Double jeopardy: hypoglycaemia and advanced hepatocellular carcinoma

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Abstract

Nonislet cell tumour-induced hypoglycaemia is an uncommon, but serious complication of malignancy. The aetiopathogenesis is largely as a result of tumoral overproduction of incompletely processed insulin-like growth factor-II. We describe the case of a 30-year-old black male patient who presented with recurrent hypoglycaemic episodes in the absence of diabetes or any medications known to cause hypoglycaemia. Extensive investigations revealed that the hypoglycaemia was the result of an advanced hepatocellular carcinoma.

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Introduction

Hypoglycaemia is a common medical emergency. It occurs mostly as a consequence of therapy with insulin and/or oral sulphonylureas in the setting of diabetes mellitus. There are numerous other causes that include neoplastic diseases. The most common cause of this type of hypoglycaemia is tumoral overproduction of insulin-like growth factor-II (IGF-II).

Case description

A 30-year old Malawian male presented to Chris Hani Baragwanath Academic Hospital in a comatose state. There was no history of diabetes mellitus, drugs or toxin exposure. In addition, there was no history of trauma or seizures.

Neurologically, there was no meningism or focal signs. His blood pressure was 111/79 mmHg, with a pulse rate of 87 beats per minute and a temperature of 36.8°C. The rest of his examination was unremarkable except for a 15cm (vertical span) firm and irregular hepatomegaly.

Initial blood investigations confirmed hypoglycaemia with a glucose level of 2.1 mmol/l. C-peptide and insulin levels taken at the time of the hypoglycaemic event were appropriately suppressed (Table I). The cortisol level of 331 nmol/l was inappropriately low for the degree of hypoglycaemia. However, a synacthen stimulation test excluded any evidence of adrenal insufficiency. Liver function tests showed an enzyme pattern that was consistent with space-occupying lesions. The α-fetoprotein was markedly elevated (Table I). Hepatitis B studies indicated a chronic carrier state.

Table I: Relevant blood results during a hypoglycaemic episode

Blood test	Patient's value	Normal values
Glucose	2.1 mmol/l	3.6-5.5 mmol/l (fasting)
Insulin	< 2.0 µU/l	0.0-29.1 µU/l (fasting)
C-peptide	0.2 ng/l	0.9-7.1 ng/l (fasting)
α-fetoprotein	10 728 µg/l	0-7 µg/l

An abdominal sonar revealed multiple hypodense lesions throughout the liver. Computed tomography of the abdomen confirmed numerous lesions in both the right and left lobes of the liver, highly suggestive of a hepatocellular carcinoma (HCC) (Figure 1). The liver biopsy confirmed the diagnosis of HCC (Figures 2-4).

The patient continued to experience ongoing hypoglycaemic episodes, despite a continuous intravenous infusion of 5% dextrose water. A serum sample, taken during a hypoglycaemic episode, was analysed at the Royal Surrey County Hospital NHS Foundation Trust in Surrey, UK, for the measurement of insulin-like growth factors I and II (IGF-I and IGF-II), by radioimmunoassay technique. The results demonstrated a virtually suppressed IGF-I level with an elevated IGF-II:IGF-I ratio (Table II). These findings were in keeping with the diagnosis of nonislet cell tumour-induced hypoglycaemia.

The patient was managed with a continuous dextrose (10%) infusion, together with a complex carbohydrate diet, but he continued to experience ongoing hypoglycaemic events. Subsequently, oral prednisone was initiated at a dose of 40 mg daily, which dramatically

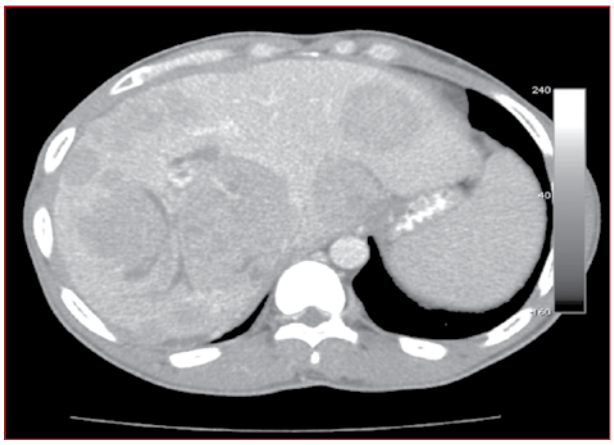

Figure 1: Computed tomography imaging of the liver, showing multiple lesions

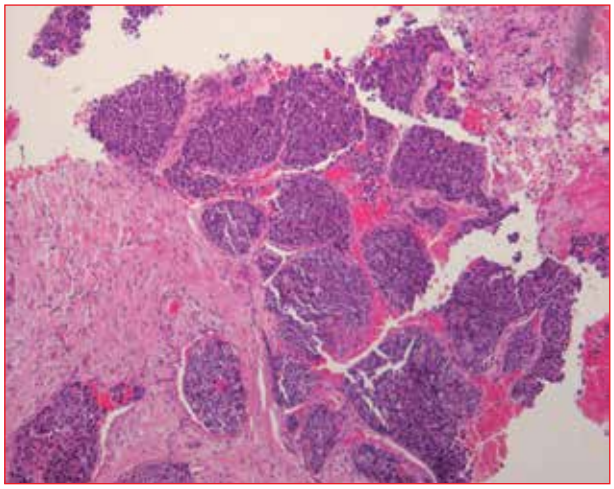

Figure 2: Haematoxylin and eosin stain, demonstrating nests of atypical hepatocytes (x 40)

Table II: Insulin-like growth factor levels

Blood test	Patient's values	Normal values
IGF-I	< 3.2 nmol/l	13-50 nmol/l
IGF-II	99.8 nmol/l	55-150 nmol/l
IGF-II:IGF-I molar ratio	28.3:1	< 10:1

IGF-I: insulin-like growth factors I, IGF-II: insulin-like growth factors II

improved the ongoing hypoglycaemic episodes. Palliative care was implemented in view of the advanced stage of the patient's malignancy.

Discussion

Nonislet cell tumour-induced hypoglycaemia is an uncommon, but serious complication of malignancy. Usually, it is caused by a variety of benign and malignant tumours, including HCC. The hypoglycaemia is mediated by tumoral overproduction of incompletely processed IGF-II.[1] Rarely, it may be mediated by other factors, including insulin receptor antibodies, metastatic destruction of the liver and various other hypoglycaemic cytokines. The exact incidence and prevalence of nonislet cell tumour-induced hypoglycaemia is not known, but it is estimated to be four times less common than insulinoma.[2]

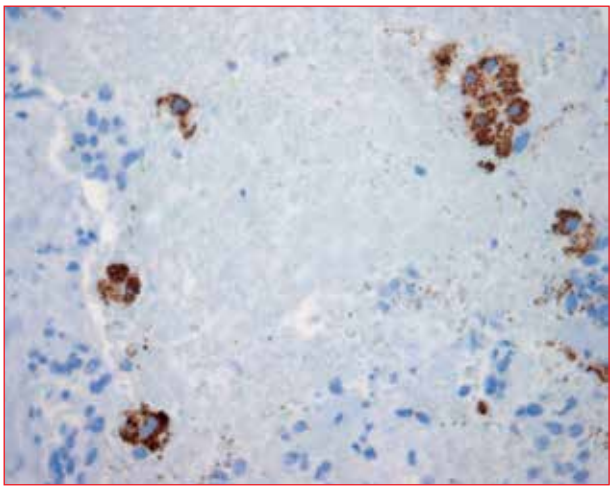

Figure 3: A focal Hep Par 1 stain, confirming that the tumour is of hepatic origin (x 400)

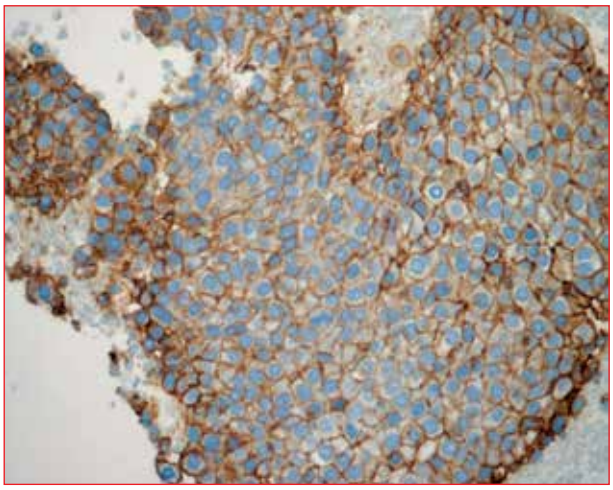

Figure 4: A diffusively positive MOC-31 stain, suggesting a poorly differentiated variant of hepatocellular carcinoma (x 400)

The IGF-II gene is an imprinted gene, with parental allele specific expression. It is maternally imprinted and encoded on chromosome 11p15, together with two tumour-suppressor genes, H19 and p57. As a consequence of imprinting loss or mutations in either of these two genes, IGF-II is overexpressed and hence overproduced.[3]

Under normal circumstances, the precursor molecule, prepro-IGF-II, is converted to pro-IGF-II, which in turn is converted to mature IGF-II in the presence of various enzymes, the majority of which are bound to IGF-binding proteins (IGFBP). Mature IGF-II is mostly bound to IGFBP3, and to a lesser extent IGFBP5, as a 150-kDa ternary complex, together with an acid-labile subunit. Because of its high molecular mass, this complex is unable to pass through the capillary membrane and remains confined to the intravascular space, and hence is less bioactive at a cellular level. Most of the biological actions of IGF-II are mediated via the IGF-I

receptor and insulin receptor, which effect a strong mitogenic and antiapoptotic activity.[4] Seventy per cent of IGF-II exists in the mature form and 30% as incompletely processed pro-IGF-II in normal human serum.[5]

In the setting of tumours, the major form of circulating IGF-II is a high molecular weight IGF-II, designated "big" IGF-II, the generation of which is unclear, but has been proposed to be the result of abnormal processing of pro-IGF-II.[6] "Big" IGF-II has a greater bioavailability than mature IGF-II as it mostly circulates as smaller (150-kDa) binary complexes or in a "free", unbound form and is thus biologically more active at a cellular level. Upon binding to the insulin and IGF-1 receptors, various secondary changes in the circulating levels of insulin, growth hormone, IGF-I and IGFBP result, mediating an insulin-like hypoglycaemic activity of "big" IGF-II.[7]

Increased levels of "big" IGF-II, as well as an elevated ratio of total IGF-II:IGF-I are useful markers in diagnosing nonislet cell tumour-induced hypoglycaemia. The normal molar ratio of IGF-II:IGF-I in plasma is usually 3:1. A ratio of greater than 10:1 is considered to be pathognomonic of nonislet cell tumour-induced hypoglycaemia.[2] In response to the hypoglycaemia, and via activation of the insulin receptor by IGF-II, endogenous insulin and C-peptide levels are suppressed.

Conventional radiological imaging, using computed tomography or magnetic resonance imaging, readily detects tumours that cause nonislet cell tumour-induced hypoglycaemia as they are usually large on presentation.

Therapeutic strategies include complete removal of the tumour or reduction of the tumour mass, which alleviates the metabolic alterations caused by nonislet cell tumour-induced hypoglycaemia.[1,7] If surgery is not feasible, and curative resection not possible, various approaches to the treatment of nonislet cell tumour-induced hypoglycaemia have been tried. These include diazoxide, glucocorticosteroids, somatostatin analogues and growth hormone therapy. Interestingly, diazoxide-chlorothiazide treatment often alleviates nonislet cell tumour-induced hypoglycaemia, though less predictably than with insulinomas.

Usually, large doses of glucocorticoids are the most effective therapy in terms of long-term relief from hypoglycaemia through the stimulation of gluconeogenesis and suppression of the production of "big" IGF-II.[8-10] This beneficial effect is dose-dependent and is reversed when therapy is withdrawn. To date, no clear benefit has been demonstrated with either human growth hormone or somatostatin analogues alone. However, the combined usage of growth hormone and steroids may alleviate symptoms.[8,11]

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