Ovarian carcinoma producing hypoglycaemia

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A 26-year-old woman presented with six months of abdominal discomfort. At laparotomy a 40 x 40 cm omental tumour invading the stomach and involving the spleen was found with multiple tumour nodules over all the peritoneal surface. Both ovaries were enlarged and a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and debulking procedure was undertaken. Significant residual disease remained. Histology showed an undifferentiated ovarian carcinoma. CA-125 was elevated at 225 U/ml (normal range 0–22). Immunostaining of the tumour showed CAM 5.2 positive, most marked in the larger cells, epithelial membrane antigen focal and faint positive, mixed cytokeratins (AE1) positive, beta human chorionic gonadotropin negative, alpha-fetoprotein focal and faint.

A diagnosis of stage 4 ovarian carcinoma was made and she underwent chemotherapy with six cycles of cisplatin, etoposide and bleomycin. Following an initial response, she relapsed five months later and received six cycles of epirubicin, cisplatin and fluorouracil. Eighteen months after diagnosis her condition worsened and she was given one course of paclitaxel.

Two months later she presented with a two-week history of increasing lethargy. On the day of admission she had become increasingly agitated and, then, unrousable. There were no other symptoms of note. On examination, she had a Glasgow Coma Scale score of 8/15 and no focal neurological deficit. Full blood count, urea, electrolytes, liver function tests and serum calcium were normal. The laboratory venous serum glucose was 1.6 mmol/l.

She was given 50 ml of 50% dextrose intravenously with immediate correction of the hypoglycaemia and regained consciousness. Cranial computed tomography scan and lumbar puncture were normal. Although eating a high carbohydrate diet with frequent snacks the episodes of fasting hypoglycaemia became more frequent over the following week requiring continuous dextrose infusions, of at least 350 g of glucose per 24 hours, with intramuscular glucagon when her intravenous lines failed.

When the venous serum glucose concentration was 0.9 mmol/l, insulin (<25 pmol/l), C-peptide (<75 pmol/l) and beta-hydroxybutyrate (<20 mmol/l) were undetectable while serum growth hormone (GH; somatotropin) was 8.6 mU/l. Insulin-like Growth Factor-I (IGF-I) concentration was 0.18 U/ml (0.4–2.0) while the serum IGF-II concentration was elevated at 2.0 U/ml, giving an IGF-I:IGF-II ratio of 0.09 (normal >0.2). 'Big' IGF-II concentration was elevated at 21.6 nmol/l (reference range 0–14.4) and IGF-binding protein-3 levels were in the lower end of the normal range at 2.1 mg/l (reference range 2.0–4.8). A short tetracosactrin test was normal.

She was treated with oral prednisolone (30 mg/day) and recombinant human somatotropin, at an initial dose of 0.125 U/kg/week given as a once daily subcutaneous injection. This allowed discharge home after two weeks with only oral supplements during the day and occasional intramuscular glucagon overnight.

Questions

- 1 What is the cause of this patient's hypoglycaemia ?
- 2 What is the rationale for giving prednisolone and somatotropin ?

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Answers

QUESTION 1

Non-islet cell tumour hypoglycaemia (NICTH). In a patient with a metastatic carcinoma, not receiving insulin or sulphonylurea therapy, an insulinoma is possible but other causes such as liver failure, adrenal insufficiency and NICTH are more likely.¹ In this patient, undetectable insulin and C-peptide during hypoglycaemia with normal adrenal and liver function tests suggested that she had NICTH. This was confirmed by the IGF assays. Other tumours associated with NICTH are shown in the box.

QUESTION 2

Therapeutic somatotropin (growth hormone) increases IGF-I and, therefore, IGF-BP3 concentration so reducing the bioavailability of 'big' IGF-II.¹ Prednisolone decreases tumour secretion of pre-IGF-II forms such as 'big' IGF-II and increases binding to acid-labile subunit, so further reducing its bioavailability.¹ The combination of these therapies is therefore beneficial, and facilitated the management of this patient at home.

Discussion

In any patient with significant hypoglycaemia, and no evidence of adrenal or hepatic disease, the initial question is whether there is insulin and C-peptide present. If insulin is high but no C-peptide is found, exogenous administration of insulin should be considered. With high insulin and C-peptide this may be from an insulinoma or pharmacological agents such as sulphonylureas, or less commonly sulphonamides in patients with renal disease. If insulin levels are low, such as in our patient, then what is reducing the glucose? IGFs can do this and checking IGF-I, IGF-II and binding proteins will help to decide the cause.

NICTH usually occurs with large mesenchymal or epithelial tumours weighing over 1 kg and measuring more than 5 cm in diameter²; some potential causes are shown in box 1. This phenomenon has not, to our knowledge, previously been reported with an ovarian carcinoma. These tumours may produce 'big' IGF-

Potential causes of NICTH³

Tumours of mesodermal origin

- fibroblastomas
- fibromas
- fibrosarcomas
- haemangiopericytomas
- haemangiopericytoma
- histiocytomas
- leiomyosarcoma
- mesenchymal tumours of the diaphragm, pancreas and pleura
- mesoblastic nephromas
- mesothelioma

Tumours of epithelial origin

- adrenal carcinomas
- carcinomas of the gastrointestinal tract, lung, or prostate
- hepatomas
- medullary thyroid carcinoma

Tumours of haemopoietic origin

- leukaemia (CML)
- lymphoma (gastrointestinal)

Tumours of neuroectodermal origin

- neuroblastoma

II, an incompletely processed precursor molecule of IGF-II,^{1,2} which binds to insulin receptors as well as IGF-I and IGF-II receptors so causing hypoglycaemia.^{1,2} Most circulating IGFs are in a biologically inactive 150 kDa complex with two binding proteins, IGF-BP3 and an acid-labile subunit.^{1,2} In this form IGF is unable to leave the circulation.³ 'Big' IGF-II can bind to IGF-BP3 but its affinity for the acid-labile subunit is reduced. Complexed with IGF-BP3 alone it can leave the circulation, so increasing its bioavailability.^{1,2} 'Big' IGF-II suppresses somatotropin production, so reducing both IGF-I and IGF-BP3 production, again increasing its bioavailability.¹

Final diagnosis

Non-islet cell tumour hypoglycaemia.

Keywords: hypoglycaemia; non-islet cell tumour

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