Rare disease

A rare case of hypoglycemia in a patient with elevated right hemidiaphragm

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A 57-year-old woman was admitted to the emergency department, presenting with episodes of altered consciousness and behaviour which, upon further examination, were linked to periods of recurrent hypoglycaemia. Imaging revealed a large mass in the right thoracic cavity while blood analysis demonstrated diminished C-peptide, (pro-)insulin, insulin-like growth factor 1 (IGF-I) and IGF binding protein 3 levels. Based on these findings, an IGF-II secreting tumour was suspected. Before the excision of the tumour, euglycaemia could only be achieved by means of intravenous glucose administration and the use of oral corticosteroids. Anatomopathologically the diagnosis of a solitary fibrous tumour (SFT) was confirmed. Immunoblot analysis on the serum revealed elevated 'big'-IGF-II levels, confirming our initial diagnosis of Doege–Potter syndrome in SFT.

BACKGROUND

Being even four times less frequent than insulinoma-associated hypoglycaemia,^{1 2} the Doege–Potter syndrome is an extremely rare cause of hypoglycaemia. In this case report, we emphasise the need to screen for this type of tumour in patients where hypoglycaemia is associated with suppressed serum insulin, C-peptide and insulin-like growth factor 1 (IGF-I) level, and without further evidence for adrenal, kidney or liver insufficiency.

CASE PRESENTATION

A 57-year-old woman was admitted to the emergency department with symptoms of altered behaviour and consciousness. One week prior, she experienced a comparable episode of lypothymia. Blood glucose concentration at initial presentation was 33 mg/dl (70–100 mg/dl). No history of personal nor environmental intake of insulin or oral antidiabetics could be noted.

For several months, the patient had experienced breathing difficulties both in rest and upon exertion, which were intermittently associated with palpitations. Over the past year, she gained 10 kilograms, after initially losing 45 kg following a stringent diet (without bariatric surgery).

A few months before, the patient underwent radioactive iodine treatment for a polynodular goitre. At the time of presentation, the patient appeared euthyroid. Other antecedents included arterial hypertension and deep venous thrombosis, G2P2A0 and appendectomy. In the family history, a brother died of thyroid cancer at young age. There was no evidence for diabetes in the family. The patient did not smoke, with only sporadic alcohol consumption.

Upon physical examination, a pale overweight woman, with slightly acromegaloid signs at the level of the chin and the nose could be observed. Hypoventilation at the inferior part of the right thoracic space was noted upon

auscultation, while a lowered burden of the liver was palpated.

High input of intravenous glucose supplement was mandatory to avoid hypoglycaemia. Just after 2 h, a 72-h fasting test had to be terminated due to occurrence of symptomatic deep hypoglycaemia (<30 mg/dl). After each period of hypoglycaemia, blood samples for C-peptide, pro-insulin and insulin measurement were taken. When glucose was administered, hypoglycaemic symptoms relieved, and glucose level rose, consistent with Whipple's triad.

INVESTIGATIONS

At a serum glucose level of less than 30 mg/dl (70–100), the insulin concentration was less than 1 mU/l (2.6–24.9), C-peptide 0.10 µg/l (1.10–4.40) and pro-insulin 4.40 pmol/l. Thyroid stimulating hormone level was 2.180 mIU/l (0.27–4.2) and free thyroxine 15.2 ng/l (9.3–17.0). IGF-I was 33 µg/l (81–225), IGF-binding protein 3 (IGFBP-3) 1890 µg/l (3400–6860), growth hormone <0.15 µg/l (<8) and IGFBP-3/IGF-I ratio 15.3 (<10.0). Total IGF-II was normal, 320 ng/ml (280–610), but, the level of IGF-IIe (68–88) was elevated: 64 ng/ml (+6.5 SDS). Fasting cortisol was 232 µg/l (62–194) with adrenocorticotrophic hormone (ACTH) 21.1 ng/l (7.2–63). ACTH-stimulation test, urinary catecholamine excretion, kidney and liver function tests appeared normal. On admission, mild hypokalaemia of 3.2 mEq/l (3.6–5.0) and hypernatraemia of 150 mEq/l (137–145) was observed, which persisted during further hospitalisation. There were no signs of inflammation, infection nor anaemia. As mentioned above, 72-h fasting test was interrupted prematurely because of symptomatic (sweating, shakiness, restlessness) and deep hypoglycaemia, less than 30 mg/dl (70–100).

X-ray (figure 1) of the chest was initially described as normal, except for the presence of an elevated right hemi-

Figure 1 (A) X-ray upon admission, showing elevated right hemi-diaphragm, in fact mimicking a large mass at the basis of right lung; (B) Status after surgery.

Figure 2 MRI image of a large solitary fibrous tumour of the inferior right thoracic cavity.

diaphragm. MRI (figure 2) of the abdomen showed no evidence for pancreatic lesions, however, the upper images serendipitously revealed a large lobulated mass at the basis of the right lung, associated with fluid expulsion. Octreotide scanning did not reveal areas of increased somatostatin uptake, while fluorodeoxyglucose positron emission tomography demonstrated moderate and solitary uptake at the level of the thoracic mass. X-ray CT described a thoracic mass of 16.6 cm latero-lateral by 19 cm anteroposterior by 15 cm craniocaudal, without signs of local nor lymph node invasion, but with limited shifting of the heart to the left-anterior side.

DIFFERENTIAL DIAGNOSIS

Non-congenital causes of hypoglycaemia, excluding postprandial reactive hypoglycaemia, are either tumour dependent or non-tumour dependent. The latter can be elicited by drugs (insulin or insulin-secretagogues, β -blockers, quinine, pentamidine and sulfamethoxazole-trimethoprim), fasting, alcohol abuse, critical illness (eg, hepatic or renal failure), insulin auto-antibodies or endocrine deficiencies

(eg, hypocortisolaemia, growth hormone deficiency, sometimes combined in panhypopituitarism).

Tumour-dependent hypoglycaemia² can occur upon adrenal or renal invasion or by glucose consumption in case of a large tumour bulk. Endogenous secretion of insulin occurs in pancreatic insulinoma, ectopic insulin secreting tumours or nesidioblastosis (β -cell hyperplasia). In addition, hypoglycaemia can be induced by factors altering glucose metabolism such as insulin receptor antibodies, catecholamines and various cytokines (eg, tumour necrosis factor- α , interleukin-1 and -6 or IGF-I). Finally, rare cases of non-islet cell tumour-induced hypoglycaemia (NICTH) have been described. NICTH can arise in any kind of benign or malignant tumour. It mainly occurs in solid tumours of mesenchymal or epithelial origin.¹ In this case, hypoglycaemia is induced by secretion of partially processed precursors of IGF-II, named 'big'-IGF-II. This latter orchestrates important secondary changes, notably severe hypoglycaemia, accompanied by suppressed levels of insulin, C-peptide, growth hormone, IGF-I and IGF-binding proteins.¹

TREATMENT

On admission to the hospital, intravenous glucose was administered, according to the blood glucose level. After investigation and decision to perform debulking and curative-intentional surgery, without preoperative fine needle aspiration (FNA), oral glucocorticoid treatment, at a dose of 32 mg methylprednisolone daily, was initiated orally. This dose was continued until surgery, and enabled cessation of intravenous glucose infusion; it also allowed us to perform PET-FDG scan.

Arteriography showed vascularisation of the tumour via the inferior diaphragmatic and T10 until T12 intercostal arteries, which were subsequently embolised.

The patient was ultimately treated by surgical resection of the large tumour, via postero-lateral thoracotomy. Intraoperatively, a large, dark, lobulated and hard mass which seemed to originate from the diaphragm was detected. A piece of diaphragm was resected, which revealed no tumour invasion microscopically. The bulk mass could be removed easily, however adherence to the right lower lung lobe necessitated partial lobectomy. The resected lung tissue showed no tumour invasion. After surgery, oral glucocorticoids could be reduced gradually, and finally stopped, without recurring of hypoglycaemia.

OUTCOME AND FOLLOW-UP

Since we hypothesised the diagnosis of NICTH, serum samples for 'big'-IGF-II were taken before and after surgery. Preoperative serum IGF-II(68–88) level was elevated with 64 ng/ml (+6.5 SDS) and dropped to 9.6 ng/ml (–1.84 SDS) postoperatively with concomitant regain of intravenously glucose independency and the possibility to gradually taper off the corticosteroid regimen.

The anatomopathological examination of the resected tumour revealed the presence of a 1930 g weighing solitary fibrous tumour (SFT) with maximal diameter of 20 cm and tumour-free excision borders (no tumour invasion could be noted in tissue samples of right lower lobe, diaphragm, nor in a pleural fragment) (figures 3 and 4). Immunohistochemically, vimentin staining was positive. Necrosis and partial loss of CD-34 positivity, both negative prognostic factors, were reported. However, the observed cell death could at least partly be attributed to the embolisation procedure performed preoperatively.

After tumour resection and cessation of glucocorticoid treatment, glycaemia levels did not drop below 60 mg/dl and IGF-I, growth hormone and IGFBP-3 levels normalised. The patient was dismissed 1 month after initial admission. Upon clinical reassessment 3 months after diagnosis and resection, our patient was symptom-free. No further episodes of hypoglycaemia were measured

by intermittent capillary blood glucose measurements at home. A follow-up CT scan after 3 months, did not reveal tumour relapse.

DISCUSSION

We present a rare case of hypoglycaemia in a female patient with a large solitary tumour. The patient was admitted to hospital with serious and symptomatic hypoglycaemia, requiring large doses of intravenous glucose and oral corticosteroids. After resection of a large tumour in the right thorax, hypoglycaemia disappeared. Until present, no signs of extratumoural lesions could be detected.

Solitary fibrous tumours (SFT) are rather uncommon, with approximately 800 cases of pleural SFT described in English literature until 2009.^{3,4} Moreover, extrathoracic SFT have been described, which can also be associated with hypoglycaemia. Concomitant pleural SFT with hypoglycaemia is rare, approximately 5% of pleural SFTs develop hypoglycaemia. However, virtually every benign or malignant tumour can give rise to hypoglycaemia. This paraneoplastic phenomenon of non-islet cell tumour-induced hypoglycaemia (NICTH), in which tumour cells secrete insulin-like factors, was first described in 1930 by Doege and Potter, independently from each other, and is therefore mostly referred to as the 'Doege–Potter syndrome'.^{1,5}

FNA can be considered, in order to obtain pathologic diagnosis and differentiation of certain tumours. However, in the case of pleural SFT, cytological examination is often inconclusive and reports of missed diagnosis on cytology have been published. Nonetheless, in combination with radiological findings, cytology may lead the clinician towards a valid diagnosis.⁶ For determination of malignancy, cytological examination is not sufficient.⁷ Taken into account these shortcomings, as well as the suggestive radiological findings, surgical excision was performed without preoperative FNA. In addition, we believed that surgery, if not curative, would have a debulking effect and consequently enable us to control severe hypoglycaemia.

At the molecular level, an excessive overproduction of pro-IGF-II occurs due to IGF-II mRNA overexpression, together with insufficient translation to mature IGF-II. Under normal conditions, mature IGF-II forms a large ternary complex (150 kDa) with IGF-binding protein (mostly IGFBP-3) and with an acid labile subunit (ALS). In contrast, pro-IGF-II, or 'big'-IGF-II only forms binary complexes, with IGFBP (mostly IGFBP-3), resulting in a molecule with a lower molecular mass (40–50 kDa), capable to diffuse out of the vascular bed and bind to IGF- and insulin receptors, resulting in insulin-like effects (hypoglycaemia due to inhibition of hepatic gluconeogenesis and increase of peripheral glucose uptake). Due to subsequent negative feedback, growth hormone secretion is suppressed, leading to decreased IGF-I, IGFBP-3 and ALS levels.¹

NICTH can be expected in patients with low C-peptide, insulin, IGF-I, IGFBP-3 and growth hormone levels. Total serum concentration of IGF-II can be low, normal or increased. Pro-IGF-II level measured by immunoblot assay, is elevated in NICTH.⁸ A pathognomonic sign is an IGF-II to IGF-I ratio higher than 10 or elevated pro-IGF-II.^{2,9}

Hypoglycaemia can be resolved with temporary measurements, such as intravenous glucose infusion and oral corticosteroids. However, ideal treatment consists of

Figure 3 Well-delineated tumour with smooth surface and gray-white to red-brown colour on cut section.

Figure 4 Highly cellular tumour showing a patternless architecture with branching pericytoma-like blood vessels (HES, 400x).

tumour resection. When the tumour is benign and completely excisable, hypoglycaemia usually resolves. In case of malignancy or metastasis, glucocorticosteroid, growth hormone or combination must be considered, distinct from oncological measures.^{1 10}

Learning points

- ▶ Hypoglycaemia of unknown cause check if there is a large tumour in the thorax or elsewhere.
- ▶ NICTH is a paraneoplastic phenomenon, due to overproduction of pro-IGF-II that binds in to insulin receptors, causing hypoglycaemia.
- ▶ Treatment: temporary: intravenous glucose and oral corticosteroids, curative: tumour resection.

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Competing interests None.

Patient consent Obtained.

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