CASE REPORT

Non-diabetic hypoglycaemia secondary to non-islet cell tumour. A diagnosis that cannot be missed!: a case report

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SUMMARY

Non-islet cell tumour hypoglycaemia (NICTH) is a paraneoplastic syndrome primarily due to excessive insulin-like growth factor-2 (IGF-2) production. It should be suspected in patients with tumours of any origin and hypoglycaemia. It is potentially misdiagnosed or underdiagnosed due to its rarity, non-classical clinical presentation and ambiguous lab picture. We present the case of a 48-year-old man with no known medical illness brought to the emergency department for altered sensorium, incoherent speech and abnormal movement of bilateral limbs. Initial assessment identified severe hypoglycaemia, and hepatomegaly was detected on physical examination. Five months before the current presentation, he had been seeking medical attention a few times in the primary health center for early morning lethargy and hunger pangs but failed to find clues to his symptoms. He was admitted for observations and further investigations. Subsequent investigations confirm a diagnosis of malignant pancreatic lesion with lymph node, liver and lung metastases. He refused the palliative chemotherapy offered and passed on 3 months later. This case highlights the importance of thorough clinical assessment in the case of non-diabetic hypoglycaemia to prevent the consequences of inappropriate patient management despite poor pancreatic cancer prognoses.

INTRODUCTION

Non-diabetic hypoglycaemia is an uncommon occurrence. There is a paucity of studies on non-diabetic hypoglycaemia incidence. In one retrospective, single-center study of 37,898 non-diabetic, non-critical care hospital admissions, the estimated frequency of a low glucose level (at 3.3mmol/l cut-off) was 50 cases per 10,000 admissions per year.[1] Another single-centre study in Helsinki University Hospital showed the incidence rate of non-diabetic hypoglycaemia encountered was 1082 per 100 000 populations per year.[2]

Hypoglycaemia in non-diabetic patients can occur via two mechanisms: insulin-mediated and independent of insulin. Insulin-mediated mechanisms may occur due to endogenous insulin secretion, such as insulinoma, or exogenous insulin intake, such as accidental ingestion of insulin secretagogue.[3,4] Meanwhile, hypoglycaemia independent of insulin occurs via several mechanisms such as (1) adrenocortical insufficiency, (2) increased glucose utilisation exceeding the glucose production as in those with sepsis, (3) reduced glucose intake together with body fat and muscle depletion as observed in those with malnutrition, (4) inhibition of gluconeogenesis and depletion of hepatic glycogen stores in those with advanced and extensive hepatic destruction or (5) tumoral overproduction of incompletely processed IGF-2 in non-islet cell tumour.[4]

Labelling a non-diabetic patient to have hypoglycaemic disorder requires the presence of Whipple's triad: symptoms and signs consistent with hypoglycaemia, low plasma glucose concentration at the time of symptoms and resolutions of those symptoms and signs after plasma glucose is raised.[4] Cryer et al. recommended documentation of Whipple's triad as the initial step for diagnosing hypoglycaemic disorder. He strongly suggests further evaluation and management only in those who were concluded as having hypoglycaemic disorder to avoid unnecessary investigations, cost and potential harm without benefit to the patient.

We presented a delayed diagnosis of unexplained severe hypoglycaemia in a non-diabetic patient secondary to a non-islet cell tumour. The initial approach in a primary care setting is crucial to prevent delayed or missed diagnoses in the future.

CASE PRESENTATION

This is a case of a 48-year-old man with no known medical illness presented at the emergency department (ED) with altered sensorium, incoherent speech and abnormal movement of bilateral limbs. On initial assessment, severe hypoglycaemia (1.2 mmol/l) was detected, and he was treated with 50 ml of 50% dextrose. His consciousness level improved afterwards, while his incoherent speech and abnormal movement disappeared.

On further history, he had an oesophagogastroduodenoscopy (OGDS) scheduled that morning and had to fast for the procedure. Despite his usual early morning lethargy and hunger sensation, he abstained from eating or drinking. The last thing he remembered was feeling dizzy and sweating while waiting for his relative to pick him up. Collateral history-taking from his relatives revealed that the patient looked unusual when they arrived that morning. He is conscious but looks anxious and sweaty. While on their way to the hospital, they noticed that he could not engage in conversation and had incoherent speech. Shortly after, he

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Table I: Endocrine-related blood result during hypoglycaemic episode

Investigations	Result	Reference range
Random plasma glucose	1.2 mmol/L	
C-peptide	60 pmol/L	367–1467
Insulin	<1.3 pmol/L	17.8–173

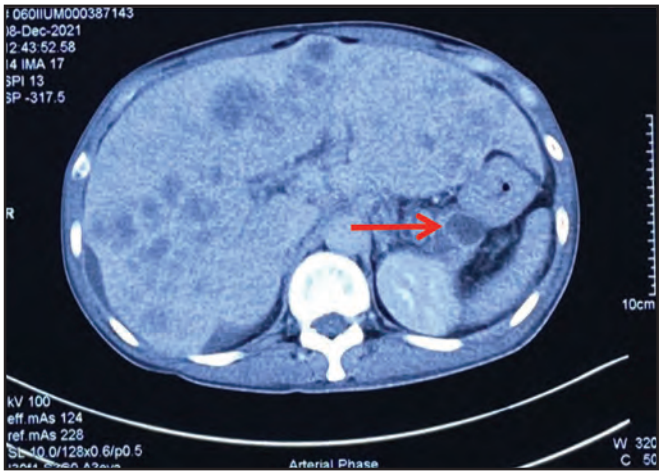

Fig. 1: CT TAP showing multi-loculated cystic lesion (arrow)at the tail of pancreas.

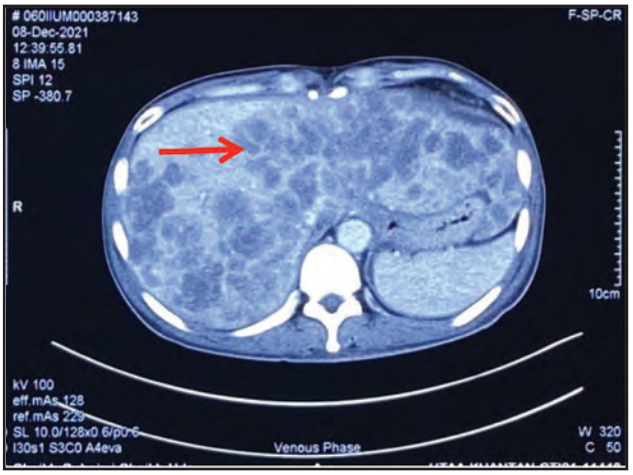

Fig. 2: CT TAP showing extensive (arrow) liver metastases.

was less responsive and started having abnormal movement of his limbs; thus, he was brought to the ED.

Five months prior, he had three visits to health care providers for recurrent early morning lethargy and hunger sensation. He was asymptomatic during each visit. There is no history of diabetes mellitus or bariatric surgery, and he was not taking any medication that could cause hypoglycaemia. There is also no history of poor oral intake, alcohol abuse or illicit drug use and no family history of malignancy. Initial assessments at all clinics revealed normal vital signs and blood glucose. All physicians concluded that his symptoms were likely attributed to hypoglycaemia but needed further investigations and follow-up. He was told to check his blood sugar level during hypoglycaemic episodes and scheduled for blood taking to check for diabetes, renal and liver function and lipid profile. He defaulted on the blood-taking procedure and subsequent follow-up due to his busy schedule. On top of that, he felt relatively well, and his symptoms did not affect his work or daily activities.

Two months after his last visit to the health center, he started losing his appetite and had early satiety and abdominal discomfort. He also experienced hypoglycaemic symptoms more frequently, at any time of the day. Nevertheless, his fourth medical consultation occurred two months after the onset of new symptoms. By this time, he had already lost 4 kg of weight. His fourth visit took place at a district hospital. Given his symptoms and examination findings of hepatomegaly, he was told that he needed further investigations urgently to find out the cause. He was scheduled for an OGDS and abdominal ultrasound the following week. While fasting for his OGDS procedure, he had another hypoglycaemic attack, which led to his latest presentation.

He was admitted for observations and further investigations after his hypoglycaemia was treated in the ED. While in the ward, he had recurrent attacks of severe hypoglycaemia refractory to the glucose supplement. Endocrine input was sought. C-peptide and insulin levels were taken during one of his hypoglycaemic episodes, and the result was consistent with hypoinsulinemic hypoglycaemia, as shown in Table I.

Due to the hepatomegaly finding, he underwent an ultrasound (US) abdomen, which showed multiple liver and pancreatic lesions. The US finding warrants urgent Computed Tomography of Thorax, Abdomen and Pelvis (CT TAP). His CT TAP results suggest a malignant pancreatic lesion with lymph node, liver and lung metastases (Figures 1 and 2). A liver biopsy taken showed metastatic adenocarcinoma of the liver. He was planned for palliative chemotherapy but opted for conservative management and passed on 3 months later.

DISCUSSION

Hypoglycaemia is a typical medical emergency. The symptoms occur when the blood glucose level falls below 4 mmol/L. In a healthy individual, when hypoglycaemia occurs, various effective counter-regulatory mechanisms will take place to restore the blood glucose to its physiological range. Glucagon and epinephrine secretions work synergistically to raise blood glucose via stimulation of hepatic glucose production through glycogenolysis and gluconeogenesis and contribute primarily to immediate response to hypoglycaemia. On the other hand, growth hormone and cortisol work over a more extended period to raise blood glucose via lipolysis and ketogenesis and are not involved in immediate recovery from hypoglycaemia.[5] When the blood glucose concentration falls further below 3 mmol/L despite all these corrective mechanisms, plasma insulin

secretion will be suppressed almost entirely to a level below 18 pmol/L while the C-peptide level will also be deficient (below 200 pmol/L) to prevent the deleterious effect of hypoglycaemia to the brain.[4]

Hypoglycaemia mostly occurs due to complications of therapy with either insulin or other hypoglycaemic agents, but in rare conditions, it can manifest an underlying neoplastic disease. Tumours of any origin can give rise to hypoglycaemia via various mechanisms: excess insulin secretion such as in pancreatic insulinoma or ectopic insulin-producing tumour, massive tumour infiltration of the liver and adrenal gland and secretion of substances which disrupt glucose metabolism such as cytokines, catecholamines, insulin receptor antibodies, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2).[6] The latter is known as NICTH.

NICTH should be suspected in patients with tumours of any origin with recurrent hypoglycaemia. Early recognition and diagnosis of NICTH are crucial as they can cause persistent and profound hypoglycaemia if left untreated. Early diagnosis is essential as the curative treatment is surgical resection, which is feasible if done early in the illness.

This patient initially presented with early morning lethargy and hunger sensation without any symptoms that point toward underlying malignancy such as loss of appetite, weight loss or mass per abdomen. It was concluded that these two symptoms are attributed to hypoglycaemia. However, the doctors could not demonstrate low glucose readings since the patient had no glucometer at home and presented to the clinic when he was asymptomatic. Despite the setback in establishing Whipple's triad, we should be able to rule in the initial diagnosis of non-diabetic hypoglycaemia when the patient denied having diabetes, thus denying oral hypoglycaemic agents or insulin intake. When non-diabetic hypoglycaemia is suspected, the history should be directed to rule out any alcohol or drug use, underlying liver disease or critical illness, or previous history of bariatric surgery. Suppose the hypoglycaemia occurrence is devoid of relation to any of the stated above. In that case, a doctor should know that they should never skip the physical assessment and must be more vigilant when conducting it as it can be the only clue to the cause of hypoglycaemia.

The hepatomegaly finding can be missed when the physical assessment is not done thoroughly. Early finding of hepatomegaly means early imaging and early intervention. Nevertheless, if the hepatomegaly finding was missed, acknowledging that a specific tumour can cause hypoglycaemia will be reflected in the next step in choosing initial blood investigations. Besides renal and liver function tests, this patient lacks the necessary investigations for non-diabetic hypoglycaemia, such as serum cortisol, insulin, and C-peptide levels.[3,4] These three investigations can be sent from primary care at no added cost for the patient, unlike in a general practitioner setting, which can be costly.

Insulin and C-peptide levels must be taken during a hypoglycaemic event to reflect the underlying disorder accurately, and this patient's major setback was establishing low plasma glucose readings. All three encounters took place when he was asymptomatic. His early morning hypoglycaemia suggested that he had fasting hypoglycaemia. Fasting hypoglycaemia occurs typically after at least 6–8 hours of fasting.[4] It occurs due to a defective counter-regulatory mechanism toward falling blood glucose. A fasting hypoglycaemia state can be achieved by asking the patient to withhold his meal and come to the clinic for blood taking at the initial hypoglycaemic symptoms. This manoeuvre is not only helpful for the blood-taking process; it can also be used to establish Whipple's triad. It confirms someone's hypoglycaemic state from low glucose reading and the disappearance of hypoglycaemic symptoms and signs upon therapeutic intervention (giving meals or intravenous glucose load).

Diagnosis of NICTH would be apparent if all other initial blood investigations were within the range while C-peptide and insulin levels would be suppressed.[3,4] If the diagnosis is still unclear despite preliminary investigations, consultations with an endocrinologist can be sought. This case has taught us several lessons that may be beneficial to share with others. The initial approach to non-diabetic hypoglycaemia in primary care is summarised below (Algorithm 1). Primary care practitioners should utilise the algorithm for managing non-diabetic hypoglycaemia in order to avoid overlooking a critical diagnosis. It is crucial for treating physicians to be aware of when it is necessary to refer patients to a tertiary care centre.

CONCLUSION

In conclusion, thorough clinical assessment and relevant laboratory evaluation are crucial to guide early diagnosis. Consequently, early management can be initiated, and potentially severe complications can be prevented.

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CONFLICT OF INTEREST

None to declare.

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