806.8
ACTH (pg/ml)	20.9	<10.2
Cortisol post ODST (nmol/l)	749.1	<50
Cortisol post 48-hour LDDST (nmol/L)	415.5	<50

ACTH adrenocorticotropic hormone; *ODST* overnight dexamethasone suppression test; *LDDST* low dose dexamethasone suppression test.

Table III : BIPSS

Parameters	Parameter Value	Reference Interval
Central to peripheral ACTH max ratio (baseline) –right side	9.9:1	≥ 2
Central to peripheral ACTH max ratio (baseline) –left side	2.5:1	≥ 2
Central to peripheral ACTH max ratio (5 minutes post CRH stimulation)- right side	6.9:1	≥3
Central to peripheral ACTH max ratio (5 minutes post CRH stimulation)- left side	>8.1:1	≥3
Baseline ACTH gradient right: left	4:1	

BIPSS Bilateral inferior petrosal sinus sampling; *CRH* corticotrophin releasing hormone.

cortisol diagnostic of CS, a high false-positive rate of up to 53% may be seen in obese individuals (3). It is for this reason that our obese patient was subjected to a 48-hour LDDST which provided a higher specificity of close to 100% (1).

How do we establish the cause of CS?

Early morning ACTH levels <10 pmol/L favour ACTH-independent hypercortisolism while inappropriately raised ACTH like that in our patient favours ACTH-dependent hypercortisolism (3).

MRI, despite being the most accurate imaging modality, is unable to distinguish ACTH- secreting tumours from non-functional ones and has limited power in identifying subcentimeter lesions (4). Blurring artefacts and similar enhancement characteristics of small microadenomas compared to the normal pituitary gland may contribute to false positive and false negative results on imaging (5). Furthermore, the Consensus Statement on Diagnosis and Complications of CS recommends a 6 mm cut-off for an MRI detected-pituitary mass to be considered a corticotroph adenoma rather than an incidentaloma (4). Our patient's pituitary lesion on MRI was right on the cut-off value of 6 mm, rendering the diagnosis challenging, hence BIPSS had to be done to confirm the diagnosis.

BIPSS, with a diagnostic sensitivity and specificity close to 100% is regarded as the gold standard examination to discern between ectopic ACTH and CD, especially so when performed by an experienced interventional radiologist (4). In BIPSS, a lower ACTH concentration is expected in the systemic circulation, in contrast with a higher ACTH concentration at sites closer to the pituitary gland, implying hypercortisolism originating from pituitary ACTH excess (4). ACTH is secreted sporadically (4). Sampling during ACTH nadir may lead to false negative results (4). As such, CRH is used to stimulate continuous ACTH secretion, therefore improving diagnostic accuracy of BIPSS (4). By translating the pathophysiology of BIPSS to figures, a petrosal sinus to peripheral ACTH ratio of ≥ 2.0 at 0 minute or ≥ 3.0 after CRH administration in the setting of hypercortisolism suggests ACTH secretion from a pituitary source (4). In our patient, the baseline ACTH IPS/ periphery ratio of >2 and post CRH ACTH IPS/ periphery ratio > 3 were strongly indicative of a pituitary CS rather than an ectopic source.

Studies have proven that blood from the anterior pituitary continues to be lateralised as it runs into the IPS. The principal petrosal sinus containing a higher fraction of the total pituitary ACTH may differ in different individuals. In view of this, venous blood is drawn concurrently from bilateral IPS, allowing for comparison between two sides of the pituitary to localise the ACTH-secreting tumour (3).

The intersinus gradient, defined as the ratio of ACTH concentrations between the two IPS of >1.4, indicates

lateralisation of ACTH secretion to the side with the highest concentration (4). This diagnostic accuracy has been reported to be between 50%-100% (4,5), with incorrect lateralisation contributed by unequal patterns of pituitary venous drainage, extension of tumour epicentre to the opposite site, as well as suboptimal skill of the interventional radiology team (5). An intersinus gradient of right:left of 4:1 seen in our patient (table III), is predictive of tumour lateralisation to the right.

Interestingly, albeit regarded as a gold standard by many, indications for BIPSS differs across regions. Some clinicians suggest BIPSS for patients suspected of having CD when there is a discrepancy between biochemistry and imaging findings, negative MRI image or microadenomas smaller than 6 mm; while some include BIPSS as a standard workup in any individual with established ACTH-dependent CS (biochemical results in CD and ectopic CS may overlap as some neuroendocrine tumours secrete glucocorticoids and CRH) (5), reflecting variances in protocols worldwide. In our centre, BIPSS is reserved for those with negative or equivocal MRI findings because although BIPSS is a safe procedure, side effects such as haemorrhage and thromboembolic events are possible (4).

CONCLUSION

24-hour urinary free cortisol, late-night salivary cortisol, and ODST are first line tests for diagnosis of CS while early morning ACTH helps in differentiating ACTH dependent or independent hypercortisolism. BIPSS reflects lateralisation of CD and is used to guide neurosurgical investigation in patients (especially those with equivocal radiological evidence). In our case, BIPSS correctly identified a pituitary source of ACTH secretion as well as precise lateralisation of a subcentimeter mass which was poorly detected by MRI. Our patient has a good long-term prognosis following a successful right partial hypophysectomy with conservation of healthy pituitary tissue.

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