CASE REPORT

Acromegaly-induced cardiomyopathy with dobutamine-induced outflow tract obstruction

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SUMMARY

A 50-year-old man with a history of acromegaly was referred for preoperative cardiac evaluation preceding trans-sphenoidal resection of a pituitary macroadenoma. Dobutamine stress echocardiography was negative for myocardial ischaemia. Resting left ventricular (LV) LV ejection fraction (LVEF) was 64% and there was hypertrophy of ventricular septum (18 mm) without resting LV outflow tract obstruction. With 40 µg/kg/min of dobutamine, the LVEF became hyperdynamic at 80%, and there was a maximal instantaneous LV outflow tract gradient of 77 mm Hg. There was no delayed myocardial enhancement on cardiac MRI and the pattern of hypertrophy was concentric. Acromegaly-induced cardiomyopathy can mimic hypertrophic cardiomyopathy in the setting of dobutamine provocation. Because cardiomyopathy is an important cause of mortality in acromegaly, diagnosis and appropriate management are critical to improve survival.

BACKGROUND

Acromegaly is a rare endocrine disorder with an incidence of 3 per million per year.¹ Acromegaly can present with multisystem involvement and cardiac manifestations remain an important cause for mortality.² Phenotypic cardiac manifestations include left ventricular (LV) hypertrophy and may ultimately manifest as heart failure. These findings are attributed to the role of excess secretion of growth hormone (GH) and insulin-like growth factors in the development of cardiac myocytes, and alteration of cardiac structure and function.³ In this case, LV hypertrophy was noted in a patient with acromegaly who developed an induced LV outflow tract (LVOT) gradient in the setting of dobutamine stress echocardiography. Recognition of acromegaly-induced cardiomyopathy and distinguishing it from other cardiomyopathies is crucial given the differences in treatment, prognosis and family screening.

CASE PRESENTATION

A 50-year-old man with a history of acromegaly, hypertension, ongoing smoking (35-pack-year) and exertional chest tightness was referred for pre-operative pharmacological stress echocardiogram prior to trans-sphenoidal resection of pituitary macroadenoma. There was no family history of hypertrophic cardiomyopathy (HCM) nor of sudden cardiac death. Cardiac auscultation revealed normal first and second heart sounds. There was no murmur on examination at rest, nor with Valsalva manoeuvre, nor with squat-to-stand

manoeuvre. There were no additional heart sounds. Jugular venous pressure and pulsation were normal. ECG demonstrated sinus bradycardia at 51 bpm and there were no findings suggestive of enlarged cardiac chambers or LV hypertrophy.

Stress echocardiogram at rest showed no evidence of regional wall motion abnormalities but did note hypertrophy of the ventricular septum at 18 mm and findings consistent with normal LV filling pressures at rest. Resting LV ejection fraction (LVEF) was 64%, with no resting LVOT obstruction. Following dobutamine infusion from 5 to 40 µg/kg/min, LV systolic function became hyperdynamic (LVEF 80%) and, at peak dobutamine, there was evidence of dynamic LVOT obstruction, with a peak instantaneous gradient of 77 mm Hg. There was no associated systolic anterior motion (SAM) of the mitral valve. There were no ischaemic changes with stress and the patient underwent the surgical procedure without complication. However, given the findings of LV hypertrophy and dynamic obstruction, further cardiology evaluation was requested.

The patient was seen 2 weeks postoperatively and noted daily episodes of chest heaviness accompanied by shortness of breath. These episodes were exertional and typically lasted minutes (up to 2 h). He also described occasional light-headedness and two episodes of presyncope.

INVESTIGATIONS

Holter monitor was ordered for underlying arrhythmias to explain the patient's dyspnoea, chest pain and presyncope. It demonstrated sinus rhythm with an average heart rate of 69 bpm. There was occasional ventricular ectopy with rare supraventricular ectopy. There was no ventricular tachycardia, nor atrial fibrillation.

Given an exertional component to the symptoms and to better characterise exercise capacity, exercise cardiopulmonary testing was performed. Cardiopulmonary stress testing via symptom-limited treadmill exercise performed following a modified Naughton protocol with oxygen consumption measurement demonstrated a reduced functional aerobic capacity at 66% of predicted (7.5 METS), a limited peak VO₂ (22.6 mL/kg/min, 66% of predicted) and low O₂ pulse, felt to reflect impaired cardiac output.

At this point, the patient's history and echocardiographic findings raised the question of coexistent HCM in a patient with acromegaly (table 1). A cardiac MRI was ordered for further differentiation. Cardiac MRI demonstrated a normal sized LV chamber, concentric LV hypertrophy (septum

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Table 1 Differential characteristics of conditions resulting in thickened cardiac walls

	Distinguishing characteristics
HCM	<ul style="list-style-type: none"> ▶ A genetic mutation results in LV hypertrophy (wall thickness >15 mm). LV hypertrophy is not the result of a secondary cause.⁴ ▶ SAM of the mitral valve (abnormal motion of the mitral apparatus into the LVOT during systole) is not a pathognomonic sign, but favours the diagnosis of HCM. SAM is caused by turbulent blood flow through a narrowed LVOT. This 'pushes' the mitral valve into the LVOT, given that mitral valve leaflets are often enlarged and anteriorly positioned within the LV cavity in HCM.⁵ ▶ Dynamic LVOT obstruction is present in approximately 2/3 of patients with HCM. Continuous wave Doppler across the LVOT demonstrates a characteristic late-peaking dagger-shaped appearance. However, a pharmacological stress-induced gradient is not specific to HCM and most frequent occurs in small hyperdynamic left ventricles, increased septal wall thickness from causes other than HCM and in younger patients.⁶ ▶ Cardiac MRI demonstrates delayed myocardial enhancement after gadolinium contrast injection in the majority of patients with HCM, corresponding to areas of fibrosis. This typically is patchy in distribution, and frequently involves the right ventricular insertion on the ventricular septum.
Acromegaly-induced cardiomyopathy	<ul style="list-style-type: none"> ▶ Classic echocardiographic findings are biventricular hypertrophy, global hypokinesia and left ventricle systolic dysfunction.⁷ LV systolic function can be preserved in cases with no active heart failure.⁸ Ventricular dilatation often occurs, but was not seen in this case. ▶ Symptoms and signs of heart failure with normal systolic function are present in approximately 10% of newly diagnosed acromegaly.⁹ ▶ Cardiac MRI may identify LV hypertrophy in acromegaly-induced cardiomyopathy with greater sensitivity than echocardiography; delayed myocardial enhancement is classically absent.
Hypertensive heart disease	<ul style="list-style-type: none"> ▶ Symmetrical LV hypertrophy is seen in patients with a history of long standing hypertension. ▶ Typically, the maximal LV thickness is less than 13 mm.
Cardiac amyloidosis	<ul style="list-style-type: none"> ▶ Suspicion of cardiac amyloidosis rises with the combination of low ECG voltage (present in 50% of patients) and concentric LV hypertrophy. ▶ Classically, a pericardial effusion and thickened valve leaflets are present. ▶ Echocardiographic strain assessment shows relative preservation of apical strain. ▶ Presents as a restrictive cardiomyopathy with preserved LVEF. ▶ Global subendocardial delayed gadolinium enhancement and difficulties with myocardial nulling on MRI highly characteristic of cardiac amyloid.^{10 11}
Athlete's heart	<ul style="list-style-type: none"> ▶ Mild LV dilatation may be present in trained athletes. ▶ Diastolic function is normal or supernormal. ▶ LV hypertrophy pattern is symmetric. ▶ Deconditioning results in reduction in LV mass.¹²

HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; SAM, systolic anterior motion.

20 mm) and hyperdynamic LV systolic function (LVEF 75%). There was no SAM of the mitral valve. The right ventricle was of normal size, with normal systolic function (ejection fraction 67%) and no evidence of right ventricular hypertrophy (video 1). There was no delayed myocardial enhancement.

DIFFERENTIAL DIAGNOSIS

Given the known history of acromegaly, the absence of delayed myocardial enhancement, symmetric hypertrophy, as well as absence of SAM of the mitral valve, acromegaly-induced cardiomyopathy was confirmed, as opposed to HCM.

TREATMENT

The mainstay of therapy for acromegaly-induced cardiomyopathy is treatment of the underlying excess GH secretion. Surgical resection of the pituitary adenoma is often the first-line treatment. In patients with persistent or recurrent disease, somatostatin analogues and GH antagonists are effective in suppressing GH secretion or blocking GH action, as well as reversing acromegaly-induced cardiomyopathy. Stereotactic radiosurgery or fractionated radiation offers a chance for a delayed cure. These treatments may result in anterior pituitary dysfunction requiring cortisol, thyroxine or sex hormone replacement therapy. In this patient, somatostatin analogues were continued along with hormonal replacement therapy, and surgical resection of his macroadenoma had been performed.

Dynamic LVOT obstruction can present in a host of conditions other than HCM. While most commonly seen in patients with hypertrophy, dynamic LVOT obstruction with dobutamine can be seen in patients without LV hypertrophy.¹³ Beyond relative wall thickness, LVOT size and chamber size have been correlated with presence of dynamic LVOT obstruction with

dobutamine.¹⁴ Treatment is similar across conditions and involves avoidance of low preload states (dehydration, perioperative blood loss, etc) and discontinuation of direct afterload

Video 1 Cardiac MRI short axis steady state free precession sequence. Cardiac MRI demonstrated normal left ventricular (LV) chamber size, concentric LV hypertrophy and hyperdynamic LV systolic function. There was no systolic anterior motion of the mitral valve. The right ventricle size was normal with preserved systolic function.

reducing agents (such as vasodilators) when possible, as these can worsen dynamic obstruction. Initiation of pharmacotherapy should be guided by presence of symptoms. Agents with negative inotropic and negative chronotropic mechanisms are the mainstay of therapy (either β blockers or calcium channel blockers). Should perioperative hypotension arise, positive inotropes may worsen hypotension, and direct afterload increasing agents (phenylephrine, vasopressin) are favoured. In this patient, given coexistent hypertension and potential exertional symptoms related to dynamic LVOT obstruction, β blockers were initiated with metoprolol tartrate 12.5 mg twice daily.

OUTCOME AND FOLLOW-UP

Congestive heart failure affects <3% of patients with acromegaly.¹⁵ Diastolic dysfunction and LV hypertrophy in acromegaly-induced cardiomyopathy are expected to improve with proper treatment and normalisation of GH secretion, while improvement in systolic dysfunction is less likely to occur.¹⁶

Telephone follow-up was arranged to monitor the newly initiated β -blocker side effects, blood pressure control and symptom improvement. The patient advocated symptom improvement following initiation of β -blockade.

Due to the significant impact of acromegaly-induced cardiomyopathy on mortality, recommendations were made for annual cardiomyopathy follow-up to monitor symptoms, cardiac chamber size and systolic function.

DISCUSSION

Acromegaly is suspected in patients with clinical features of excess GH including bone enlargement of the extremities and face, soft tissue swelling and excess sweating. Diagnosis is confirmed with biochemical testing including serum IGF-1 concentration and oral glucose suppression test. MRI of the pituitary identifies a pituitary adenoma in the vast majority of cases. Once the diagnosis is confirmed, treatment options include surgery, medical therapy and/or radiation therapy, with the goal of normalisation of GH secretion to obviate adverse effects on multiple vital organs including the cardiovascular system.¹

Given different management strategies between acromegaly-induced and hypertrophic cardiomyopathies, detailed evaluation is necessary to ensure correct diagnosis. Therapeutic interventions can result in significant improvements in cardiac function. A recent report describes a 60-year-old man with acromegaly and a partial empty sella who presented with dilated cardiomyopathy (LV ejection fraction 20%), which normalised following 1 year of treatment with somatostatin analogues and GH receptor blockers.¹⁷

The patient's diagnosis was challenging. While acromegaly-induced cardiomyopathy could be anticipated in a patient with acromegaly, the finding of a dobutamine-induced LVOT gradient raised concerns for coexistence of HCM in this patient. HCM is a relatively common cardiomyopathy with an estimated prevalence of 1/500 in the young adult population;¹⁸ however, it is a diagnosis of exclusion. Other conditions causing thickened cardiac walls, including hypertensive heart disease, athlete's heart and cardiac amyloidosis, were excluded (table 1). Cardiac MRI was performed for further characterisation of the patient's thickened LV walls. The presence of a dobutamine-induced LVOT gradient on echocardiography does not specifically identify HCM, as it can occur in various conditions with LV hypertrophy or hyperdynamic systolic function. Dynamic LVOT obstruction in this case was felt to be secondary to dobutamine provocation in a patient with hypertrophy secondary to acromegaly.

Accurate diagnosis of acromegaly-induced cardiomyopathy is essential because cardiac manifestations are an important cause of mortality. A detailed history is crucial in interpreting test results, as a family history of sudden cardiac death or HCM would raise clinical suspicion for HCM. Cardiac MRI may also be a helpful tool in differentiating between HCM and acromegaly-induced cardiomyopathy.

Learning points

- ▶ Cardiac manifestations of acromegaly need to be evaluated carefully given their significant adverse effect on survival.
- ▶ Acromegaly-induced cardiomyopathy can present with inducible left ventricular outflow tract obstruction mimicking hypertrophic cardiomyopathy (HCM).
- ▶ HCM is a diagnosis of exclusion; a patient's personal and family histories are a key in differentiating HCM from other causes of left ventricular hypertrophy.
- ▶ Cardiac MRI may help in differentiating HCM and acromegaly-induced cardiomyopathy.
- ▶ Therapy in acromegaly-induced cardiomyopathy is directed towards normalising growth hormone (GH) secretion and action by surgery, medical treatment with somatostatin analogues or GH blockers and/or radiation therapy; while in HCM, β blockers and calcium channel blockers are the first-line treatment to manage symptoms.

Competing interests None declared.

Patient consent Obtained.

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