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Refractory Hypoglycaemia in a 45-year-old Lady with Malignant Peritoneal Mesothelioma

KEYWORDS
Palliative care, Refractory hypoglycaemia, End-of-life care, Mesothelioma.

ABSTRACT

BACKGROUND
Non-islet tumour hypoglycaemia (NICTH) is an uncommon paraneoplastic syndrome characterized by refractory hypoglycaemia potentially impacting quality of life.

CASE PRESENTATION
A 45-year-old lady with peritoneal mesothelioma developed unexplained refractory hypoglycaemia. Investigations supported NICTH. A management plan respecting her preferences and autonomy was made: a combination of high-dose dexamethasone, encouraging oral intake and as-needed intravenous (IV) dextrose. This avoided symptomatic hypoglycaemic episodes.

CONCLUSION
We describe an uncommon clinical manifestation of malignant mesothelioma and a pathophysiology overview. We explore the importance of timely diagnosis and appropriate management of hypoglycaemia in keeping with patients' preferences and prioritising quality of life at end-of-life.

INTRODUCTION

Hypoglycaemia is a common medical emergency in diabetic patients. However, hypoglycaemia in nondiabetic patients with malignancy is not well-reported in the literature, despite reports of it dating back to 1929.[1]

Hypoglycaemia in healthy individuals triggers counterregulatory, sympathetic and nervous system responses. 25-60% of palliative patients nearing the end-of-life, may lack such responses.[2]

Mechanisms for hypoglycaemia episodes in the palliative care population include malignancy-related increased metabolic stress and increased glucose utilisation, reduced endogenous glucose production via decreased oral intake and organ failure, defects in assimilation and cachexia, and impaired hepatic gluconeogenesis related to hepatic failure.[2] Multiorgan failure can also trigger endocrine organ dysfunction leading to hypoglycaemia.[2]

In NICTH, overproduction of insulin-like growth factor–2 (IGF-2) and its precursors activate the insulin receptor, resulting in hypoglycaemia.[3] It is a rare condition with unknown true incidence but it is estimated to be one per million people years.[3] Tumours associated with NICTH include hepatocellular carcinoma, fibrosarcoma, mesothelioma, adrenocortical carcinoma, hemangiopericytoma, stomach carcinoma, pancreatic carcinoma, medullary thyroid carcinoma, lymphoma, leukaemia, and carcinoid syndrome.[4,5]

Treatment of NICTH-related hypoglycaemia in palliative care is challenging, and no formal guidance is available. A few case reports and series describe ways of managing this, summarised in Table 1.

This case report describes the clinical presentation of NICTH in a 45-year-old lady with advanced peritoneal malignancy. It focuses on the management of refractory hypoglycaemia, in an inpatient palliative care setting, using a shared decision-making approach. This case highlights the need to be aware of this uncommon paraneoplastic syndrome, as management can improve symptom control and end-of-life care.

THE PATIENT WANTED TO LIVE AS LONG AS POSSIBLE, FOR HER TWO YOUNG CHILDREN

Table 1. Summary of available literature.

Title	Author	Type	Case/s	Main learning points
Management of Severe Hypoglycemia at the End of Life in Non-Diabetic Patients: A Case Study and Recommendations	Gonzalez et al., 2013	Case report	73-year-old, non-diabetic, presented with symptomatic hypoglycaemia and recurrent lung sarcoma.	Hypoglycaemia continued despite glucagon and dietary interventions. 4 mg once daily dexamethasone was used and patient died comfortably. Use of IV/PO glucose in the acute hypoglycaemic setting was recognised.[6]
Refractory hypoglycaemia from paraneoplastic insulin-like growth factor 2 secretion in a patient with hepatocellular carcinoma	Behringer-Massera., 2017	Case report	22-year-old with metastatic hepatocellular carcinoma with persistent hypoglycaemia. Non-diabetic.	Despite high dose glucocorticoid therapy, hypoglycaemia continued requiring continuous IV dextrose (continued in hospice setting). They noted the ongoing need for IV dextrose may represent disease progression. They noted that extensive hepatic involvement may have exacerbated hypoglycaemia.[7]
A case of non-islet cell tumor hypoglycemia associated with malignant mesothelioma requiring a multifaceted approach for optimal glycemic control	Ono et al., 2021	Case report	77-year-old Japanese man with mesothelioma and NICTH resulting in refractory hypoglycaemia. Patient had a history of well-controlled diabetes.	Chemotherapy and daily supplementation with hydrocortisone 40 mg daily prevented hypoglycaemia. When chemotherapy was stopped due to tumour progression, hypoglycaemic episodes were controlled by increasing steroid dose. Regular oral and IV glucose was also needed. This strategy helped keep the patient conscious until he died of respiratory failure.[8]
Hypoglycemia as a Symptom of Neoplastic Disease, with a focus on Insulin-like Growth Factors Producing Tumors	Schovanek et al., 2019	Review article		The authors noted that acute treatment should involve glucose or glucagon. Overall management depends on tumour type and goal of care. Increasing oral glucose intake is effective but not a permanent solution and glucocorticoid therapy is effective.[4]
Non-islet Cell Tumour Hypoglycaemia (NICTH) in Malignant Mesothelioma: Case Report	Wong et al., 2014	Case report	56-year-old non diabetic with unresectable malignant pleural mesothelioma.	A combination of dexamethasone and recombinant human growth hormone was used successfully to ameliorate the hypoglycaemic episodes.[9]
Paraneoplastic hypoglycemia in a patient with a malignant solitary fibrous tumor	Mohammedi et al., 2014	Case report	77-year-old lady with a malignant solitary fibrous tumour.	They found that treatment with corticosteroids, growth hormone, or both can improve hypoglycaemic symptoms.[10]
Nonislet Cell Tumor Hypoglycemia	Thomas and Kumar., 2013	Case report	63-year-old male, squamous cell carcinoma of the oesophagus, non-diabetic, with recurrent hypoglycaemia.	Hypoglycaemia continued despite continuous feed and resolved within a day of treatment with steroids.[11]
Non-islet Cell Hypoglycemia: Case Series and Review of the Literature	Garla et al., 2019	Case series, 2 cases	33-year-old male, liver tumour and NICTH.	Hypoglycaemia continued despite prednisolone treatment (max dose of 40 mg daily). Patient refused surgical excision.[5]
			54-year-old with uterine tumour with NICTH.	Hypoglycaemia persisted despite IV dextrose 20% and resolved after surgical excision.[5]

CASE PRESENTATION

A 45-year-old lady with peritoneal malignant mesothelioma presented to the emergency department with loss of consciousness. Blood glucose (BG) levels were 0.2 mmol/L (normal fasting BG: 3.8–6.1 mmol/L). Initial management included hourly BG checks and IV infusions of 10% dextrose. She regained consciousness but continued to have severe hypoglycaemic episodes, requiring glucose IV infusions in an acute medical ward. One week later, she was transferred to the palliative care unit (PCU) at SAMOC.

Seven months previously she had been diagnosed with malignant peritoneal mesothelioma. The outcome from a local multidisciplinary team meeting with a specialised centre in the United Kingdom confirmed epithelioid peritoneal mesothelioma, and treatment with Nivolumab/Ipilimumab was commenced. A few months later oncological treatment was stopped due to poor response and deterioration in general condition.

Past medical history included an appendicectomy. She was not taking regular medications. She lived with her husband and two children (5 and 7 years old). She stopped smoking a few months prior to her admission, had no history of excess alcohol intake and worked at a grocery store.

She was cachectic and had ascites but had good oral intake. She spent over 50% of her waking time in bed and required support for most activities of daily living.

A full workup ruled out surreptitious use of hypoglycaemic agents and results in keeping with a diagnosis of NICTH as seen in Table 2.

NICTH was discussed with the patient and her husband. The potentially fatal outcome of severe hypoglycaemia and the irreversibility of this issue due to it being caused by her incurable cancer were discussed at length. The patient wanted to live as long as possible, for her two young children. Using a shared decision-making approach, the management plan focussed on symptom control and giving her more time, for as long as she felt she had good quality of life. All parties recognised the plan had to be fluid and adapt according to her overall health and unavoidable deterioration.

She was started on dexamethasone 8 mg, 12-hourly and given regular snacks, including after during the night. Hypoglycaemic episode frequency was reduced, but some episodes (less than 4 mmol/L) required IV dextrose, especially in the early hours of the morning. The patient agreed to an overnight feed via a nasogastric tube, however, she didn't tolerate this. Instead, she opted for a yogurt drink before bed and early in the morning, accepting the increased risk of dying from a severe hypoglycaemic episode. She agreed to have a peripherally inserted central catheter (PICC) line for IV dextrose when glucose level was below 4. BG monitoring was reduced from hourly to four times a day and she rarely developed symptomatic hypoglycaemia.

Other specialists were consulted - the endocrine team agreed with the management plan and didn't feel octreotide would be of benefit. The oncology team did not consider hypoglycaemia to be caused by her previous oncology treatments.

A few weeks later she died, in hospital, due to advanced mesothelioma. Up until that time she had no symptomatic hypoglycaemic episodes that reduced her consciousness level or ability to be with her family.

DISCUSSION

Normally, the majority of mature IGFs bind to IGFBP-3 and an acid labile subunit (ALS) to form ternary complexes. In NICTH, tumours secrete immature IGF-II, which forms binary complexes with IGF-binding proteins, resulting in small molecular weight complexes, having a greater capillary permeability causing hypoglycaemia by acting on the insulin or IGF-I receptors.[12] Increased IGF-II activity suppresses the secretion of insulin, IGF-I, and growth hormone (GH). Therefore, as presented in our case, typical laboratory findings in NICTH include low levels of glucose, insulin, C-peptide, and IGF-1.

NICTH is an uncommon problem. However, up to 8% of all NICTH cases have been accounted for by mesothelioma and therefore should be considered in refractory hypoglycaemia.[13]

Table 2. Patient investigation results.

Test	Result	Normal Range
Insulin	0.61 mu/L	3 – 25 mU/L
Insulin-like growth factor, IGF-1	<15 ug/L	53.3 - 219 ug/L
C-peptide	0.1 ng/mL	1.1 - 4.4 ng/mL
Morning cortisol	279 nmol/L	138 - 690 nmol/L
Thyroid Stimulating hormone, TSH	3 miclU/mL	0.3 - 3 miclU/mL

Definite treatment of NICTH often requires surgery and/or chemotherapy. However, this may not always be possible and a multidisciplinary approach focusing on quality of life and symptom control is needed.

As often is the case in the palliative care population, uncertainty can challenge decision-making. We involved the patient and her husband in decision-making and were transparent about expectations. The agreed aim was to manage hypoglycaemia to prevent unconsciousness whilst accepting the limitations because of the underlying incurable condition. We agreed to stop treatments that became unacceptable to her, or futile. We monitored for deterioration and when appropriate, discussed less invasive management options.

The hypoglycaemia was initially successfully managed with as-needed IV dextrose. However, a longer-term, sustainable strategy was sought.

Corticosteroids have been shown to be effective by stimulating gluconeogenesis, suppressing the production of big IGF-II, and correcting the biochemical abnormalities that involve the GH–IGF axis.[14] We initially used a dose of dexamethasone 16 mg daily (equivalent to prednisolone 120 mg) and titrated according to clinical response. Symptom control was achieved at a dose of about 4-6 mg dexamethasone daily. Side effects were well tolerated and her appetite improved, a welcomed side effect. This supports the beneficial effect of corticosteroids on NICTH.

Appropriate oral intake is also important in NICTH. Although oral intake was good, including slow-release carbohydrates, this alone didn't maintain her BG levels and she found feeding via NG intolerable. She required ongoing IV glucose via PICC line. She knew this would mean living the rest of her life in hospital, but this was acceptable as it meant time with her young children.

Another useful tool is the concept of time-limited therapeutic trials. Although it maintained her glucose level, the NG tube was not acceptable to her and was withdrawn. With each treatment proposed the patient/family was involved in decision making and her autonomy and priorities were respected. It was also discussed that treatment would need to be withdrawn, once it was not giving her a quality of life which was acceptable to her.

Our approach can be applied to patients with a possible life expectancy of a couple of weeks or to give a person more time to deal with personal affairs before they die. However, if prognosis is felt to be hours to days, a focus on supportive care addressing symptoms rather than actively correcting blood glucose levels should be considered.

Our approach avoided regular occurrence of severe, symptomatic hypoglycaemic episodes and helped keep the patient conscious until she deteriorated from disease progression and died a few weeks later.

The endocrine team agreed that octreotide was unlikely to work. Previous case reports have reported that octreotide in NICTH generally doesn't alleviate hypoglycaemia, as somatostatin receptors are likely to be non-functional or not present in the tumour.[15] Glucagon was used in the emergency department but not re-visited as it was considered that it wouldn't work due to cachexia. Recombinant human growth hormone (rhGH) was not used as acceptable control with our treatment was achieved, though previous case reports have mentioned benefit from this.[9]

In summary, in patients with mesotheliomas and hypoglycaemia of unclear aetiology, NICTH should be considered. It can cause severe refractory hypoglycaemia. As tumour resection is not feasible in many cases, a multifaceted therapeutic approach needs to be taken and look at other ways to avoid hypoglycaemic episodes, such as corticosteroids, nutrition, slow-release snacks, and IV glucose. Other important factors to consider are prognosis, patient autonomy, family wishes, and considering not treating hypoglycaemia when death is imminent. Shared decision-making in complex clinical scenarios is challenging, but understanding the issue being dealt with and providing adequate information can aid in this.

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