Final diagnosis

Intracerebral haemorrhage complicating thrombolytic therapy for acute myocardial infarction.

Keywords: acute myocardial infarction, thrombolytic therapy, intracerebral haemorrhage

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Ectopic acromegaly

JK Platts, DF Child, P Meadows, JN Harvey

A 53-year-old woman presented to her general practitioner in November 1992 asking to be considered for hormone replacement therapy. She had noticed excessive sweating and tiredness but had no other symptoms. Her general practitioner noticed features suggestive of acromegaly.

In 1988 she had developed cough and haemoptysis and was investigated elsewhere. The chest X-ray at that time showed a right hilar mass. Thirteen years earlier she had had pneumonia. The mass was found to be present on X-rays taken then and had changed little over the intervening period. It had been felt to be benign with no further investigation necessary. In 1990 she presented with a nodular goitre which she felt to be unsightly. She was euthyroid. Surgery was offered but declined and no further action was taken. She was a life-long non-smoker on no medication.

Examination in 1992 revealed acromegalic facial features and enlargement of the hands and feet. She was normotensive and had a large multi-nodular goitre. Photographs taken nine years previously appeared normal. She was an anxious woman who at times declined investigation or treatment.

In a 75 g oral glucose tolerance test the plasma glucose was 5.6 mmol.l⁻¹ fasting and 7.3 mmol.l⁻¹ after 2 h; growth hormone (GH) was 68.5 mU.l⁻¹ fasting and did not suppress. After 200 µg intravenous thyroid-releasing hormone, serum GH increased from 67.4 to >150 mU.l⁻¹ at 20 min. Thyroid function, prolactin and a short synacthen test were normal. Luteinising hormone and follicle-stimulating hormone concentrations were at normal post-menopausal levels. The chest X-ray revealed a 9 cm diameter mass contiguous with the right hilum (figure 1). Computed tomography (CT) scan of the pituitary region was normal.

Figure 1 Chest X-ray showing right hilar mass

Questions

- 1 What is the most likely diagnosis?
- 2 What further investigations might be helpful?
- 3 What line of management should be pursued?

University of Wales
Academic Unit and
Department of
Diabetes and
Endocrinology,
Maelor Hospital,
Wrexham, Clwyd,
UK
JK Platts
DF Child
P Meadows
JN Harvey

Correspondence to Dr JN
Harvey, Renal and
Diabetes Centre, Maelor
Hospital, Croesnewydd
Road, Wrexham, Clwyd
LL13 7TD, UK

Accepted 6 June 1996

Answers

QUESTION 1

Acromegaly secondary to a bronchial carcinoid tumour secreting growth-hormone-releasing hormone (GHRH).

QUESTION 2

Peripheral venous GHRH measurement: $\text{GHRH}_{1-40}\text{OH}$ was 850 pg.ml^{-1} and GHRH_{1-44} was 460 pg.ml^{-1} (normal for both is $< 20 \text{ pg.ml}^{-1}$). Circulating concentrations of vasoactive intestinal polypeptide, pancreatic polypeptide, gastrin, glucagon and neurotensin were normal. Urinary excretion of metanephrines, free catecholamines and 5-hydroxy-indoleacetic acid were also normal. At bronchoscopy a polypoid fleshy tumour was visualised. Histological examination demonstrated a carcinoid tumour without cellular atypia or any features of malignancy. An octreotide scan was performed using $115 \text{ Mbq } [^{111}\text{In-DTPA-D-Phe}^1]\text{octreotide}$ (^{111}In -pentetreotide, Mallinckrodt, Holland). This radiolabelled ligand binds to somatostatin receptors and identifies neuroendocrine tumours. There was intense isotope accumulation over the thoracic tumour (figure 2). Selective sampling showed no clear gradient of GHRH concentration in the thorax or elsewhere but the azygous vein was not entered.

QUESTION 3

Excision of the bronchial tumour with subsequent endocrine testing to prove cure.

A CT scan of the thorax showed prominent calcification in the walls of the tumour. Angiography was undertaken prior to surgery because the surgeon wished to be sure he was not dealing with an angioma or arteriovenous malformation. Samples taken at surgery showed a modest gradient of GHRH concentration across the tumour bed. The concentration of GHRH_{1-40} in the artery feeding the tumour was 6600 pg.ml^{-1} and in the draining vein 8000 pg.ml^{-1} . A right middle and lower lobectomy was performed. Post-operative peripheral venous concentrations of both GHRH_{1-40} and GHRH_{1-44} were less than

5 pg.ml^{-1} . In a 75 g oral glucose tolerance test the GH concentration was suppressed to 1.6 mU.l^{-1} .

One of the classical techniques to prove ectopic hormone synthesis is to demonstrate hormone production *in vitro*. Cells from tumour tissue were grown in primary culture. Samples were taken from three wells after seven days. The concentrations of $\text{GHRH}_{1-40}\text{OH}$ were 15, 19 and 27 pg.ml^{-1} , and those of $\text{GHRH}_{1-44}\text{NH}_2$ were 190, 1000 and 200 pg.ml^{-1} , respectively, from the same wells.

Discussion

Acromegaly associated with an apparently normal pituitary and a mass elsewhere may be a chance association. In this case a causative association was proven by high circulating levels of GHRH which became normal when the lung tumour was removed and the finding that tumour cells produced GHRH *in vitro*.

Acromegaly may be the result of GH secretion from somatotropinomas arising in embryonic cell rests along the course of migration from Rathke's pouch to the sella turcica, or autonomous GHRH production may occur in hypothalamic or pituitary gangliocytomas. However, the majority of cases of true ectopic acromegaly (hormone synthesis arising from other than the normal tissue of origin) are due to extracranial GHRH synthesis.¹ The diagnosis of ectopic acromegaly may be suspected in any case of biochemically proven acromegaly where there is no clear pituitary adenoma, although in the review by Sano *et al*, 24 of 28 cases had an abnormal pituitary or sella on imaging and several underwent surgery as a result.² In six of these, serial studies were undertaken and a reduction in sellar size was seen in five after successful treatment (surgery or octreotide) of the source of GHRH. Initial peripheral venous levels of GHRH, when measured, were invariably raised to at least 299 pg.ml^{-1} .

Dynamic tests of pituitary function do not discriminate ectopic acromegaly from a pituitary adenoma source.¹ Assessment of GH pulsatility and diurnal variation is also of no diagnostic value. Selective sampling for GHRH and octreotide scanning are useful primarily in

Figure 2 Scintiscan image 4 h after injection of $115 \text{ MBq } ^{111}\text{In}$ -pentetreotide

Learning points

- acromegaly with an apparently normal pituitary CT/MRI scan and with or without a mass elsewhere suggests a diagnosis of ectopic GHRH synthesis
- single peripheral venous GHRH measurement is usually sufficient to confirm the diagnosis. Selective sampling or octreotide scanning may be useful for localisation
- some pituitary enlargement is often seen secondary to ectopic GHRH synthesis
- histological diagnosis of benign bronchial tumours is worthwhile and long-term follow-up of carcinoid tumours may be advisable

localisation. However, selective sampling is invasive and technical problems may be encountered. The attempt to show a GHRH concentration gradient across the tumour bed at surgery was only partly successful, probably as a result of the considerable tissue manipulation required to gain access to the feeding and draining vessels. Scanning with labelled octreotide is a useful means of identifying neuroendocrine and gastrointestinal endocrine tumours and can support the notion that an identified mass is the source of GHRH.³

Of the 39 fully documented cases of acromegaly due to extracranial tumours synthesizing GHRH identified by Faglia,¹ 21 were bronchial carcinoids, nine were islet cell tumours of the pancreas and three were duodenal or jejunal carcinoids; 17 had metastases. These tumours were mostly large.

Where full excision is not possible octreotide has proved effective in producing sustained improvement in symptoms and biochemically measured parameters, whereas bromocriptine or pergolide generally have not.^{1,4}

Final diagnosis

Acromegaly secondary to a bronchial carcinoid tumour secreting GHRH.

Keywords: growth hormone, bronchial tumour, acromegaly, octreotide

Our thanks to Professor M Scanlon and Dr M Lewis who performed the GHRH assays, to Dr D Parker who carried out the octreotide scan and Mr AS Soorae who excised the tumour.

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Acute abdomen after total hip replacement

M Nashi, B Banerjee

A 67-year-old woman was admitted for a routine total hip replacement for advanced osteoarthritis. She had a history of gall bladder stones and had undergone a cholecystectomy 30 years earlier. The patient was a non-smoker and there was no history of alcoholic indulgence. The operative procedure was uneventful but on the first postoperative day, the patient developed upper abdominal pain, nausea and vomiting followed by generalised abdominal pain and distension. Abdominal X-rays showed a few distended loops of bowel in the upper abdomen but no other abnormalities. Laboratory investigations prompted an urgent computed tomography (CT) of the abdomen (figure). The patient's condition rapidly deteriorated and she was transferred to the intensive care unit. The patient died due to respiratory and renal failure on the tenth postoperative day.

Figure CT scan of abdomen

Questions

- 1 What does the contrast-enhanced CT scan show?
- 2 What is the diagnosis?
- 3 What abnormal laboratory test prompted the CT scan?
- 4 How is the condition managed?

Tameside Trust
Hospital, Fountain
Street, Ashton under
Lyne, OL6 9RW, UK
M Nashi
B Banerjee

Accepted 29 March 1996