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LETTER TO THE EDITOR

Successful treatment of non-islet cell tumor hypoglycemia in hepatocellular carcinoma with doxorubicin

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Paraneoplastic syndrome is not infrequently presented in hepatocellular carcinoma (HCC), whose incidence is up to 27–43% during the clinical course in some series [1, 2]. These patients usually have a larger tumor volume, a higher serum alpha-fetoprotein and less favorable outcomes [3]. However, paraneoplastic syndrome as the first manifestation of HCC is uncommon, and only 13% of patients with HCC develops hypoglycemia early in the course of their illness. This group of patients tends to have a longer average survival, but require more intensive hypoglycemic treatment [4]. Systemic chemotherapy alone was ineffective for hypoglycemia in patients with HCC [5]. The author reports here the successful treatment with doxorubicin in HCC patient who first presented with non-islet cell tumor hypoglycemia.

A 16-year-old man presented with a history of progressive abdominal pain, weight loss and recurrent episodes of transient loss of consciousness, which rapidly reversed by glucose administration for 2 months. His previous medical history was unremarkable. He denied taking any medications. Physical examination revealed huge hepatomegaly without chronic liver signs. Laboratory investigations showed preserved liver function test. There was positive serology to hepatitis B virus with measurable HBV-DNA of 40,000 copies/mL. Serum alpha-fetoprotein (AFP) was 105,095 ng/mL (normal 0–15). Computed tomography of the abdomen showed liver masses occupying entire left hepatic lobe with few lesions in the right hepatic lobe with obliteration branches of left portal vein. There were multiple pulmonary nodules in both basal lungs and splenomegaly. Ultrasonography-guided fine-needle biopsy of liver masses revealed tumor cells consistent with moderately differentiated hepatocellular carcinoma.

There was appropriate rising of serum cortisol, while serum insulin, C-peptide and IGF-I level were suppressed during hypoglycemia attack. Unfortunately, the IGF-II and big IGF-II levels could not be measured. He still had intermittent mild hypoglycemia, although he was treated with intravenous glucose infusion and high carbohydrate meals. Palliative systemic chemotherapy with doxorubicin was started. He further discontinued intravenous glucose infusion and did not have hypoglycemic attack until discharge.

Hepatocellular carcinoma accounts for 23% of non-islet cell tumor hypoglycemia (NICTH), second to mesenchymal tumors that accounts for 45% of NICTH [6]. The prevalence of hypoglycemia in HCC ranged from 4 to 27% [7]. The cause of hypoglycemia in HCC is either from impaired gluconeogenesis due to decompensated liver (glucose underproduction) or from high big insulin-like growth factor II (IGF-II) level produced by tumors. Big IGF-II is from a defect in processing pro-IGF-II to 7.5 kDa IGF-II (normal IGF). Normally, 75% of IGFs are formed in ternary complexes. This complex is a compound of IGF, insulin like growth factor binding protein-3 (IGFBP-3) and acid-labile α-subunit. Big IGF-II-IGFBP-3 complex cannot bind with acid-labile α-subunit. As a result, smaller complexes facilitate transport across the capillary membrane and increase access to target tissues. Big IGF-II binds IGF-I receptor and inhibits pituitary GH secretion. It leads to decreased growth hormone (GH) and IGFBP-3 [8]. Diagnosis of hypoglycemia from this mechanism is proved by demonstration of suppressed 7.5 kD IGF-II level and elevated big IGF-II

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level in serum, whereas total IGF-II level may be within normal range [5]. Immunohistochemical studies may also show a high level of IGF-II peptide in the HCC section [9]. The diagnosis of NICTH is therefore made by demonstrating low insulin/C-peptide level together with an inappropriate increase in the ratio of IGF-II to IGF-I. Although in the presented patient, measurements of the IGF-II and big IGF-II levels were unavailable, the depressed IGF-I, insulin and C-peptide levels during hypoglycemic attack were suggestive of diagnosis of NICTH.

The occurrence of hepatocellular carcinoma in young adult, like the presented patient, is unusual. It could be possibly be explained by the strong relationship of hepatocellular carcinoma to hepatitis B virus, which he might be infected since neonate (by perinatal transmission) or childhood. However, the referred data could not be obtained.

The optimal therapeutic strategies in NICTH involve removal of the tumor or reduction of the tumor mass. Percutaneous ethanol injection [7] or intrahepatic adriamycin [10] administration may be beneficial in inoperable patients. Systemic chemotherapy was previously shown as unfavorable outcomes, contrary to the presented patient. Palliative treatment includes administration of counter-regulatory hormones like glucocorticoids, glucagon [5], growth hormone or octreotide [8, 10], but the effects might be transient. Combination therapy may provide additional benefits in some patients [8].

In conclusion, systemic chemotherapy with doxorubicin should be considered as therapeutic option of NICTH in hepatocellular carcinoma.

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