CASE REPORT

Possible functional regression of insulinoma with prolonged octreotide

C E H Craig, I W Gallen

A 75 year old woman was treated for over three years with the somatostatin analogue, octreotide, for an insulinoma. She had presented in a hypoglycaemic coma. C-peptide and insulin concentrations were both raised and an area of increased vascularity within the pancreas was shown by angiography. No lesion was found at laparotomy and no resection was performed. After over three years of octreotide treatment it was withdrawn for a week. Her insulin and C-peptide concentrations were greatly reduced at this time and remained so.

The somatostatin analogue, octreotide inhibits secretion of a wide variety of peptide hormones including insulin. It has been successfully used in previous cases of insulinoma. Other well differentiated endocrine tumours have reduced in size when treated with drugs that inhibit hormone production—for example, bromocriptine in prolactinoma. Here we report a case of markedly reduced insulin production from an insulinoma, once octreotide treatment was withdrawn.

CASE REPORT

A 75 year old woman presented, unconscious, after a collapse at home. An initial diagnosis of a cerebrovascular accident was made. However, the capillary blood glucose concentration was measured at 1.1 mmol/l. She was resuscitated with intravenous 50% dextrose solution. After regaining consciousness she reported episodes of feeling sweaty, weak and dizzy, especially at night, one of which had preceded this collapse. She denied taking any alcohol or hypoglycaemic drugs that day and reported a weight gain of 2 kg.

She had a three year history of ischaemic heart disease, with left ventricular failure secondary to an inferior myocardial infarct, confirmed by echocardiography. This had been treated with captopril 50 mg twice a day, frusemise (furosemide) 120 mg once a day, isosorbide mononitrate 20 mg twice a day, and aspirin 75 mg once a day. She also had a three year history of histologically confirmed ulcerative colitis, treated with sulphasalazine and enemas containing hydrocortisone and mesalazine. She had taken only her usual medicine.

On examination she was pale, with no increased pigmentation. Her pulse was 100 beats/min, blood pressure 165/95 mm Hg, and her jugular venous pressure was not raised. A third heart sound and pansystolic murmur consistent with mitral regurgitation, were heard. She had bibasal inspiratory crepitations and a chest radiograph confirmed pulmonary oedema. Examination of her neurological and abdominal systems were both normal. An electrocardiogram showed both first degree heart block and left bundle branch block.

Bleeding on presentation showed glucose of 0.7 mmol/l, normal electrolytes and an appropriately raised cortisol, excluding adrenal insufficiency. A normal thyroid stimulating concentration excluded hypothyroidism. Her admission insulin and C-peptide levels were later reported as 438.7 pmol/l (21.5–115.0) and 2810 pmol/l (180–630) respectively. A urinary sulphophyllurea screen was negative. As her C-peptide levels were raised, the presence of exogenous insulin was also excluded. Gastrin, vasoactive intestinal peptide, pancreatic peptide, glucagon, neurotensin, somatostatin, and urinary 5-hydroxyindoleacetic acid levels were all normal, making carcinoid an unlikely cause.

She was managed with a dextrose infusion for a week and subsequently started on octreotide 50 µg three times a day. The dose was later increased to 100 µg times a day. Her blood glucose remained between 4.1 mmol/l and 7.9 mmol/l thereafter.

To localise the insulinoma, computed tomography with contrast and magnetic resonance imaging with axial T1 and T2 spin echo sequences through the pancreas, were performed. As these did not demonstrate an adenoma, a coeliac angiogram was then performed. An area of increased vascularity supplied by the dorsal pancreatic branch of the splenic artery, at the junction of the body and tail of the pancreas, was demonstrated, measuring an estimated 2 cm (fig 1).

Two months after her admission she underwent a laparotomy, through a bilateral subcostal incision. The entire body, tail, and head of the pancreas was mobilised and palpated after a Kocher manoeuvre. Intraoperative ultrasound could not be performed. There was no tumour visible in the liver. Biopsies taken from the pancreas and two adjacent lymph nodes were all histologically normal. A blind resection was not undertaken because of the success of octreotide treatment in this case and to avoid the associated complications, such as pancreatitis, fistulas, pseudocysts, bleeding, and diabetes.

She was discharged on octreotide and followed up in clinic. Over the next year she had two episodes of hypoglycaemia,
after forgetting to take her octreotide. She measured her blood glucose every two weeks and it remained between 4 and 4.5 mmol/l.

Two years later, home glucose monitoring showed she was still having considerable periods of asymptomatic, relatively severe hypoglycaemia. There was no evidence of a pancreatic tumour on repeat computed tomography or three years later. Bilary sludge was shown, probably caused by the octreotide, a recognised adverse effect. From that time she had no episodes of hypoglycaemia.

Three and a half years after starting octreotide, it was stopped. After one week, fasting concentrations of glucose, C-peptide, and insulin were measured. Fasting glucose was 5.7 mmol/l, insulin at that time was 56.4 pmol/l (21.5–115.0), and C-peptide was slightly raised at 690 pmol/l (180–630).

**DISCUSSION**

Insulinomas are uncommon tumours of the β-cells of the pancreas, which can present with severe and disabling hypoglycaemia, although presenting symptoms are often more subtle. They can occur at any age and have an equal sex distribution. As many as 90% have been reported as benign, 90% solitary, and 75% less than 3 cm.

To reach a diagnosis of insulinoma other causes of hypoglycaemia had to be excluded. Hypoglycaemia can be caused by drugs such as sulphonylureas, β-blockers, alcohol, and of course insulin. Sulphonamides can act like sulphonylureas so this patient’s sulphasalazine was stopped.

Tumours such as insulinomas, carcinoids, hepatic carcinomas, and sarcomas may also cause hypoglycaemia. However, insulin concentrations remain normal or low in carcinomas and sarcomas.

Certain endocrine deficiencies may lead to hypoglycaemia such as Addison’s disease, adrenocorticotrophic hormone deficiency, pituitary failure, and hypothyroidism. Rarely, insulin autoimmune syndrome may occur where antibodies to insulin enhance its effect. It may be precipitated by drugs containing sulphydryl groups including captopril and sulphalazine, which this patient was taking. However, the onset has been reported as between four and six weeks after starting the drug and our patient had taken both these medicines for three years. In addition there have been reports of hypoglycaemia in some cases of end stage liver or renal failure and sepsicaemia. There was no evidence for any of these conditions. This left a differential diagnosis of insulinoma or adult neiodoblastosis.

Previous studies have shown benefits from the use of octreotide in patients with insulinomas. None of the previous studies have shown any evidence of tumour shrinkage. Well differentiated tumours may remain under the same hormonal control mechanisms as the tissue from which they derive. With such tumours, altering the hormone environment can have dramatic effects on growth. For example, prolactinomas reduce in size when treated with bromocriptine, and VIPomas when treated with octreotide.

Octreotide itself has also caused shrinkage of some carcinoid tumours. A 20% reduction in the size of lymph node and liver carcinoid metastases has been reported. Histologically proved metastatic carcinoid was treated successfully for 12 years in a separate patient who then died of a haemorrhagic stroke. At postmortem no evidence of tumour was found, despite extensive macronodular liver sclerosis secondary to tricuspid regurgitation.

In this case octreotide caused a reduction in insulin and C-peptide concentrations and maintained glucose levels. Although there is no imaging evidence of a reduction in size of the tumour, the persistently lower levels of insulin after withdrawal of octreotide could only be accounted for by a reduction in the functional size of the tumour. A repeat selective angiogram could not be condoned on clinical grounds as she has become asymptomatic.

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