Unexpected outcome (positive or negative) including adverse drug reactions

Disappearance of pituitary macro adenoma with combination of ketoconazole and cabergoline treatment: an unusual case of Cushing's syndrome with interesting findings

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Summary

Cushing syndrome is associated with significant morbidity and mortality if left untreated because of associated metabolic and cardiovascular complications. An extremely ill patient with Cushing's syndrome caused by adrenocorticotrophic hormone producing pituitary macro adenoma responded dramatically to ketoconazole and cabergoline treatment. His 4 month long medical treatment resulted in improvement of hypercortisolism clinically and biochemically and in complete disappearance of pituitary macro adenoma without any surgical intervention.

BACKGROUND

Cushing syndrome caused by prolonged exposure to elevated levels of either endogenous or exogenous glucocorticoids is associated with significant morbidity and mortality.¹ Endogenous Cushing's syndrome is further divided on the basis of adrenocorticotrophic hormone (ACTH) levels into ACTH dependent and independent Cushing's. ACTH dependent Cushing's can result from excess secretion of ACTH by a pituitary adenoma (commonly called Cushing's disease) or by ectopic tumours secreting ACTH or corticotropin-releasing hormone. Cushing's disease is the most common form of endogenous Cushing's syndrome, accounting for 60%–80% of all cases.² ACTH dependent Cushing's is an entity which usually creates diagnostic dilemma and sometimes the underlying aetiology is never established and bilateral adrenalectomy remains the only solution for these patients.³ In cases where the pituitary adenoma is the underlying aetiology for Cushing's, transsphenoidal surgery (TSS) remains the definitive treatment with

immediate remission rates of 70% followed by radiotherapy or gamma knife in cases of late remission or residual disease.^{4–6} Medical treatment in the form of ketoconazole, cabergoline, pasireotide and mifepristone have a proven role in suppression of biochemical and clinical features of hypercortisolism.⁷

We report a case of ACTH dependent hypercortisolism having concomitant chest lesions and pituitary macro adenoma with complete disappearance after short term treatment with cabergoline and ketoconazole without any surgical intervention.

CASE PRESENTATION

A 38-year-old man known case of type 2 diabetes and hypertension for 5 years presented to an Endocrinologist in 2011 for the investigation of generalised weakness, proximal myopathy and significant weight loss of 14 kg for the last 6 months. Physical examination revealed a man with mild pigmentation. He had very subtle signs of Cushing's. His blood pressure was 150/80 mm Hg. He had

Figure 1 MRI scan showing pituitary macro adenoma.

very significant proximal myopathy. Visual field assessment was normal. There was significant history of depression. He was also struggling to control his diabetes with extremely high doses of insulin therapy.

INVESTIGATIONS

Investigations revealed significant hypokalemia ($K=1.9$ mmol/l) and hypercortisolism ($44 \mu\text{g/dl}$) which failed to suppress with both low ($51 \mu\text{g/dl}$) and high dose ($46 \mu\text{g/dl}$) dexamethasone suppression tests. Serum ACTH was done which was found to be 60 and 70 pg/ml ($7-63 \text{ pg/ml}$) on two occasions. His 24 h urinary cortisol was remarkably elevated with values of $4290 \mu\text{g}$.

In view of hypercortisolism and high normal ACTH levels, the case was diagnosed to be ACTH dependent Cushing's syndrome. Clinically, because of the presence of significant myopathy and hypokalemia, initially suspicion was more towards ectopic ACTH secretion.

Figure 2 CT scan showing necrotic soft tissue density mass lesion measuring 4×2.9 cm in anterior segment of right upper lobe.

Figure 3 Chest x-ray showing necrotic pulmonary nodule in the right mid lung zone.

Further investigation was planned to differentiate between Cushing's disease and ectopic ACTH secretion.

His MRI brain showed solid mass lesion in the pituitary region measuring 2×1.9 cm expanding the sellar region and causing slight rightward deviation of pituitary stalk (figure 1).

Subsequently CT scan chest and abdomen was also done and it reveals necrotic soft tissue density mass lesion seen in the anterior segment of right upper lobe with speculated margins measuring 4×2.9 cm (figure 2) with the same finding on chest x-ray (figure 3). Multiple tiny nodules in right lung, largest one measuring 7 mm was also noted along with multiple hypodense lesions in spleen. Liver, gall bladder, pancreas, kidneys, adrenals and bowel loops appeared unremarkable.

Due to the presence of lesions in lungs and pituitary gland, inferior petrosal sinus sampling was planned which failed to show any significant central to peripheral gradient for ACTH (table 1).

DIFFERENTIAL DIAGNOSIS

1. Cushing's disease
2. Ectopic ACTH secretion.

TREATMENT

As the source of ACTH was not evident, the patient was started on ketoconazole and cabergoline. Subsequently,

Table 1 Results of inferior petrosal sampling are shown below

	Serum ACTH
RT petrosal	258
RT petrosal	347
Lt petrosal	276
Lt petrosal	281
RT peripheral	199
SVC	254
IVC	104
PA	136

ACTH, adrenocorticotrophic hormone; IVC, inferior vena cava; Lt, left; PA, pulmonary artery; RT, right; SVC, superior vena cava.

Figure 4 Chest x-ray showing resolution of chest nodule after antibiotic treatment.

Figure 5 Post-treatment MRI showing disappearance of pituitary macro adenoma.

the doses were gradually increased to 1200 mg/day and 0.5 mg twice weekly, respectively. Spironolactone was also added because of persistent hypokalemia along with potassium replacement. For the chest lesion broad-spectrum intravenous antibiotics was given for 2 weeks.

OUTCOME AND FOLLOW-UP

After 1 month, CT scan of chest and abdomen were repeated which showed significant reduction in the size of soft tissue density mass noted in right upper lung measuring 11×10 mm (previously 43×34 mm). Previously noticed lung nodules on right side were not visualised in this study. Mediastinal lymph nodes appeared to have increased in size. Mediastinal lymph node biopsy was done through video assisted transthoracic surgery to further explore the nature of the lymph nodes. The cultures were sent for acid-fast bacilli culture (AFB). The histopathology showed benign reactive changes.

One month after mediastinal lymph node biopsy, repeat chest x-ray was completely normal with no abnormal finding (figure 4).

With resolution of chest lesions and negative histopathology report, pituitary macro adenoma was considered to be an underlying aetiology of Cushing's. MRI pituitary was repeated and surprisingly it revealed complete disappearance of the pituitary lesion in comparison to previous MRI findings (figure 5).

Clinically, the patient is asymptomatic clinically with resolution of diabetes, hypertension, proximal myopathy, hypokalemia and depression. Biochemically potassium, cortisol (24 h urinary value=39 µg) and blood sugars have also been improved remarkably with medical treatment. Spironolactone and cabergoline were tapered and then stopped and ketoconazole has been reduced from 1200 mg to 200 mg/day now with a plan of stopping it altogether after 1 month.

His AFB culture later on showed growth of AFB for which he has been started on antituberculosis treatment.

DISCUSSION

This patient was diagnosed to have Cushing's syndrome on the basis of clinical and biochemical parameters. The history of significant proximal myopathy, refractory hypokalemia and chest lesion supported the diagnosis of ectopic ACTH producing Cushing's. Detection of pituitary macro adenoma with non-conclusive inferior petrosal sinus sampling results created further challenge. Furthermore, resolution of chest lesion with antibiotic treatment with negative mediastinal lymph node biopsy ruled out the possibility of ectopic source of Cushing's making the diagnosis of Cushing's disease likely.

Surgical removal of the pituitary adenoma is the definitive treatment for Cushing's disease and it yields immediate disease remission in about 70% of patients and the late disease remission rate is around 50%.⁸

Pharmacotherapeutic agents used for medical treatment of Cushing's syndrome can be separated into three kinds of agents that A) inhibit adrenal steroidogenesis, B) works at hypothalamic/pituitary level and C) at the glucocorticoid receptor level.

Medical treatment in patients is not curative and is usually used before surgery or as a transient palliative measure before the definitive treatment.⁹

However, there are case reports in literature of patients demonstrating clinical and biochemical remission of Cushing's and complete disappearance of pituitary micro and macro adenoma treated with cabergoline, a dopamine receptor subtype 2 agonist, for 1 year in case of Nelson's syndrome.^{10 11} Withdrawal of cabergoline led to reappearance of pituitary adenoma in those cases.

In contrast, adrenal steroidogenesis inhibitors like ketoconazole, metyrapone and mitotane are an effective therapy in patients with Cushing's syndrome to achieve biochemical control preoperatively or in cases where surgery has failed and radiotherapy has not taken effect.¹² However it does not have any effect on size of pituitary adenoma in case of Cushing's disease or non-functioning pituitary adenoma.

Learning points

- ▶ This case demonstrates disappearance of the pituitary macro adenoma in just a period of 4 months of medical therapy which is very unusual with resolution of clinical and biochemical hypercortisolism. As discussed above, reduction in size of pituitary adenoma has been reported with use of cabergoline for at least 1 year previously in cases of Nelson's syndrome.
- ▶ Cabergoline has also been used in combination with ketoconazole and showed clinical and biochemical improvement but it has never been shown to cause disappearance of pituitary adenoma with short-term treatment.⁷ This warrants further studies to see the effects of combination of cabergoline and ketoconazole on pituitary lesion in the treatment of Cushing's disease.

Competing interests None.

Patient consent Obtained.

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