Case Report

Non-islet Cell Tumour Hypoglycaemia (NICTH) in Malignant Mesothelioma: Case Report

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Abstract

Non-islet cell tumour hypoglycaemia (NICTH) is an uncommon but important clinical condition. It can occur in a setting of known malignancy. Here, we report the case of a 56-year-old, non-diabetic, female patient with unresectable malignant pleural mesothelioma who presented with unexplained recurrent hypoglycaemia. Surreptitious use of insulin or other hypoglycaemic agents were ruled out. Investigations revealed markedly suppressed insulin-like growth factor-I, normal insulin-like growth factor-II and elevated "big"-insulin-like growth factor-II, supporting the diagnosis of NICTH. Plasma growth hormone concentration was low. Initial treatments using prednisone alone, as well as the subsequent addition of diazoxide, were unsuccessful in maintaining euglycaemia. A combination of dexamethasone and recombinant human growth hormone was used successfully to ameliorate the hypoglycaemic episodes. We herein describe an uncommon clinical manifestation of malignant mesothelioma and provide an overview of the pathophysiology of this syndrome, as well as explore a different treatment regimen as reported in the literature.

Keywords: *hypoglycemia, insulin-like growth factors, mesothelioma, dexamethasone, prednisone*

Introduction

Hypoglycaemia can be a manifestation of different neoplasms. Previous reports have indicated that it can arise from neoplasms of mesenchymal origin as well as lymphoma, fibromas and carcinoid tumours. Non-islet cell tumour hypoglycaemia (NICTH) is very uncommon, but even more so in malignant mesothelioma. There is limited evidence regarding treatment modalities. This case report aims to describe the uncommon clinical presentation of NICTH in a patient with inoperable malignant mesothelioma. The combined treatment used to control hypoglycaemia, as well as the current state of literature regarding its pathophysiology, is described.

Case report

A 56-year-old woman presented to our hospital with confusion, sweats, and weakness. Blood glucose level was 0.8 mmol/L (normal: 3.8–6.1 mmol/L). Infusion of 10% dextrose was required to correct her severe hypoglycaemia. She was not diabetic and denied surreptitious use of insulin or oral hypoglycaemic agents.

Two months prior, she was diagnosed with malignant pleural mesothelioma. Computed tomography (CT) demonstrated extensive right pleural disease with mediastinal involvement (Figure 1). Histological examination of biopsied specimens confirmed mesothelioma of the epithelial subtype. No evidence of distant metastases was noted. Given the extensive nature of the tumour, surgical resection or chemo/radiotherapy were deemed to be non-beneficial.

Whilst an inpatient, she continued to experience further episodes of spontaneous hypoglycaemia requiring intravenous infusions of 10% dextrose. A full work-up for unexplained hypoglycaemia revealed markedly suppressed serum concentrations of insulin (< 3 mu/L; normal: 3–25 mU/L) and insulin-like growth factor I (IGF-I). We could not detect any sulphonylurea derivatives or C-peptide (60 pmol/L; normal 350–700 pmol/L). Insulin antibodies and pheochromocytoma screening tests were negative as well.

Further results are as follows: IGF-I was < 25 ng/ml (normal: 55–225 ng/ml), IGF-II was 76 nmol/L (normal: 47–94 nmol/L), "big"-IGF-II level was 22.6 nmol/L (normal < 5 nmol/L), growth hormone was 0.01 ng/ml (normal 0.01–3.61 ng/mL).

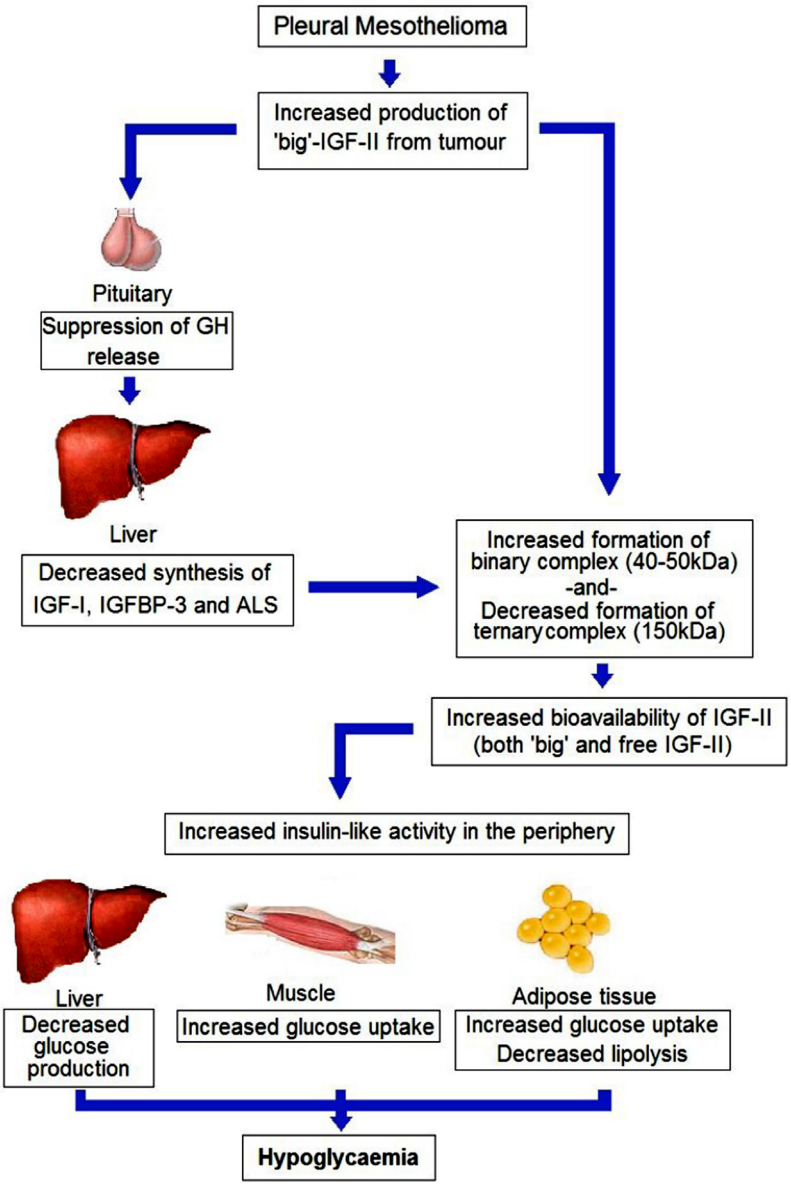

Figure 1: Proposed mechanism NICTH disease process.

She was diagnosed with NICTH. She was started on oral glucocorticoids but the hypoglycaemic spells persisted despite being on 100 mg of oral prednisone a day. She needed dextrose infusion to maintain euglycaemia. Diazoxide 100mg three times daily was added to the treatment regimen, but she continued to have repeated episodes of hypoglycaemia, and these medications were stopped. She was then started on a combination of dexamethasone 8 mg twice daily and recombinant human growth hormone (rhGH) 2.65 mg/day. Her hypoglycaemic episodes subsided and no further dextrose infusion was needed. Table 1 depicts the glycaemic response to the different therapies the patient received.

She died of complications related to her mesothelioma a week after commencing on dexamethasone and rhGH therapy, during which no further episodes of hypoglycaemia were reported.

Table 1: Glycaemic responses to different therapies

Therapy	Titration of dose	Treatment duration (days)	Average blood glucose level; range (mmol/L)
Prednisone	30 mg/day (0.5 mg/kg/day)	3	2.2; 1.4 to 6.7
Prednisone	60 mg/day (1.0 mg/kg/day)	4	3.1; 1.8 to 7.5
Prednisone	100 mg/day (1.7 mg/kg/day)	3	3.3; 2.2 to 6.8
Diazoxide (added to prednisone 100mg/day)	300 mg/day in three divided doses (5 mg/kg/day)	3	3.2; 2.6 to 7.9
Prednisone and diazoxide stopped			
Dexamethasone	8 mg/day (0.13 mg/kg/day)	2	5.6; 2.9 to 8.7
+ rhGH	2.65 mg/day (0.043 mg/kg/day)		
Dexamethasone	16 mg/day in two divided doses (0.26 mg/kg/day)	5	6.4; 4.1 to 12.3
+rhGH	2.65mg/day (0.043 mg/kg/day)		

Blood glucose level reference range 3.8–6.1 mmol/L; rhGH: recombinant human growth hormone

Discussion

Hypoglycaemia induced by neoplasm can occur in the presence of decreased or excess insulin. The former is termed NICTH (1,2). The present case illustrates the difficulties in treating recurrent, intractable hypoglycaemia in the setting of inoperable malignant pleural mesothelioma.

Daughaday et al. first demonstrated that NICTH is associated with increased tumour production of an immature form of IGF-II (3). This is colloquially termed the "big"-IGF-II (2,4). It makes up approximately 10% to 20% of the entire IGF-II reservoir in healthy subjects. In NICTH, up to 70% of the total IGF-II appeared to be in the "big"-IGF-II form. Several reports have suggested that "big"-IGF-II assumes a pivotal function in NICTH (4–6). It has been postulated that tumour cells cannot process the increased amounts of the immature form of IGF-II when synthesized, causing a massive dump of "big"-IGF-II into the blood stream (7).

The IGF system is made up of IGF-I and IGF-II, both peptide hormones. They resemble insulin on a molecular and structural level as they share close to half of their amino acids. The role of IGF-II birth remains uncertain. The IGFs exert their physiologic effects by binding to the IGF-I receptor (IGF1R) and may also bind to the insulin receptor to exhibit glucose-lowering effects (3).

The IGFs circulate while attached to one of 6 different IGF-binding proteins (IGFBPs) (1). Normally, 80% of IGFs bind to IGFBP-3 and an acid labile subunit (ALS), resulting in the formation of a 150kDa ternary complex. Close to a quarter of IGFs form much smaller binary complexes with predominantly IGFBP-2. Only about one percent of IGFs exist freely and unbound to any proteins (3).

In NICTH, "big"-IGF-II retains the ability to form binary complexes, but the resultant binary complexes do not bind to ALS to form a ternary complex (5,8). The exact mechanism for this phenomenon is still unknown. The smaller binary complexes have a greater capillary permeability,

while the ternary complex is virtually confined to the intravascular compartment owing to its larger molecular mass. As a result, the binary complexes can exit circulation more rapidly and the bioavailability of IGF-II in the tissues is dramatically increased (1).

A low serum level of growth hormone (GH) is also often observed in NICTH (1). Suppression of GH secretion by negative feedback was thought to be due to increased serum levels of unbound IGF-I and IGF-II in NICTH. Higher than normal fractions of unbound IGF-I and IGF-II have been postulated to be secondary to increased displacement of IGF-I and IGF-II from the IGFBPs by "big"-IGF-II (9).

Because of suppressed GH production, levels of IGF-I, IGFBP-3 and ALS fall. These compounds are regarded as GH-dependent proteins (1,9). Subsequently, the availability of IGFBPs and ALS for ternary complex formation is decreased. This leads to a vicious cycle as a ternary complex formation is impaired, and increased insulin-like activity ensues (1,2).

In this case, the hypoglycaemia was initially successfully treated with the short-term measure of parenteral administration of dextrose. A long-term treatment strategy was sought in order to facilitate the patient's discharge back to hospice care. Although not an option for our patient, surgical removal of the tumour, and hence the supply of "big"-IGF-II, may restore euglycaemia (1,3,4,7). Diazoxide treatment has also been used, with mixed success, in preventing hypoglycaemia (1,2). In the present case, diazoxide treatment had been unable to ameliorate the hypoglycaemia.

Previous case studies have shown that prednisone monotherapy, at 30 mg per day (0.5 mg/kg/day), improved hypoglycaemia (10,11). This observation was not reproducible in this patient as treatment at much higher doses of prednisone (100 mg per day) failed to abolish the hypoglycaemia. In our case, a more potent glucocorticoid, dexamethasone, given at 8 mg twice daily, was utilised. Glucocorticoids are known to stimulate gluconeogenesis and glycogenolysis, leading to increased blood glucose levels. It is also hypothesised that potent glucocorticoids suppressed IGF-mediated growth by causing tumour shrinkage, leading to significant reductions in serum levels of "big"-IGF-II (5,6,11).

The rhGH has been used successfully in the treatment of NICTH (6,10). It was also noted that the ALS level was increased considerably by rhGH (10). This allows restoration of ternary complex formation. Stimulation of hepatic gluconeogenesis and glycogenolysis such as that seen in acromegaly may also be another way in which rhGH works in counteracting hypoglycaemia. Concerns about the possible involvement of growth hormone in the mitogenic effects of tumour growth and long term effects of tumorigenesis have been purported by different authors (12). The dose of rhGH used varies considerably, but the dose based on literature is in the range of 1–4 mg every 6 to 24 hours (0.016–0.043 mg/kg/day) (13). Tolerance at high levels has also been shown (10,13). Long-acting glucagon may also be used alongside human growth hormone to alleviate refractory hypoglycaemia in such cases (2,11).

We did not use somatostatin analogues such as octreotide because previous case reports have reported the administration of octreotide in NICTH generally does not alleviate the hypoglycaemia, as somatostatin receptors are likely to be non-functional if existing at all in the neoplasm (6). We also did not perform an octreoscan because we were managing a biopsy-proven malignant mesothelioma and not a neuroendocrine tumour. In hindsight, an octreoscan would have been useful in assessing the possibility of treatment with somatostatin analogues.

To summarise, the management of NICTH is challenging and required a number of medications. A combination therapy consisting of high doses of both glucocorticoid and rhGH was shown in our case to control hypoglycaemia. Further studies to elucidate the mechanism of action of these therapeutic agents will be invaluable.

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Conflict of Interest

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