CASE REPORT

Biventricular hypertrophy and heart failure as initial presentation of Cushing's disease

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SUMMARY

We present a unique case of a 32-year-old woman with severe biventricular hypertrophy and acute heart failure with reduced left ventricular ejection fraction of 25–30% due to Cushing's disease. The patient was admitted to a specialised cardiac unit and treated with conventional therapy against heart failure. The department of endocrinology was consulted because of clinical suspicion of Cushing's syndrome. Initial biochemistry indicated the presence of adrenocorticotrophic hormone (ACTH) dependent Cushing's syndrome and a dexamethasone suppression test confirmed the diagnosis. A cerebral MRI scan revealed a pituitary adenoma and a sinus petrosus inferior catheterisation confirmed increased production of ACTH from the pituitary. The patient was referred to the neurosurgical department and the adenoma was successfully removed by transsphenoidal catheterisation and ablation. Five months following the initial hospitalisation the patient was nearly in full recovery with respect to her cardiac function and biochemically there were no signs of Cushing's syndrome.

BACKGROUND

Cushing's disease (CD) is a rare and serious condition known to affect the cardiovascular system in various ways, but the presence of biventricular hypertrophy and reduced systolic function of both the left and right ventricle has never been described before in CD.

CASE PRESENTATION

A 32-year-old non-smoking woman with no medical history was admitted to the intensive care unit at a local hospital with pulmonary oedema, sinus tachycardia (heart rate 170 bpm) and hypertension (systolic blood pressure 200 mm Hg). There was a history of familiar hyperlipidaemia, but no history of diabetes, hypertension or ischaemic heart disease. The patient had a natural and uncomplicated pregnancy and birth 7 years previously, however the patient had been amenorrhoeic for the past 3 years. In the same period she had developed increasing swelling of the face, abdominal striae and insomnia. Three weeks prior to the hospitalisation the patient complained of dyspnoea, fatigue and muscle aches. As the local general practitioner found abnormally high testosterone levels, she was referred to a gynaecologist for further evaluation, and was admitted to the hospital due to acute illness (present case) before attending the gynaecologist.

Figure 1 Echocardiography with a parasternal long-axis view of the left ventricle showing biventricular hypertrophy.

The patient responded well to the initial treatment with diuretics and afterload reduction and was moved to a specialised cardiac unit (SCU) for further assessment.

INVESTIGATIONS

The initial echocardiography performed at the local hospital demonstrated reduced biventricular systolic function with reduced left ventricle ejection fraction (LVEF) of 25–30% (normal range >60%) and reduced tricuspid annular plane systolic excursion of 14 mm (normal range >18 mm). The echocardiography also showed hypertrophy of the left and right ventricles; the septal wall of the left ventricle measured 13 mm (normal range <11 mm), the posterior wall of the left ventricle 18 mm (normal range <11 mm) and the free wall of the

Figure 2 Colour-code tissue tracking image of systolic longitudinal fibre shortening in a four chamber apical view. Stroke length is colour coded with blue colours encoding the greatest stroke length and red encoding lowest stroke length.

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Figure 3 Echocardiography with global longitudinal strain values in a 'bulls eye plot' demonstrating reduced left ventricle longitudinal systolic function.

right ventricle 10 mm (normal range <4 mm). The echocardiography was repeated at the SCU with similar findings (figure 1). Left ventricle systolic function was further examined with tissue Doppler imaging-derived stroke length and two-dimensional speckle-tracking estimated deformation (strain); both demonstrated severely reduced left ventricle longitudinal function. Longitudinal stroke lengths in basal segments were reduced to 0–2 mm (normal >10 mm; figure 2) as a consequence of reduced longitudinal strain (figure 3). Owing to severe left ventricle hypertrophy and reduced LVEF a coronary angiography was performed with normal findings, and a myocardial biopsy demonstrating signs of hypertrophy, but no other structural disease of the heart could be demonstrated. The ECG showed signs of biventricular hypertrophy and irregular sinus rhythm, inverted T waves in aVL and no other signs of ischaemia (figure 4).

There was a strong clinical suspicion of Cushing's syndrome (CS) as the physical examination revealed moon facies, facial plethora, buffalo hump, ecchymosis of the skin, truncal obesity, body mass index of 29 kg/m², and striae of the abdomen, and the department of endocrinology was consulted. Initial

biochemical tests showed high levels of cortisol: fasting cortisol at 833 nmol/L (normal range 200–700 nmol/L) and adrenocorticotrophic hormone (ACTH) at 10 pmol/L (normal range 2–14 pmol/L) indicating the presence of ACTH dependent CS (CD). Subsequently we measured the 24 h urine cortisol level two times, both showing increased values of cortisol (444 and 554 nmol/day, normal values 8–125 nmol/day). The diagnosis was confirmed by a dexamethasone suppression test (using 4 mg dexamethasone over 3 days), showing no suppression of cortisol or ACTH (day 1: cortisol 850 nmol/L, ACTH 11; day 3, cortisol 615 nmol/L, ACTH 10). There was no evidence for insufficiency of the other pituitary axes or any clinical or biochemical signs of hyperandrogenism. Furthermore the biochemical tests revealed elevated total cholesterol at 6.6 mmol/L (normal range <5 mmol/L), low-density lipoprotein cholesterol at 2.5 (normal range <2.5 mmol/L), high-density lipoprotein cholesterol at 0.7 mmol/L (normal range >1 mmol/L) and normal fasting plasma glucose values. A cerebral MRI scan showed a 6.5×7×3.5 mm large adenoma in the pituitary gland (figure 5) and a sinus petrosus inferior catheterisation further confirmed the earlier findings. The patient was referred to the department of neurosurgery for removal of the adenoma.

TREATMENT

In the acute setting the patient was treated with nitroglycerin and furosemide. Afterwards a conventional heart failure regimen with a non-selective β -receptor and α 1-receptor blocker (carvedilol), an ACE inhibitor (ramipril) and an aldosterone receptor antagonist (spirone) was initiated.

Four months after the initial clinical presentation the adenoma was removed by ablation of the tumour by transsphenoidal catheterisation and glucocorticoid replacement therapy was initiated.

OUTCOME AND FOLLOW-UP

The hormonal profile of the pituitary was re-evaluated 3 months after surgery. There were no signs of CS (ACTH was not measurable and a short Synacthen test was performed with insufficient response; stimulated value of cortisol 216 nmol/L, normal >500 nmol/L). As a consequence, the patient still needs treatment with cortisone. The patient still has physical signs of CS but has just started to menstruate again.

Figure 4 An ECG showing irregular sinus rhythm, signs of biventricular hypertrophy, and negative T wave in aVL with no other signs of ischaemia.

Figure 5 A cerebral MRI scan showing 6.5×7×3.5 mm adenoma of the pituitary (red arrow).

Five months following the initial hospitalisation the patient was almost asymptomatic with NYHA class I-II exercise induced dyspnoea. The echocardiography showed persistent biventricular hypertrophy. In contrast the systolic function of the left ventricle had improved to an LVEF of 45%. Further titration of the heart failure medication and assessment of the LVEF is performed by the heart failure clinic at the SCU.

DISCUSSION

CS is the manifestation of a chronic exposure to excess glucocorticoid. There are several possible causes of CS such as iatrogenic-induced CS, ectopic corticoid production, glucocorticoid producing pituitary gland tumours (CD) and adrenal gland tumours. As CS covers a broad spectrum of phenotypes, specific incidence and prevalence numbers are uncertain. The best estimates described in the literature are incidence rates of 2.4/million/year and prevalence rates of 31.9/million.^{1 2} The most common cause of CS is iatrogenic CS, with ACTH dependent CD as the second most common cause; all other causes are very rare.² The manifestations and symptoms of CS show great variety, with skin changes, fungal infections, hirsutism, adiposity, menstrual irregularities, hypertension, diabetes, osteoporosis, left ventricular hypertrophy and diastolic dysfunction of the left ventricle described as some of the most common manifestations. The background for hypertrophy of the left

ventricle observed in CS is unknown. However, it has been suggested that the structural changes in the left ventricular wall in patients with CS is due to the changes in hormone levels, rather than the elevated systolic blood pressure.³ Excess of glucocorticoids may lead to secondary diabetes and hypertension and as a consequence effects on the cardiovascular system, for instance causing ventricular hypertrophy. On the other hand, it has been shown that glucocorticoids can affect the myocardium directly through the local renin–angiotensin–aldosterone system in the heart, by inducing cell proliferation in the cardiomyocytes, and altering the expression of angiotensinogen mRNA leading to hypertrophy of the cardiac myocytes.⁴ In our case both the right and the left ventricle are hypertrophic and dysfunctioning, which cannot solely be explained by arterial hypertension. An anabolic hormonal state and its cardiotoxic mechanisms is therefore more likely to have affected the myocardium directly causing biventricular hypertrophy and reduced systolic function of both the left and the right ventricle. No other reports on biventricular hypertrophy and heart failure due to CS have been published and further examination of the mechanism behind cardiac dysfunction due to CS is required to determine the pathway of glucocorticoid effects on the cardiomyocytes.

Learning points

- ▶ Hypertrophy and dysfunction of the left and right ventricles is rare and a systemic disease should be considered.
- ▶ Hypertrophy of the cardiac muscle could be explained by the excess of glucocorticoid and its local effects on the cardiomyocytes rather than a rise in systemic blood pressure.
- ▶ Steroid excess is known to cause hypertension, ventricular hypertrophy and even heart failure; thus any patients suspected of having Cushing's disease may need to have a cardiac evaluation including echocardiography as part of the routine evaluation prior to surgery.

Contributors TMH wrote and designed this case report with the active contribution of all coauthors. Each author has participated in preparing and critically revising it for important clinical information and content changes. Furthermore each author approved the final version of the article prior to submission.

Competing interests None.

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