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Lenvatinib in severe hypoglycemia associated with hepatocellular carcinoma

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Dear Editor,

We present the case of a 24-year-old male with multicentric hepatocellular carcinoma (HCC) over HBV-related compensated liver cirrhosis, on treatment with sorafenib and tenofovir. He had multiple admissions in recent months for severe hypoglycemia episodes with neurological symptoms.

Serologic tests were requested given the suspicion of non-islet cell tumor hypoglycemia (NICTH), which revealed low insulin, proinsulin, C-peptide, and beta-hydroxybutyrate levels, the absence of anti-insulin antibodies, and an IGF-2/IGF-1 ratio of 20.4. He was not eligible for tumor debulking because of a low liver reserve. Sorafenib was changed to lenvatinib given the patient's difficult glycemic control with oral diet, oral glucose solutions, and corticosteroids. Glycemic control improved in a few days, glucose intravenous infusions were suspended, and the patient was discharged. He required a new admission 3 weeks later because of worsening and a torpid evolution of his HCC, with a fatal outcome.

DISCUSSION

Hypoglycemia in HCC is usually multifactorial. NICTH is an infrequent paraneoplastic syndrome, probably underdiagnosed, severe, and difficult to manage, in the context of benign and malignant tumors, including HCC (1,2).

NICTH usually presents mainly with neuroglycopenic manifestations, which may constitute the presentation of HCC (2). It is characterized by excessive production of proIGF-2 and IGF-2, as well as low levels of insulin, proinsulin, C-peptide, and beta-hydroxybutyrate. An IGF-2/IGF-1 ratio > 10 confirms the diagnosis (1-3).

Publications about NICTH management are scarce. Complete tumor resection is curative, but commonly contraindicated, therefore attempts are made to reduce tumor volume. If this is not possible, corticosteroid therapy may be effective (prednisone, 30-60 mg/day), with or without rhGH (3-12 mg/day). An alternative for short-term management is glucagon infusion (1,3). Recent data suggest that lenvatinib, an oral receptor tyrosine kinase inhibitor with an antiangiogenic effect, may be a suitable alternative (8 mg/day) (4).

NICTH should be suspected in the presence of refractory hypoinsulinic hypoglycemia in patients with HCC, mainly with neurological symptoms without a clear etiology. Its recognition will improve the quality of life of these patients, and lenvatinib could be a novel option in refractory cases with reduced functional reserve.

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