Hypoglycemia, the first presenting sign of hepatocellular carcinoma

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ABSTRACT

Hypoglycemia is a well-known paraneoplastic manifestation of hepatocellular carcinoma usually occurring in the terminal stages of the disease. However, during initial presentation this manifestation is uncommon. We report a 77-year-old man who presented with signs and symptoms of severe hypoglycemia (for example drowsiness). After clinical work-ups, we detected a large mass in the liver. Interestingly, after surgical excision of the tumor, the attacks of decreased level of consciousness and hypoglycemia seized.

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Hypoglycemia in patients with hepatocellular carcinoma (HCC) usually occurs during the terminal stages of the illness. When it occurs as a paraneoplastic manifestation the underlying mechanism is the production of peptides with insulin-like structure and bioactivity exerting their effects via the insulin receptor, particularly, insulin-like growth factor-II (IGF-II). Hypoglycemia, presenting as the first manifestation of HCC is very rare. We present a case of HCC with severe, uncontrollable hypoglycemia, which was managed with surgical tumor resection

Case Report. In April 2003, a 77-year-old man was referred to the emergency room due to recurrent episodes of drowsiness and fluctuations in his consciousness. He was healthy until 15 days prior to his first referral. Initially, he was evaluated by a general practitioner and was sent to a neurologist. Clinical investigations carried out by a neurologist revealed hypoglycemia and so he was referred to an internist. His differential diagnosis was insulinoma or non-islet cell tumor hypoglycemia and performed several work ups (abdominal sonography had revealed a 4 × 5 cm mass in the right lobe of liver), which were in favor of chronic hepatitis B and a large mass in the right lobe of the liver. The patient was then referred to our department for therapeutic options and management. On physical examination, the liver was not palpable. Laboratory tests showed normal liver enzymes and low fasting blood sugars (**Table 1**). Anti-hepatitis C antibodies were negative. An abdominal computed tomography scan was performed in which a 5 cm mass in the posterior aspect of the right lobe of the liver just in front of the upper pole of the right kidney was detected (**Figure 1**). An ultra-sound guided with fine needle aspiration was carried out and was diagnostic of HCC with no signs of cirrhosis. During his hospital stay, he was kept on a 24-hours infusion of 20% dextrose and in situation in which the patient develops symptoms or signs of hypoglycemia, a 50% dextrose were supplemented.

The patient received no previous chemotherapy. In addition, as he had no proof of extrahepatic manifestations of the tumor or signs of metastasis, surgery was considered for him. The tumor was

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Table 1 - Laboratory data of the reported patient during the episode of symptomatic hypoglycemia.

Laboratory parameters	Unit	Measured value	Normal range
Serum glucose	[mg/dL]	45	60-110
2 hours post prandial sugar	[mg/dL]	104	>120
Serum insulin	[mU/L]	2.4	3.3-6.7
C-peptide	[ng/mL]	1.4	1.0-3.0
Glucagon	[pg/mL]	350	<100
Growth hormone	[ng/mL]	1.5	< 5
Cortisol	[nmol/L]	1600	121-618
ALT	[U/L]	33	< 42
AST	[U/L]	35	< 37
IGF-I	[ng/mL]	15	178-344
Total IGF-II	[ng/mL]	803 ± 40*	900-1200
IGF-II (7.5kD)	[ng/mL]	425 ± 70*	> 700
Big- IGF-II	[ng/mL]	356 ± 21*	< 180
Serum AFP	[ng/ml]	15309	< 20

ALT - alanine transaminase, AST - aspartate transaminase, IGF-I - insulin-growth factor, AFP - alfa feto protein, *Mean ± SD of 2 independent measurements. Measurement of the parameters were carried out using commercially available kits.

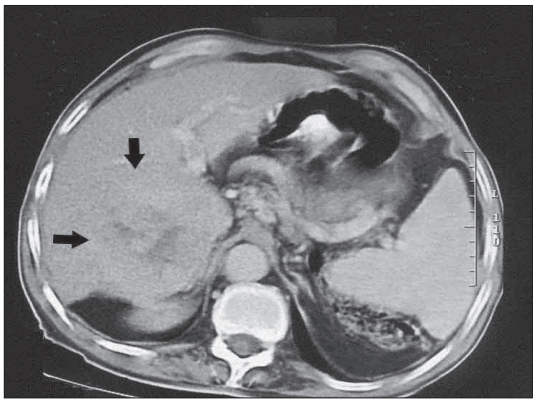

Figure 1 - Hepatocellular carcinoma of the liver. The arrows mark the mass in the center of the liver.

completely enucleated from the right liver lobe through bilateral subcostal (Chevron) incision. After operation, he stayed in the hospital for 2 weeks and passed through his post operation course uneventfully without any event of hypoglycemia and all his blood samples returned to normal values. He was followed 2 months later and had no problems related to his operation.

Discussion. Hepatocellular carcinoma may be associated with several paraneoplastic manifestations such as hypoglycemia, hypercalcemia, sexual changes, carcinoid syndromes and skin changes.[1] Hypoglycemia in HCC has 2 types: type A and B.[2] In type A patients, the tumor grows rapidly, appetite is impaired and muscle wasting and weakness is marked. Hypoglycemia, if present is mild and occurs as a terminal event within hours to 2 weeks of death. It results from inability of the liver extensively infiltrated by the tumor and often cirrhotic to satisfy the demands for glucose by both a large, often rapidly growing tumor and other tissues of the body.[1,3] In contrast, type B patients have a slow growing tumor and little or no muscle wasting and weakness. Hypoglycemia, which is present in all, appears 2-10 months before death[2] and manifests as severe hypoglycemia early in the course of the disease. Affected patients present with confusion, delirium, acute neuropsychiatric disturbances, convulsions, and stupor or coma. The type B hypoglycemia is believed to result from the defective processing by malignant hepatocytes of the precursor to the insulin-like growth factor II (pro-IGF-II). As a result big IGF-II circulates in 60-kd complexes that are appreciably smaller than the normal complexes. They transfer more readily across the capillary membranes and increase access of IGF-II to IGF-I, IGF-II, and insulin receptors. The effect is, increase in glucose uptake and thereby severe hypoglycemia.[1,3]

Our patient had type B hypoglycemia, however, interestingly it had occurred early in the course of the disease and as the first manifestation of his HCC. Ostensibly, management of these cases is always frequent feeding or parenteral infusion. Large doses of corticosteroid or frequent administration of growth hormone can also give temporary relieve, however, these are both associated with adverse side effects.[2,4] When hypoglycemia occurs in patients with HCC, the tumor is usually already massive and not amenable to surgery.[2] Medical treatments such as cytoreduction or percutaneous ethanol injection, and chemotherapy are the preferred treatment options. However, since our patient had presented early, and seem to be operable, we decided to resect the tumor. Interestingly, our patient had the dramatic response to surgical excision, despite the large size of the tumor, with no postoperation need for frequent feeding or parenteral infusions. All the laboratory data returned to normal values. Two months follow up of the patient was satisfactory with no signs of recurrence.

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