

## CASE REPORT

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# Severe hypoglycemia complicating hepatocellular carcinoma

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## ABSTRACT

**Introduction:** Paraneoplastic or ectopic endocrine syndromes are the consequence of aberrant hormonal production or of substances with hormonal effect, by a neoplastic tissue originally devoid of this endocrine activity. In this sense, hypoglycemia by extra-pancreatic tumors “non-islet cell tumor hypoglycemia” especially of hepatic origin is often severe and iterative. **Case Report:** We report the clinical case of a 56-year-old patient, type 2 diabetic for 10 years, diagnosed with hepatocellular carcinoma with the onset of severe hypoglycemia attacks, persistent even after stopping treatment. The first-line assessment in search of renal failure, adrenal insufficiency, and hypothyroidism returned without abnormality. However, glycemic monitoring showed venous hypoglycemia at 0.38 g/L with concomitant insulinemia and low peptide C. Considering the clinical context, the insulin-like growth factor-1 (IGF1) was low. IGF2 was within normal limits. Given the inextricable and incurable nature of the tumor, dietary measures were required in our patient for stabilization of the blood sugar. **Conclusion:** Hypoglycemia induced by tumor secretion of IGF2 is a rare paraneoplastic syndrome. It should be considered with tumor syndrome and organic hypoglycemia. Management remains poorly defined.

**Keywords:** Hepatocellular carcinoma, Insulin-like growth factor-2, Paraneoplastic syndrome, Severe hypoglycemia

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## INTRODUCTION

Hypoglycemia by extra-pancreatic tumors “non-islet cell tumor hypoglycemia” is often severe and iterative. The tumor responsible for hypoglycemia are frequently of mesenchymal origin and usually large [1]. Their location is intrathoracic in one-third of cases and retroperitoneal in two-thirds of cases. About three-quarter of these tumors are malignant. The endocrine paraneoplastic syndrome, including paraneoplastic hypoglycemia, occurring in hepatocellular carcinoma is suspected in blood glucose, insulin, proinsulin, C-peptide, and  $\beta$ -hydroxybutyrate collapse due to the hormonal hypersecretion of insulin-like growth factor-2 (IGF2) and the Big IGF2 [2]. The IGF2 has structural homology with the insulin-like growth factor-1 (IGF1) and insulin.

We report a clinical observation of paraneoplastic hypoglycemia in a patient with advanced hepatocellular carcinoma.

## CASE REPORT

We report the clinical case of a 56-year-old patient, type 2 diabetic for 10 years on metformin with a HbA1c at 8.16 and average blood sugar of 180 mg/dL. His medical condition was complicated by a metabolic steatopathy (non-alcoholic fatty liver disease) without any other pathological history. There was no history of viral liver disease, any drug intake or alcohol intoxication poisoning.

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On clinical examination there was no hepatomegaly. An abdominal ultrasound completed by an abdominal magnetic resonance imaging with dynamic contrast-enhanced showed a voluminous lesion ( $17 \times 10 \times 8$  cm) on left side of the liver which was hyperintensity on T2 weighted image, arterial enhancement, and washout on portal venous phase image.

The findings were compatible with hepatocellular carcinoma. Alpha-fetoprotein levels were high (870 ng/mL). A liver biopsy was performed. Histopathologic examination showed a well-differentiated tumor proliferation of hepatocellular carcinoma.

Therapeutically, the patient received anti-tumor treatment with intrahepatic arterial chemoembolization. Surgical management was ruled out because of the advanced nature of the tumor.

On follow-up, several hypoglycemic attacks occurred with signs of neuroglucopenia. Rigorous monitoring of blood glucose levels showed severe hypoglycemia mainly in the early morning, continuing even after stopping oral antidiabetic therapy. The biological assessment showed a blood glucose of 38 mg/dL without biological hepatocellular insufficiency. The insulinemia measured concomitantly at 0.5 mIU/mL (normal rate between 2 and 20 mIU/mL) and C-peptide at 0.2  $\mu$ g/L (normal rate between 1.1 and 5  $\mu$ g/L). The IGF1 and IGF2 assays showed IGF2 to 856 ng/mL (normal rate between 436 and 1058 ng/mL), while the IGF1 rate is less than 43 ng/mL (normal rate between 116 and 358 ng/mL) with an IGF2/IGF1 ratio at 19.90, well above 10. Big-IGF2 (IGF2 precursor) and insulin growth factor binding protein-2 (IGFBP-2) were not assayed, their assay is reserved for research laboratories.

Given the inextricable and incurable nature of the tumor, dietary measures were required in our patient. A suitable intake of slow absorption sugars was suggested to keep up normoglycemia. Snacks between meals or late-night snacks were instituted. The intravenous glucose infusion administration was effective in controlling hypoglycemia without resorting to other treatments. In evolution, episode of hypoglycemia decreased in frequency and severity, however, the patient died following complications from his hepatocellular carcinoma.

## DISCUSSION

Paraneoplastic or ectopic endocrine syndromes usually result from aberrant hormone precursors or hormone-like substances by tumors. Knowledge of paraneoplastic endocrine complications is important for both the early diagnosis of neoplasia and the prognosis of the patient [2].

In this sense, paraneoplastic hypoglycemia which is not related to insulin and is also called "non-islet cell tumor induced hypoglycemia" is a rare entity. It is mostly made of three tumors: abdominal or thoracic mesenchymal

tumor (Doege–Potter syndrome), adrenal cortical tumor (Anderson syndrome) and primary or secondary liver tumor (Nadler–Wolffer–Elliott syndrome), even if other tumors can sometimes be implicated [3]. The appearance of clinical signs or paraneoplastic syndromes is in large tumors with a high mitotic index [4].

The occurrence of hypoglycemia is related to the expression by the tumor of IGF2. It has homology to IGF1 (involved in growth) and insulin (binding to its receptor, hence its hypoglycemic power). It is also the form of a high molecular weight precursor (Big IGF 2) that occurs in the paraneoplastic secretion; Big-2 IGF BP3 binds to IGFBP3 which potentiates the action of IGF2 [3]. It induces a decrease in hepatic glucose production and lipolysis and an increase in glucose consumption by peripheral tissues and tumors.

Hypoglycemia induced by tumor secretion of IGF2 is severe, iterative, and occurs mostly on an empty stomach and at the distance from meals, with symptoms of neuroglucopenia.

The paraneoplastic origin of severe hypoglycemia should be considered in the context of advanced neoplasia, as in our patient, whose hypoglycemic episodes persisted even after discontinuation of oral antidiabetic therapy.

Biologically, the determination of C-peptide, insulinemia, and  $\beta$ -hydroxybutyrate during a hypoglycemic episode targets low rates. This hypoinsulinic hypoglycemia should lead to suspicion of secretion of hypoglycemic substance that inhibits insulin secretion, such as IGF2 or related substances. Typically, tumors secreting IGF2, insulin, proinsulin, C-peptide, and the  $\beta$ -hydroxybutyrate are low and secretion of GH and IGF1 is inhibited [5]. Total IGF2 levels may be high or normal, hence the interest is in assaying Big IGF2 [6]. However, its dosage is restricted to research laboratories. In practice, where IGF2 is normal, the ratio of IGF2/IGF1 will be used. The normal ratio is about 3/1; a ratio greater than 10/1 is strongly suggestive of secretion of IGF2 precursor [5, 7]. Indeed, in our patient, the ratio was 19.90, well above 10.

Blood glucose, insulin, proinsulin, C-peptide, and  $\beta$ -hydroxybutyrate levels are decreased due to the hypersecretion of the hypoglycemic hormones, such as IGF2 and Big IGF2 (long acting). The IGF2 has structural homology with IGF1 (involved in growth) and with insulin [2].

In an emergency, hypoglycemia should be corrected by continuous parenteral administration of glucose, sometimes with the injection of glucagon that allows stimulation of hepatic glycogenolysis. Complete excision of the tumor, as expected, leads to remission of symptoms. If unable to achieve a complete resection, palliative debulking surgery is recommended to reduce the tumor secretion [8].

If, as in our patient, the surgical treatment has not been achieved, several therapeutic alternatives can be proposed. Indeed chronic treatment with corticosteroids seems the most effective medical treatment in a

dose-dependent manner. The usual dose is between 30–60 mg/day prednisone equivalent introduced by titration. It prevents hypoglycemia by stimulating hepatic gluconeogenesis, reducing peripheral glucose consumption, and increasing lipolysis in adipocytes and therefore the synthesis of free fatty acids. It also appears that glucocorticoids decrease the synthesis of Big IGF2 [9].

Paraneoplastic hypoglycemia may be improved by administration of diazoxide hydrochlorothiazide, which decreases insulin secretion from  $\beta$  cells [10], but its effectiveness is less in the treatment of hypoglycemia induced hyperfunctioning IGF2. Similarly, for somatostatin analogs, some hyperfunctioning IGF2 tumors bear the somatostatin receptor [11].

Recombinant GH (rGH) showed a beneficial effect by stimulating gluconeogenesis and glycogenolysis. The rGH increases the synthesis of IGF-BP3. One disadvantage of this treatment is the risk of stimulating tumor growth [9].

Besides the medical treatment, nutritional management should be established by splitting meals and increasing the daily carbohydrate intake.

Currently, anti-IGF2 antibodies, antagonists of the IGF2, and inhibition assays of transcription of the IGF2 gene are under evaluation in various cancers [12]. The effectiveness of these therapies has not yet been demonstrated.

## CONCLUSION

Hypoglycemia induced by tumor secretion of IGF2 is a rare paraneoplastic syndrome. It should be suspected in a person having a tumor syndrome and organic hypoglycemia. The treatment is essentially symptomatic and etiologic if possible.

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## Author Contributions

Sara Derrou – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yousra Benabdelfedil – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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**Guarantor of Submission**

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Written informed consent was obtained from the patient for publication of this article.

**Conflict of Interest**

Authors declare no conflict of interest.

**Data Availability**

All relevant data are within the paper and its Supporting Information files.

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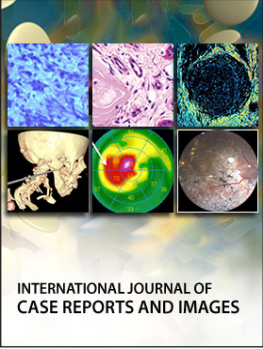
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