

Post-thymectomy collapse: an unusual case of acute adrenal insufficiency

Jonathan Richardson

Summary

A 54-year-old man who had an appearance strongly suggestive of Cushing's syndrome, collapsed after the removal of a carcinoid tumour of the thymus. The clinical suspicion of acute adrenal insufficiency was supported by invasive haemodynamic data and the diagnosis was subsequently confirmed biochemically. These post-operative events were subsequently ignored and a further crisis was probably prevented by tumour recurrence (and hence resumption of adrenocorticotrophic hormone (ACTH) production). The ectopic production of ACTH from a carcinoid tumour of the thymus is recognised but a report of acute adrenal insufficiency from its removal is probably unique.

Keywords: thymectomy, acute adrenal insufficiency, carcinoid tumour

Introduction

There are many reasons for postoperative hypotension with respiratory inadequacy following major surgery, but rare events need to be considered as well as common ones.

Report

Following sudden back pain after strenuous lifting, the chest X-ray of a 54-year-old man showed collapse of two vertebrae in the low thoracic spine, accompanied by an unexpectedly wide mediastinum. This latter chance finding prompted his referral to a thoracic surgeon, who was presented with an obese, breathless man. He was a heavy alcohol and cigarette consumer, taking frusemide and enalapril for hypertension. Computed tomography (CT) showed a 10 cm glandular mass in the anterior mediastinum. An uneventful left anterior mediastinotomy under general anaesthesia, provided tissue for a histological diagnosis of a carcinoid tumour of the thymus and he was listed for thymectomy.

His plethoric, truncally obese features, associated with striae and poor peripheral musculature, caused the anaesthetist assigned to this operation (the author), to question a possible diagnosis of Cushing's syndrome. His blood pressure was 210/125 mmHg, he had oedema to the knees and he was breathless on

minimal exertion. Haematology was normal. Potassium was 2.8 mmol/l, urea 7.2 mmol/l, venous bicarbonate 35 mmol/l. Pulmonary function tests showed an obstructive and restrictive pattern. Electrocardiography (ECG) revealed left ventricular hypertrophy.

The suspicion of Cushing's syndrome was allayed by information that he had recently been fully investigated by a consultant physician for his hypertension and although none of these results were available, his endocrine system had reputedly been found to be normal.

Following correction of his hypertension and hypokalaemia by the simple expediency of time and potassium supplementation, he underwent a median sternotomy. General anaesthesia was uneventful, although at one time he required a bolus of ephedrine for a transient period of hypotension. A discrete handful of tumour within a fatty thymus was peeled easily off the pericardium. Blood loss at surgery was about 600 ml and he was given two units of blood post-operatively on the ward when it was noted that he was hypotensive.

Forty-two hours after surgery, at 03.30 h, he complained of dyspnoea and was obviously in distress. He was afebrile, pale, clammy, and fatigued and had a peripheral oxygen saturation of 75% with an FIO₂ of 0.4. Blood pressure was 80/40 mmHg. White cell count was normal. Serum potassium was 5.9 mmol/l and blood sugar was 4.0 mmol/l. Arterial blood gases revealed a combined respiratory and metabolic acidosis with a pH of 7.24. ECG showed peaked T waves. A post-operative chest X-ray showed bilateral hilar and left basal shadowing. The provisional diagnosis made was pulmonary basal atelectasis, secretion retention, and cardiac failure due to myocardial ischaemia.

Upon immediate transfer to the intensive care unit, again the author was struck by the patient's Cushingoid appearance. Blood was taken for serum electrolytes and cortisol assay and steroids were started empirically. Because of the respiratory inadequacy and fatigue he was anaesthetised, intubated and ventilated and the anticipated ensuing hypotension was prophylactically treated with dopamine by infusion.

The question of pulmonary oedema was addressed by Swan-Ganz catheterisation. This revealed a right atrial pressure of 21 mmHg, a right ventricular pressure of 33/13 mmHg, a pulmonary artery pressure of 36/26 mmHg and a pulmonary artery occlusion

Department of
Anaesthetics,
Bradford Royal
Infirmary, Bradford
BD9 6RJ, UK
J Richardson

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pressure of 24 mmHg. These results appeared to confirm a diagnosis of congestive cardiac failure and inappropriate treatment would have been instigated except that data collection fortunately continued. Mixed venous oxygen saturation (S_vO_2) was 66% (95% arterial saturation (S_aO_2), FIO_2 of 0.5), cardiac output was 7.42 l/min and systemic vascular resistance was 775. These results were therefore not consistent with simple pump failure, but were rather a picture of systemic vasodilatation and fluid overload. Acute adrenal insufficiency was therefore likely and he was treated with hydrocortisone, frusemide, and antibiotics.

Within six hours his condition had dramatically improved. He had a mean arterial pressure of 88 mmHg, right atrial pressure of 18 mmHg and a pulmonary artery occlusion pressure of 18 mmHg. His S_vO_2 was 80% and calculated values showed a mean cardiac output of 5 l/min and a systemic vascular resistance of 1111. He was now making good quantities of good quality urine. After 24 hours, mechanical ventilation was discontinued and he was discharged from the intensive care unit.

The diagnosis of an hypoadrenal crisis was confirmed by a serum cortisol taken before treatment of 55 nmol/l (normal 140–700). Steroid treatment was continued on the ward, but unfortunately the diagnosis was not conveyed to the general practitioner, therapy was abruptly withdrawn and his endocrine status ignored.

Almost two years later the patient was listed for a resection of a recurrence of his mediastinal mass. Upon re-examination by the author, he appeared his familiar Cushingoid self. His obesity had increased, his osteoporosis had progressed with more vertebral collapses and his hypertension was out of control at 230/150 mmHg. With the benefit of the above experience, surgery was deferred until some investigations had been carried out. Baseline serum cortisol was 940 nmol/l, and a short synacthen test showed a degree of responsiveness of his adrenals, starting from a baseline of 940 nmol/l rising to 1416.7 at 30 min and 1717.3 at 60 min. Urinary cortisol was 2477 nmol/24 h (normal range up to 300).

With a settled blood pressure, further surgery went ahead, this time involving a posterolateral thoracotomy. There was found to be a 4 cm diameter tumour nodule attached to the left innominate vein with an extension on to the anterior chest wall. A piecemeal dissection was carried out. Pain relief was provided by pre-emptive, paravertebral, balanced analgesia.¹ His peri-operative course was unremarkable and a full steroid replacement and weaning regime was undertaken.

The patient died at home one year following this operation; the cause was believed to be a combination of a chest infection and unresponsive cardiac failure.

Discussion

The triad of flushing, diarrhoea, and asthma are not clinical features of thymic carcinoids, neither is an association with myasthenis gravis

Learning points

- patients with a carcinoid tumour of the thymus should have a diagnosis of Cushing's syndrome excluded
- acute adrenal insufficiency should be considered in any postoperative hypotensive collapse where thymic tissue has been removed

or red cell hypoplasia.² These tumours either present as a chance finding on chest X-ray, usually of a middle aged male (as in this patient), or because of compression of surrounding mediastinal structures.² Up to 30% of these tumours are associated with Cushing's syndrome due to ectopic adrenocorticotrophic hormone (ACTH) production and there is an association with the familial endocrine neoplasia syndrome.³ Thymic carcinoids are locally and distantly aggressive tumours with a five-year survival rate of only 15%; surgery offers the only chance of cure.²

Acute adrenal insufficiency has been recorded following the removal of apparently non-functioning adrenal masses,⁴ but a Medline search of the last 28 years failed to confirm that the removal of an ACTH-secreting carcinoid tumour of the thymus had previously been associated with this medical emergency. However, it is most likely that over the years such a mechanism must have been responsible for a number of post-operative deaths, especially those associated with hypotension and myocardial ischaemia.

The cardiovascular abnormalities noted during the hypoadrenal crisis in this patient are typical. Hypotension occurs due to a greatly lowered systemic vascular resistance. Cardiac output may be elevated. The pulmonary artery occlusion pressure can either be normal, low in the presence of hypovolaemia, or raised in the presence of congestive cardiac failure which itself can compound acute steroid depletion.⁴ All these abnormalities are reversed by steroid administration, the mechanisms of which remain obscure.

It should be noted that hormone withdrawal alone was not the only factor operable in this patient, a thoracotomy is one of the most stressful events which it is possible to inflict upon the hypothalamic–pituitary axis.¹ Indeed, it has been estimated (in the absence of regional analgesia¹) that during the first 24 postoperative hours, adrenal secretion of cortisol can be up to 150 mg.⁵

The failure to prescribe steroids during convalescence following initial tumour removal could have resulted in a further crisis. It is possible that this patient's life was saved by a residual ACTH-secreting tumour in mediastinal adipose tissue.

All patients with a known carcinoid tumour of the thymus should have a diagnosis of Cushing's syndrome excluded and acute adrenal insufficiency should be considered in any postoperative hypotensive collapse where thymic tissue has been removed.

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Methotrexate-induced pericarditis and pericardial effusion; first reported case

LN Forbat, BW Hancock, AH Gershlick

Summary

We report a case of methotrexate-induced pericarditis and pericardial effusion in a 22-year-old pregnant woman. These complications have not previously been described as isolated phenomena associated with methotrexate therapy.

Keywords: pericarditis, pericardial effusion, methotrexate, toxicity

Introduction

Methotrexate is used in different schedules in oncology and commonly in low dose oral regimens in rheumatology. The recognised features of methotrexate toxicity are shown in the box. Pericarditis and pericardial effusion have not previously been described as isolated phenomena, whereas pneumonitis and/or pleurisy are complications which occur idiosyncratically¹ in patients treated with methotrexate^{2,3} and are reported to occur in 5–12% of treated patients.^{1,4} In cyclical regimens used in oncology, pleural/pulmonary complications are very rare; however, in patients with persistent gestational trophoblastic disease receiving low-dose intramuscular repeated-course schedules, over 20% of patients may be affected.⁵ Steroids are not usually used to treat methotrexate lung; however, they may be of therapeutic value in some patients.¹ Occasionally the symptoms may be so severe and intractable that a change in cytotoxic therapy is required. We report a case of pericarditis and pericardial effusion leading to symptoms of breathlessness.

Case report

A 22-year-old woman presented with a molar pregnancy. Beta-human chorionic gonadotrophin (BHCG) levels were 6295 IU/l (normal <7) and a complete hydatidiform mole was removed at dilatation and curettage. Post-operatively BHCG levels fell to 3720 IU/l; however two months later a computed tomography (CT) scan showed a single pulmonary nodule and her BHCG levels remained elevated. She was treated with intramuscular methotrexate and folinic acid rescue.⁶ Nine courses were given over a 16-week period (total methotrexate dose 1.8 g). In month two she presented with pleuritic chest pains of the left and anterior chest. She was otherwise well and had no cough, sputum, or fever. On examination the only abnormality was a pleural rub at the left base. Methotrexate-associated pleurisy and pneumonitis was diagnosed. She was advised to ensure adequate hydration and symptoms responded to treatment with naproxen. BHCG levels remained normal during this episode. Two months after treatment she had recurrence of her symptoms of pleuritic chest pain and was also breathless on exertion. She remained afebrile and on clinical examination there were no abnormal signs. Chest X-ray showed cardiomegaly and echocardiogram revealed a large pericardial effusion (5 cm depth posteriorly and 2 cm anteriorly) without evidence of impaired myocardial function at rest. ECG, full blood count (eosinophil count $0.1 \times 10^9 l^{-1}$), urea, electrolytes and liver function were normal. Erythrocyte sedimentation rate was 18 mm/h. Pericardial aspiration was performed and 650 ml of clear fluid was drained. Cytology revealed abundant lymphocytes, reactive mesothelial cells and scattered eosinophils, but no malignant cells. Biochemistry of the aspirate was consistent with an inflammatory exudate; glucose 4.7 mmol/l (serum 5.2), albumin 28g/l, total protein 49 g/l. Bacterial cultures including tuberculosis were negative, as were serial viral titres and an auto-antibody screen. Her symptoms of breathlessness resolved and there has been no recurrence after 18 months.

Department of
Medicine, Good Hope
Hospital NHS Trust,
Sutton Coldfield, UK
LN Forbat

YCRC Department of
Clinical Oncology,
Weston Park Hospital
NHS Trust, Sheffield,
UK
BW Hancock

Department of
Cardiology, Glenfield
NHS Trust, Leicester,
UK
AH Gershlick

Correspondence to
Dr LN Forbat, Locum
Consultant Physician and
Cardiologist, Department of
Medicine, Good Hope
Hospital NHS Trust,
Rectory Road, Sutton
Coldfield, West Midlands
B75 7RR, UK

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Features of methotrexate toxicity

Acute: mild nausea/vomiting, diarrhoea, ulcerative stomatitis, conjunctivitis, pleurisy, marrow suppression
Chronic: skin rashes, cirrhosis/acute liver atrophy, nephropathy, defective oogenesis/spermatogenesis, osteoporosis, CNS: various effects following intrathecal treatment