

Cushing syndrome cardiomyopathy: an unusual manifestation of small-cell lung cancer

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Abstract

Cushing syndrome is a rare cause of dilated cardiomyopathy and heart failure with reduced ejection fraction. Cases describing this association are scarce. We describe a patient presenting with acute heart failure, new cardiomyopathy, refractory hypokalaemia, severe hyperglycaemia, and uncontrolled hypertension who was found to have hypercortisolism secondary to an ectopic adrenocorticotropic hormone-secreting primary lung neoplasm. This case highlights the effects of hypercortisolism on the myocardium. The finding of a non-dilated cardiomyopathy in this case is unique because the majority of previously reported Cushing syndrome cardiomyopathy cases have described left ventricular dilatation or significant left ventricular hypertrophy. In addition, small-cell lung cancer with adrenocorticotropic hormone production causing Cushing syndrome cardiomyopathy is rare.

Keywords Cardiomyopathy; Cancer; Acute heart failure; Reduced ejection fraction; Cushing syndrome

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Introduction

Cushing syndrome (CS) has a well-documented association with systemic manifestations including abnormalities in glucose and lipid metabolism, hypertension, and classic cushingoid appearance. CS is also a rare cause of dilated or hypertrophied cardiomyopathy and heart failure with reduced ejection fraction. The effects of hypercortisolism on the myocardium have not been well described to date. We report a patient presenting with acute heart failure, new cardiomyopathy, refractory hypokalaemia, severe hyperglycaemia, and uncontrolled hypertension who was found to have CS secondary to an ectopic adrenocorticotropic hormone (ACTH)-secreting small-cell lung cancer (SCLC).

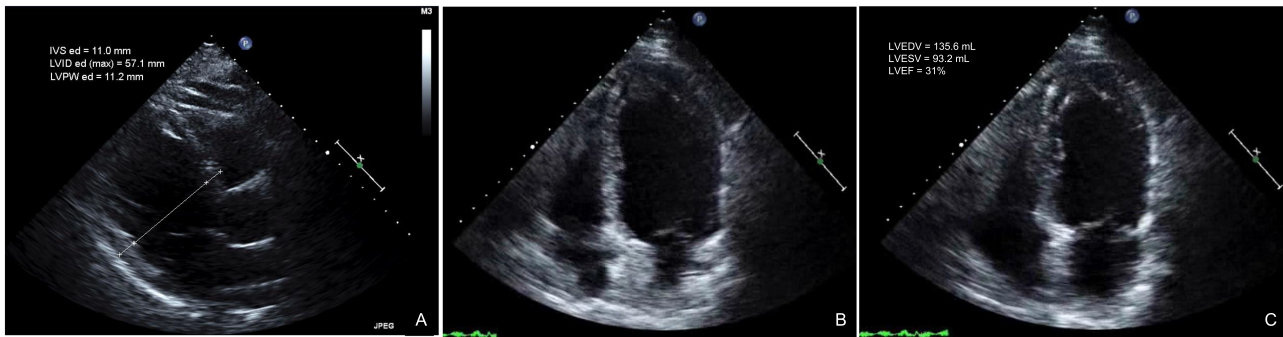
Case report

A 64-year-old man with a history of coronary artery disease (CAD), previously well-controlled type 2 diabetes mellitus

and hypertension, obstructive sleep apnoea, and tobacco use presented with shortness of breath, 20 lb weight gain, lower extremity oedema, and hyperglycaemia for the past 2 weeks. He had a prior inferolateral myocardial infarction in 2008 and stent implantation in the left-circumflex coronary artery. He had a preserved left ventricular ejection fraction (LVEF) and no prior history of congestive heart failure (CHF). On presentation, blood pressure (BP) was 189/101 mmHg. Physical examination revealed jugular venous distention, bilateral rales, and pitting oedema.

Transthoracic echocardiogram (TTE) using current American Society of Echocardiography guidelines¹ revealed a new cardiomyopathy with global hypokinesia and LVEF of 30–35% (Figure 1). He had mildly increased LV wall thickness (septum 1.1 cm, posterior wall 1.1 cm), normal LV cavity size [end-diastolic diameter 5.7 cm, end-diastolic volume 135 mL, indexed end-diastolic volume 61.6 mL/m² (normal range, 35–77 mL/m²)], normal relative wall thickness 0.39, and normal LV mass index 96.2 g/m² (49–115 g/m²). LVEF by biplane method of disks was 31%. LV peak-systolic global longitudinal strain (GLS) was reduced at –11.4%. Diastolic parameters

FIGURE 1 Echocardiogram images on presentation. (A) LV wall thickness and internal diameter in parasternal long axis view. Apical four-chamber view in diastole (B) and systole (C). LV volumes and ejection fraction were obtained by modified Simpson method (biplane method of disks). IVSed, interventricular septum at end-diastole; LVIDed, LV internal diameter at end-diastole; LVPWed, LV posterior wall thickness at end-diastole; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; LVEF, LV ejection fraction.



were as follows: peak E-wave velocity 87.9 cm/s, E/A ratio 1.6, average e' velocity 7.6 cm/s, and average E/ e' ratio 11.6, and left atrial volume index (LAVI) 36 mL/m². There was no significant tricuspid regurgitation to estimate pulmonary artery systolic pressure, but pulmonary vein S/D ratio < 1 suggested elevated left atrial pressure. These findings were suggestive of grade II diastolic dysfunction.

A coronary angiogram revealed patent stents, non-obstructive CAD, and an elevated LV end-diastolic volume of 30 mmHg. Hospital course was notable for persistent refractory hypokalaemia (serum potassium 2.7 mmol/L) despite aggressive potassium repletions. Differential diagnosis of resistant hypokalaemia included hypercortisolism, hyperaldosteronism, surreptitious diuretic or laxative use, type 1 or 2 renal tubular acidosis, and increased insulin availability.

Additional laboratory data were significant for BNP 277 pg/mL and haemoglobin A1C 10.9%. Cardiac enzymes were within normal limits. Urine potassium was elevated (39 mmol/L). Renin activity and aldosterone were both within normal limits, ruling out hyperaldosteronism. Thyroid-stimulating hormone was normal. Ferritin and iron panel were normal. Serum cortisol (59.9 µg/dL; ref range: 7–23 µg/dL) and 24 h urine free cortisol (8790 µg/day; ref range: ≤60 µg/day) were elevated, consistent with CS. ACTH was 224 pg/mL (ref range: 7–69 pg/mL), and his cortisol levels were not suppressed with high doses of dexamethasone.

CS provided a unifying diagnosis for the constellation of findings: non-ischaemic cardiomyopathy, refractory hypokalaemia, and new worsening of previously well-controlled hyperglycaemia and hypertension.

Chest computed tomography (CT) revealed enlarged mediastinal and right hilar lymph nodes and an irregular nodule in the right upper lobe of the lung measuring 1.2 × 0.9 cm suspicious for a primary lung neoplasm (*Figure 2*). Abdominal CT showed an enlarged liver with innumerable solid hypovascular masses, consistent with metastatic disease.

Fine-needle aspiration of the lung nodule revealed malignant SCLC.

He was diagnosed with stage IV ACTH-secreting SCLC with metastases to the liver. For the treatment of hypertension with concomitant hypokalaemia, lisinopril was maximized, and spironolactone was initiated and uptitrated to 150 mg twice daily. Furosemide was started once serum potassium normalized. Initiation of insulin was required for newly uncontrolled hyperglycaemia. Metyrapone was initiated for hypercortisolism. A chemotherapy regimen of etoposide, carboplatin, and atezolizumab was initiated for the treatment of his lung neoplasm.

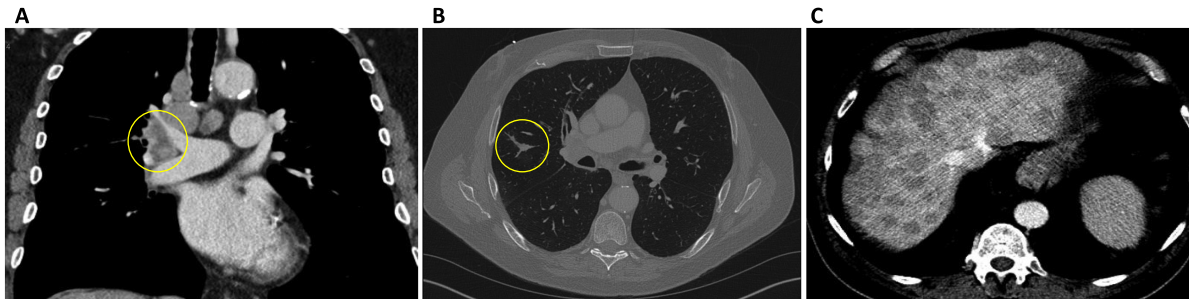
To date, he completed five cycles of chemotherapy without significant toxicities. His hypertension, glycaemic control, and potassium have improved. A repeat TTE following 2 months of therapy demonstrated an improvement in LVEF to 45–50% (*Figure 1*) and in peak-systolic GLS to –15.3%. This study showed similar LV wall thickness and normal cavity size. Diastolic parameters were consistent with normal left atrial pressure: peak E-wave velocity 85.4 cm/s, E/A ratio 1.2, average e' 8.0 cm/s, average E/ e' ratio 10.8, LAVI 32 mL/m², normal estimated mean PAP, and normal pulmonary vein S/D ratio.

Discussion

CS has been associated with cardiomyopathy in only a few reported cases.^{2–5} Most cases described were of hypertrophied and dilated cardiomyopathy. The current case is unique in two ways: (i) it demonstrates CS cardiomyopathy in the absence of dilatation, hypertrophy, or concentric remodelling that has been classically described; and (ii) it is a rare case of CS cardiomyopathy due to ectopic ACTH secretion by SCLC.

Hypercortisolism is associated with myocyte hypertrophy,² dilated cardiomyopathy with biventricular dysfunction,³

FIGURE 2 Hypercortisolism and heart failure with reduced ejection fraction leading to a diagnosis of metastatic small-cell lung carcinoma. Computed tomography (CT) chest and abdomen illustrating: (A) enlarged mediastinal and hilar lymph nodes (yellow circle); (B) irregular nodule in the right upper lobe of the lung measuring 1.2×0.9 cm (yellow circle); (C) hepatomegaly with innumerable hypodense masses consistent with metastatic disease.



myofibrillolysis, and myocardial fibrosis.^{3,6} Myocyte hypertrophy occurs owing to glucocorticoid-mediated increase in angiotensin II.² Myofibrillolysis has been partially attributed to atrogin-1 and the ubiquitin-proteasome system leading to proteolysis of contractile elements.^{2,6} Additionally, direct cortisol stimulation may lead to increased fibroblast function through Smad and TGF- β 1, causing extensive fibrosis.^{2,6} These histologic changes can be visualized following an endomyocardial biopsy, which was not performed in our patient because he did not have haemodynamic compromise or refractory heart failure, and there was low suspicion for giant cell myocarditis or an infiltrative process.⁷ Biochemical analysis and CT imaging led to the diagnosis of hypercortisolism, ectopic ACTH production, and lung cancer.

Prior cases have demonstrated an association between hypercortisolism and high LV mass index.^{4,8} On echocardiogram, specific features of concentric remodelling have been reported, including increased relative wall thickness, reduced systolic performance, and diastolic dysfunction.⁴ Further studies are needed to identify which CS patients are at a higher risk of developing concentric remodelling and cardiomyopathy. Literature suggests that restoration of normal cortisol levels can normalize LV structure and function.⁹ After treatment of hypercortisolism, a reduction in septal thickness was seen with improvements in global longitudinal and circumferential strain.⁵

However, in the case of our patient, echocardiogram measurements on presentation demonstrated normal relative wall thickness and normal LV mass, consistent with normal geometry, but reduced LVEF. After treatment, LVEF improved. This study is unique for echocardiogram parameters not showing either eccentric or concentric hypertrophy or remodelling. Our patient had been on carvedilol and lisinopril at baseline for his history of CAD and hypertension. It is possible that neurohormonal blockade prevented or slowed cardiac remodelling owing to hypercortisolism. Another possibility is that structural changes due to hypercortisolism take a longer time. He was doing well without any signs of CS just 5 weeks

prior. The time course of cardiac hypertrophy and pathologic remodelling due to hypercortisolism is not well known.

Whether the observed cardiomyopathy was caused by direct cardiotoxic effects of hypercortisolism or indirectly by severely elevated BP is difficult to discriminate. In the end stage of hypertensive heart disease, chronic sustained pressure and volume overload can lead to dilated cardiomyopathy with both diastolic dysfunction and reduced LVEF.¹⁰ Long-standing hypertensive heart disease is less likely to be the cause of his cardiomyopathy because his BP was normal in clinic just 5 weeks prior. Transient systolic dysfunction during hypertensive crisis is a possibility. However, in a study by Gandhi et al., patients with acute pulmonary oedema with marked hypertension (mean systolic BP of 200 ± 26 mmHg) experienced an infrequent finding of transient systolic dysfunction.¹¹ Finally, the cytokine production of cancer can contribute to cardiomyopathy and heart failure. Circulating inflammatory cytokines (TNF α , IL-6, IL-1- β , and IL-2) and oxidative stress, which can be increased in cancer, can exert deleterious effects on the heart and contribute to cardiac remodelling. Stress-induced or Takotsubo cardiomyopathy in the setting of cancer is also in the differential diagnosis.

CS is associated with systemic manifestations including abnormalities in glucose and lipid metabolism, hypertension, and alterations in coagulation factors, leading to a higher risk for the development of hypertensive, diabetic, and ischaemic cardiomyopathy.¹² Cortisol also affects microvascular function by targeting vascular smooth muscle and endothelial cells in the heart and reducing coronary flow reserve.¹³

SCLC is a neuroendocrine lung cancer and is the most frequent cancer type to be associated with paraneoplastic syndromes. CS secondary to ectopic ACTH production occurs in 1–5% of SCLC patients.¹⁴ Ectopic CS is associated with a large tumour burden or with the involvement of more than three organs. Thus, the presence of ectopic ACTH in SCLC confers a poor prognosis. In addition, patients with paraneoplastic CS present most frequently with muscle wasting, weakness, and syndrome of apparent mineralocorticoid excess rather

than typical Cushingoid features, leading to a disease process that is frequently overlooked.¹⁴

To date, little information is available on the development of CS cardiomyopathy and the risk of developing this syndrome in the context of SCLC. Much of the existing literature is a sampling of case reports describing probable downstream effects of cortisol on the myocardium.¹⁵ In particular, most of these case reports of CS cardiomyopathy involve either pituitary adenomas or adrenal tumours.¹⁵ This is a rare case to describe CS cardiomyopathy associated with a paraneoplastic SCLC.

In summary, this case is an interesting presentation of CHF with refractory hypokalaemia, which prompted further evaluation and ultimately led to the diagnosis of ectopic ACTH production by SCLC. Most of the previously described cases of CS

cardiomyopathy have been associated with pituitary and adrenal tumours.¹⁵ CS cardiomyopathy is classically characterized by eccentric or concentric LV hypertrophy.^{3,4} This is a unique case of CS cardiomyopathy associated with normal geometry. This case highlights the effects of hypercortisolism sourced from a rare tumour on the myocardium.

Conflict of interest

Srinath-Reddi Pingle declares that he has no conflict of interest. Tanvi Shah declares that she has no conflict of interest. Wassim Mosleh declares that he has no conflict of interest. Agnes S. Kim declares that she has no conflict of interest.

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