Hypoglycaemia presenting as sole manifestation of hepatocellular carcinoma

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INTRODUCTION

Hypoglycaemia is a well-known paraneoplastic manifestation of hepatocellular carcinoma (HCC).¹ Hypoglycaemia as the first presentation of HCC is very uncommon. Hepatocellular carcinoma-associated hypoglycaemia has been divided into two types.² In the more common type A tumours, which are poorly differentiated, hypoglycaemia of mild to moderate severity is a late event. In contrast, in the less common type B tumours, which are well differentiated and slowly growing, hypoglycaemia is severe, occurs early, and is difficult to control. We report the case of HCC who presented with sole manifestation of hypoglycaemia as recurrent loss of consciousness and profuse sweating. Being an Ex-servicemen Contributory Health Scheme beneficiary we get all the test needed to reach the exact diagnosis even through civil laboratories/scan centres.

CASE REPORT

A 66-year-old ex-serviceman was admitted here with episodes of loss of consciousness for 2–3 months. Initially his loss of consciousness was at intervals of 10–15 days but for the last 2–3 weeks he had recurrent loss of consciousness almost every day or on every alternate day lasting 4–5 minutes as witnessed by his relatives. He had one episode of generalised tonic-clonic seizure four days back. He was taken to a nearest civil hospital the last time where his blood sugar was detected to be 26 mg/dL. He also complained of anorexia, increased satiety, and generalised weakness for few months. He had no history of any chronic illness, diabetes mellitus, hypertension, liver disease, or renal disease. He was admitted in our centre for ascertaining symptoms and confirming diagnosis. Clinically there were no relevant findings.²

Investigations

Complete blood count—normal, urea—32 mg/dL, creatinine—0.8 mg/dL, serum bilirubin—1.8 mg/dL, serum glutamic

oxaloacetic transaminase—124 IU/L, serum glutamic pyruvic transaminase—164 IU/L, serum alkaline phosphatase—130 IU/L, serum albumin—3.5 g/dL, serum cholesterol—245 mg/dL, triglycerides—135 mg/dL, low-density lipoprotein—168 mg/dL, prothrombin time international normalised ratio 1.4, S. Ca⁺⁺—9 mg/dL, haemoglobin A_{1C}—5.2%, serum cortisol—18.34 µg/dL (6.2–19.4), serum insulin—21 IU/mL (3–35), serum C peptide—3.6 ng/mL (F—1.1–4.4, stimulated—3.3–13.2), insulin-like growth factor-II in plasma—892 ng/mL (374–804), serum alpha-fetoprotein—1030.75 IU/mL (0–5.8), hepatitis B surface antigen, anti-hepatitis C virus—negative, high resolution chest tomography thorax—normal, magnetic resonance imaging of abdomen (Figures 1 and 2)—a large lobulated hypointense mild contrast-enhancing solid lesion on T1W, heterogeneously

Figure 1 Magnetic resonance imaging of abdomen. Large lobulated hypointense mild contrast-enhancing solid lesion on T1W, heterogeneously hyperintense on T2W and fast imaging employing steady-state acquisition seen in left lobe (70.7 × 69.2 mm).

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Figure 2 Magnetic resonance imaging of abdomen. Numerous hypointense ring-enhancing lesion on T1W, hyperintense on T2W and fast imaging employing steady-state acquisition throughout the liver (probably metastasis/? granuloma).

Figure 3 Low power shows cellular smear showing cells in nests and cords traversed by endothelial cells. No bile noticed (Pap 100×).

Figure 4 Neoplastic hepatocytes show moderate to marked pleomorphism. Multinucleated forms seen (Romanowsky stain: 400×).

hyperintense on T2W and fast imaging employing steady-state acquisition (FIESTA) seen in left lobe— $70.7 \times 69.2 \text{ mm}^2$. Numerous hypointense ring-enhancing lesion on T1W, hyperintense on T2W, and FIESTA throughout the liver. Fine-needle aspiration cytology (FNAC) (Figures 3 and 4)—cellular smear showing cells in nests and cords traversed by endothelial cells. The neoplastic cells show moderate to marked pleomorphism.

Multinucleated forms seen and no bile noticed. All these suggestive features of HCC were seen.

DISCUSSION

The reported prevalence of hypoglycaemia in HCC varies from 4% in North American cases to 27% in Chinese patients from

Hong Kong.³ Hypoglycaemia presenting as seizures is a common occurrence in the Emergency Department and most often it occurs in a diabetic on insulin or sulphonylurea. A rare cause of hypoglycaemia is tumour-induced.⁴ Pancreatic tumours like insulinoma or non-islet cell tumours can present with hypoglycaemia. In most of the non-islet cell tumours, the mechanism suggested is the release of incompletely processed insulin-like growth factor-II (IGF-II).⁴ Ectopic secretion of insulin has been implicated in some tumours. Non-islet cell tumour-induced hypoglycaemia has been reported with tumours of mesenchymal, epithelial, or haemopoietic origin. Among mesenchymal³ tumours, most common are fibrosarcomas, mesotheliomas, leiomyosarcomas, and haemangiopericytomas. Hepatocellular carcinoma, gastric, and pancreatic exocrine and lung carcinoma are common epithelial cancers that can cause hypoglycaemia.³

Overproduction of IGF-II specifically as incompletely processed form called 'big IGF-II' that does not complex normally with circulating binding proteins and thus more readily gaining access to target tissue, is the cause of hypoglycaemia in most patients. Plasma insulin, C peptide, and proinsulin levels are low during hypoglycaemia, which distinguishes it from insulinoma. Free IGF-II levels will be elevated. Growth hormone and IGF-I concentration will be reduced due to negative feedback mediated by IGF-II.⁵ Type B occurs in 5% of the cases and is early in the course of the disease suggesting a paraneoplastic manifestation. The mechanism suggested is increased production of IGF-II by the tumour. In this case, IGF-II was detected to be high. Type A occurs in terminal stages especially in rapidly growing large tumours, when liver is unable to satisfy demands of glucose by the tumour and other tissues. Our patient had a poorly differentiated hepatoma with hypoglycaemia as the only manifestation. Other paraneoplastic syndromes associated with hepatoma include erythrocytosis, hypercalcaemia, hypercholesterolemia, porphyria, dysfibrinogenemia, cryofibrinogenemia, etc.⁶ Another peculiar thing about this case is this patient has no other organ involvement and clinically his condition was stable and well-preserved. So, it neither

fits in Type A or Type B of hypoglycaemia. Good glucose response to glucagon occurs in case of insulinoma.⁷ Hypoglycaemia disappears with definitive treatment of non-islet cell neoplasm. Control of hypoglycaemia by percutaneous ethanol injection therapy to the HCC has been reported from some centres.⁸

In conclusion, patient manifesting as hypoglycaemia in well-preserved individual malignancy should be excluded and hypoglycaemia may be the only manifestation of prolonged illness.

CONFLICTS OF INTEREST

None identified.

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