

CASE REPORT

Reversible dilated cardiomyopathy associated with glucagonoma

K Chang-Chretien, J T Chew, D P Judge

Heart 2004;90:e44 (<http://www.heartjnl.com/cgi/content/full/90/7/e44>). doi: 10.1136/hrt.2004.036905

An association between dilated cardiomyopathy and glucagonoma has not previously been described. A case of a 54 year old woman with tachycardia and congestive heart failure is described. Initial evaluation included an echocardiogram, which showed dilated cardiomyopathy with an ejection fraction of 15%. Coronary angiography and endomyocardial biopsy did not identify a secondary cause of her cardiomyopathy. She subsequently developed necrolytic migratory erythema, and imaging of her pancreas identified a pancreatic mass with a major increase of her serum glucagon concentration. Tachycardia persisted despite treatment with β blockers. After resection of her tumour, her heart rate normalised and subsequently her heart returned to normal size and function. Glucagon is used to treat overdoses of β blockers and calcium channel blockers, increasing heart rate by increasing myocardial cyclic AMP concentrations. Although rare, in the appropriate clinical setting, glucagonoma should be considered in the differential diagnosis for tachycardia and dilated cardiomyopathy.

Glucagon, a 29 amino acid peptide produced by α cells in the islets of Langerhans, counters the effects of insulin to maintain normal blood glucose. Pharmacological administration of glucagon is effective in the treatment of hypoglycaemia but extrahepatic effects are

also well known.¹ Overdose of β blockers and calcium channel blockers often responds well to glucagon administration because of the direct activation of myocardial adenylate cyclase, with a subsequent increase in cyclic AMP.² Glucagon increases both heart rate and cardiac output and it has been used to treat congestive heart failure.³

Glucagonoma is a rare neuroendocrine tumour of islet cells that has not previously been described as a cause of dilated cardiomyopathy. We describe a patient with glucagonoma whose presenting manifestations were cardiomyopathy and tachycardia. Her cardiomyopathy resolved several months after resection of her primary tumour, with normalisation of her heart rate.

CASE REPORT

A 54 year old woman presented with congestive heart failure and sinus tachycardia with resting heart rates of 100–120 beats/min. Echocardiography showed left ventricular enlargement (left ventricular end diastolic dimension 6.6 cm), normal left ventricular wall thickness (1.0 cm), and an ejection fraction of 15% without valve dysfunction (fig 1). Coronary angiography did not show any significant stenosis. Right ventricular endomyocardial biopsy showed moderate hypertrophy and vacuolisation of myocytes with mild interstitial fibrosis. There were no lymphocytes, giant cells, or granulomata. Serum thyroid studies were within normal limits. Her symptoms were not preceded by a viral illness. There was no family history of cardiomyopathy.

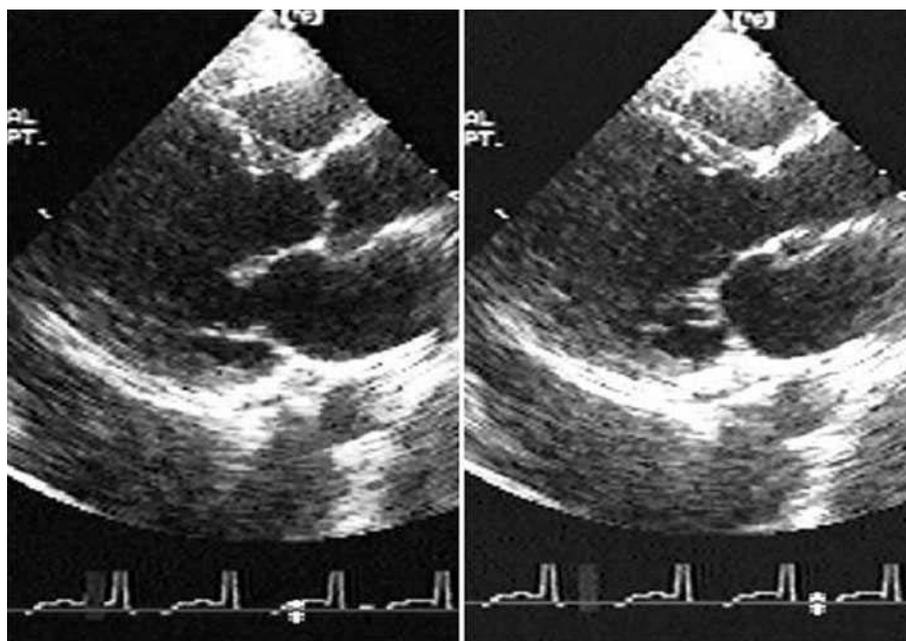


Figure 1 Parasternal long axis views of the heart by echocardiography. Left: Before resection of glucagonoma, at end diastole. Right: Before resection of glucagonoma, at end systole.



Figure 2 Left: Anterior view of rash on lower extremities with necrolytic migratory erythema. Right: Posterior view of rash.

The patient reported a long history of sore tongue, brittle nails, and dyspareunia. She also described intermittent angular cheilitis, with one episode lasting eight months before resolution. Over the past year, she had unintentionally lost about 6.8 kg (15 pounds) and had been experiencing daily morning nausea.

One year later, the patient developed a painful and pruritic perirectal rash that spread to her perineum. The rash then spread to her legs and was so painful that it limited her ambulation (fig 2). Physical examination was significant for bilateral angular cheilitis, resting tachycardia (> 100 beats/min) despite β blockade (carvedilol 12.5 mg twice daily), and an erythematous rash in various stages of healing. Biopsy of the rash showed zonal epidermal necrolysis consistent with necrolytic migratory erythema. Abdominal computed tomography showed a mass in the tail of the pancreas consistent

with glucagonoma. There were no liver metastases. Serum glucagon concentration was 1261 pg/ml (normal range 20–100 pg/ml). Serum measurement of gastrin, vasoactive intestinal peptide, insulin, and urinary 5-hydroxyindoleacetic acid were all within normal limits. Fasting serum glucose concentration was 4.39 mmol/l. A mild normocytic anaemia was present, with packed cell volume 33% and mean corpuscular volume 85.8 fl. Repeat echocardiography was notable for persistent left ventricular enlargement and systolic dysfunction, with ejection fraction unchanged (15%).

At the time of resection, the tumour measured 7.0 cm and had metastasised to seven of 24 lymph nodes. There was evidence of vascular invasion. The liver was free of metastatic disease. Pathology was consistent with a malignant islet cell tumour, which stained positively for chromogranin A, synaptophysin, and glucagon.

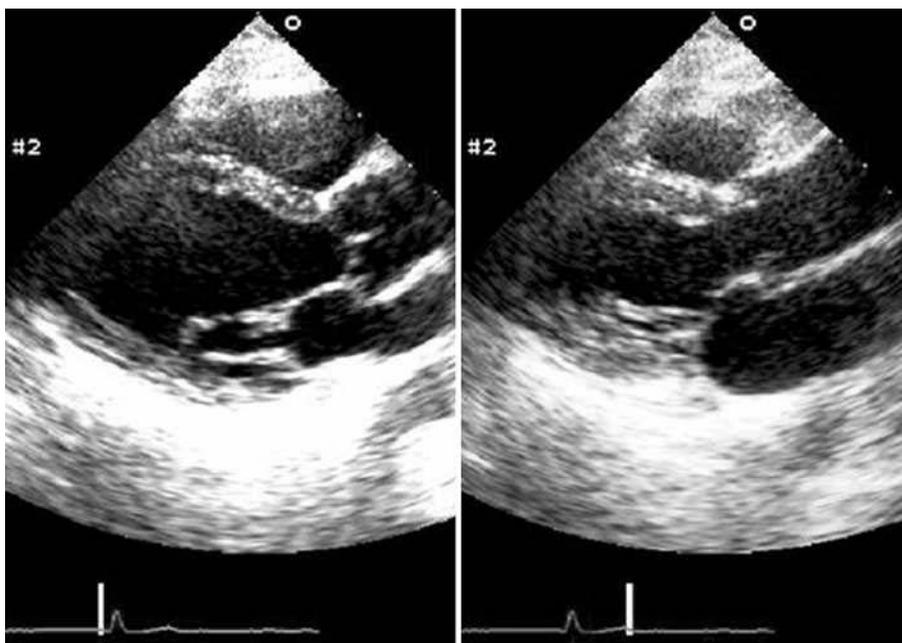


Figure 3 Parasternal long axis views of the heart by echocardiography. Left: Eight months after resection of glucagonoma, at end diastole. Right: Eight months after resection of glucagonoma, at end systole.

During the perioperative period, she had no symptoms of congestive heart failure, despite a persistently reduced ejection fraction (20%). Her postoperative course was notable for resolution of her chronic tachycardia, rash, and cheilitis. Eight months after resection of her glucagonoma, her serum glucagon concentration remains normal (26 pg/ml) and her echocardiogram is notable for normalisation of her left ventricular end diastolic dimension (4.7 cm) and a normal ejection fraction (55%) (fig 3).

DISCUSSION

Glucagonoma is a rare neuroendocrine tumour of the pancreatic α islet cell associated with a characteristic syndrome caused by hypersecretion of glucagon. Patients typically present in their fifth to sixth decade. Fewer than 400 cases have been reported worldwide. Classic features are diabetes, cheilitis, normocytic anaemia, painful glossitis, gastrointestinal disturbances, thromboembolism, and weight loss.⁴ It is hallmarked by the presence of necrolytic migratory erythema, an erythematous, painful, and pruritic rash that begins as macules, which coalesce and develop central bullae before eroding and leaving hyperpigmentation and crusting of the periphery.⁵ The eruption usually begins in the perirectal area with subsequent spread to the perineum, thighs, buttocks, and lower extremities. The development of the characteristic rash is often what leads to diagnosis. Dyspareunia, brittle nails, and a predisposition to fungal infections have also been described.⁶ Our patient exhibited many of the classic manifestations of the glucagonoma syndrome. Notably, diabetes mellitus was not present, likely due to adequate and compensatory insulin secretion.

In the medical literature, there have been no other reports of dilated cardiomyopathy and glucagonoma. In the case presented here, the patient's longstanding resting tachycardia, despite treatment with β blocker, resolved after the glucagonoma was resected. Since glucagon is known to increase myocardial cyclic AMP concentrations independent of β adrenergic receptor blockade, with coordinate increases in the heart rate and cardiac output, we propose that chronic, excessive glucagon stimulation of the heart led to cardiomyopathy in this case. Tachycardia is well known to result in dilated cardiomyopathy, which may be reversible.^{7 8} After the underlying cause is sought, with correction if possible, most patients are treated with β adrenergic receptor blockers. Our

patient received carvedilol, slowly increased to 12.5 mg twice daily, though further increases were not tolerated because of symptomatic hypotension. Despite this treatment, her tachycardia persisted, consistent with the known cardiac effect of glucagon to increase myocardial cyclic AMP concentrations independent of β adrenergic receptors.²

While glucagonomas are rare, it is important to be able to recognise the characteristic constellation of symptoms associated with the glucagonoma syndrome and to remove the tumour if possible. Cardiomyopathy may be a byproduct of this neoplastic process, likely by direct cardiac effects of the secreted glucagon.

Authors' affiliations

K Chang-Chretien, D P Judge, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland, USA

J T Chew, Howard County General Hospital, Columbia, Maryland, USA

Correspondence to: Dr Daniel P Judge, Johns Hopkins Hospital, Halsted 500D, 600 North Wolfe Street, Baltimore, MD 21287, USA; Djudge@jhmi.edu

Accepted 17 March 2004

REFERENCES

- 1 **Pollack CV Jr**. Utility of glucagon in the emergency department. *J Emerg Med* 1993;**11**:195–205.
- 2 **Sauvaget A**, Rohn T, Pecker F, *et al*. Synergistic actions of glucagon and miniglucagon on Ca²⁺ mobilization in cardiac cells. *Circ Res* 1996;**78**:102–9.
- 3 **Nord HJ**, Fontanes AL, Williams JF Jr. Treatment of congestive heart failure with glucagon. *Ann Intern Med* 1970;**72**:649–53.
- 4 **Chastain MA**. The glucagonoma syndrome: a review of its features and discussion of new perspectives. *Am J Med Sci* 2001;**321**:306–20.
- 5 **Johnson SM**, Smoller BR, Lamps LW, *et al*. Necrolytic migratory erythema as the only presenting sign of a glucagonoma. *J Am Acad Dermatol* 2003;**49**:325–8.
- 6 **Povoski SP**, Zaman SA, Ducatman BS, *et al*. Dermatitis, glossitis, stomatitis, cheilitis, anemia and weight loss: a classic presentation of pancreatic glucagonoma. *W V Med J* 2002;**98**:12–4.
- 7 **Corey WA**, Markel ML, Hoit BD, *et al*. Regression of a dilated cardiomyopathy after radiofrequency ablation of incessant supraventricular tachycardia. *Am Heart J* 1993;**126**:1469–73.
- 8 **Saavedra WF**, Paolucci N, St John ME, *et al*. Imbalance between xanthine oxidase and nitric oxide synthase signaling pathways underlies mechanoenergetic uncoupling in the failing heart. *Circ Res* 2002;**90**:297–304.