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Case Report

Paraneoplastic Hypoglycemia: A Case Report

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Abstract

Introduction: Paraneoplastic hypoglycemia unrelated to insulinoma is a rare cause of hypoglycemia and is due to paraneoplastic secretion of either IGFI, IGFII, or more rarely insulin ***Observation:*** We report a case of paraneoplastic hypoglycemia in a patient with metastases of an unknown primary. This is a 60-year-old patient admitted to the ward for recurrent hypoglycemia, the first of which was discovered following an apyretic coma. He has a history of hepatic and gluteal metastases from an undifferentiated carcinoma, the primary of which is unknown, followed in the oncology department and treated by chemotherapy. The biological assessment shows microcytic hypochromic anemia, hypoinsulinism <0.1mIU / l associated with a collapsed C peptide <0.15ng / ml (RV: 1.1- 4.4) with a concomitant glycemia of 21 mg/l. In view of the clinical context and the paraclinical explorations, the diagnosis of paraneoplastic hypoglycemia was retained after the elimination of the factitious origin and the insulinoma. The patient was put on diet, infusion of 5% glucose serum from which he was weaned after the introduction of prednisolone corticosteroid therapy: 60 mg per day with good tolerance and disappearance of hypoglycemia. ***Discussion/Conclusion:*** Paraneoplastic hypoglycemia is hypoglycemia most commonly caused by the overproduction of insulin-like growth factor 2 (IGF-2) and its precursors which can activate the insulin receptor. In general, large mesenchymal and epithelial tumors may be the cause. The diagnosis is confirmed by the discovery of an elevated IGF-2 / IGF-1 ratio. The basic treatment is surgical excision. Glucocorticoids are among the drugs that can be used in cases where surgery is not possible as a first line followed by other alternatives in case of failure.

Keywords: hypoglycemia, tumor, insulin-like, corticosteroid therapy.

INTRODUCTION

Hypoglycemias secondary to extra-pancreatic tumors were identified back in 1929 [1]. At that time, they were attributed to increased glucose consumption by the tumor.

Since then, it has been established that this consumption contributes slightly to hypoglycemia [2]. Another mechanism was identified in the 1970s, based on the finding of low insulin levels, suggestive of tumor secretion of an "insulin-like" factor [3].

It is a serious and life-threatening condition that is under-diagnosed and needs to be recognized and treated promptly. It occurs in large tumors and disappears after surgery, which represents the first-choice treatment for a lasting cure in most cases.

We report a case of paraneoplastic hypoglycemia on a patient with metastases of an unknown primary.

OBSERVATION

A 60-year-old patient referred to our practice for repeated hypoglycemia. The patient was monitored in medical oncology for hepatic and gluteal metastases of an undifferentiated carcinoma of unknown origin and treated with palliative chemotherapy with a notion of failure.

The patient's medical history does not reveal any alcohol consumption or hypoglycemic medication.

The interview with the family revealed the notion of several episodes of malaise, evolving for 3 months interval, becoming shorter and more severe,

considered as secondary to the chemotherapy, but not labeled as hypoglycemia since the concomitant measurement of blood glucose was not performed until after the occurrence of an apyretic coma requiring immediate infusion of 30% glycosated serum with recovery of consciousness. Hypoglycemia was essentially occurring outside of meals, especially during the early morning hours, with a positive Whipple's triad (venous hypoglycemia less than 50mg/dl, neuro-glucopenic signs with improvement of the symptomatology following raise of blood sugar levels back to normal). The symptomatic nature of hypoglycemia diminished significantly during the course of the disease and was mainly revealed by self-monitoring.

General examination found a hemodynamically and respiratory stable conscious patient with 85 kg weight, 175 cm height, 27 kg/m body mass index, 157/86 mmhg blood pressure, 123 beats/min heart rate, and 33 mg/l asymptomatic capillary glucose (requiring emergency hospitalization with immediate infusion of 30% serum glucose).

Physical examination found abdominal distension with a mass in the epigastrium and right hypochondrium and a large mass in the left buttock.

The patient was placed on blood glucose monitoring every 2 hours with the objectification of several episodes of hypoglycemia for which the patient benefited from boluses of 30% glucosed serum with continuous infusion of 5% glucosed serum.

A sample for insulin and c-peptide dosage was taken during an episode of symptomatic hypoglycemia at 18mg/dl measured on capillary blood and which indicated hypoinsulinism < 0.1mUI/l associated with a collapsed c-peptide < 0.15ng/ml with a concomitant venous glycemia at 21 mg/dl.

The remaining biological check-up found a microcytic hypochromic anemia, a cholestasis (alkaline phosphatases at 2 x Normal, gamma glutamyl transpeptidase at 4xNormal), normal transaminases and normal renal function and blood ionogram.

The thoracic X-ray was normal. The initial abdominal ultrasound found a large heterogeneous hepatic mass pushing back the surrounding organs.

The control thoracic-abdominal-pelvic CT scan revealed multiple hepatic lesions involving the left liver and segments VI and VII with multiple coeliomentric and retroperitoneal nodes as well as gluteal lesions with the appearance of an inferior polar renal lesion (Figure 1&2).

The biopsy of the hepatic mass revealed a moderately differentiated tumor process, and the immunohistochemistry corresponded to a carcinomatous process, leading to a primary search for a renal origin.

Considering the clinical context and the para-clinical explorations, the diagnosis of paraneoplastic hypoglycemia was retained after having eliminated the iatrogenic, factitious and insulinoma origin.

The administration of glucocorticoids (prednisolone 60 mg/d) associated with dietary rules allowed the disappearance of hypoglycemic episodes even after stopping the infusion of glycosated serum, thus allowing the patient to be discharged with outpatient follow-up. The evolution was marked by the stabilization of capillary glycemic figures at values between 70mg/dl and 150mg/dl under corticotherapy.

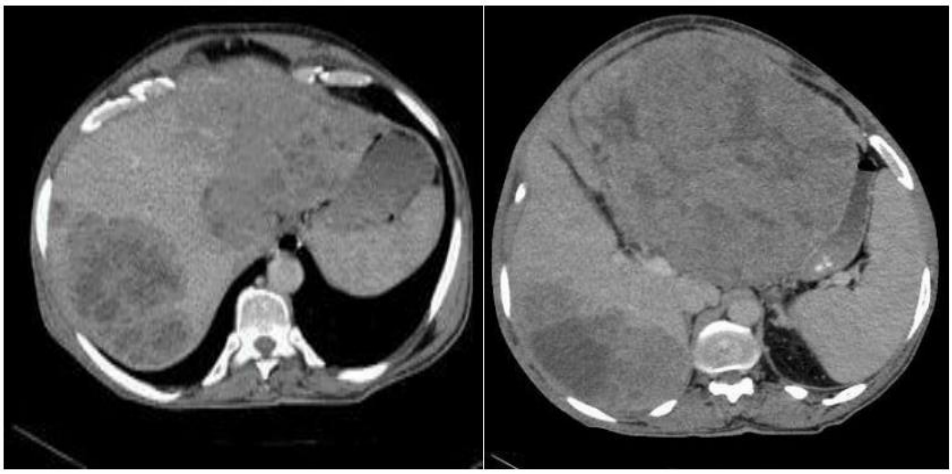

Figure 1: TAP CT: axial slice showing a large hepatic tumor process of the left liver with synchronous segment VI and VII tumor lesions

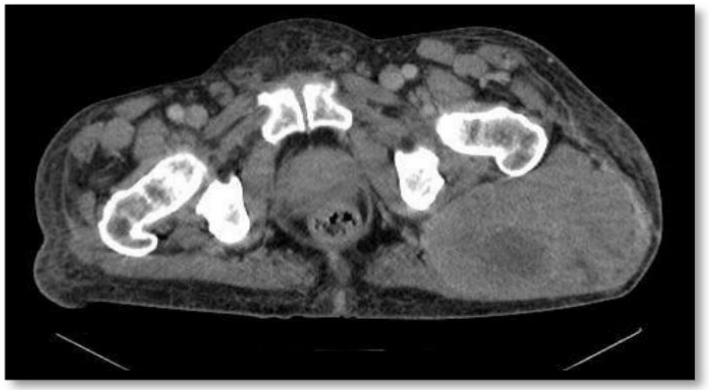

Figure 2: presence of a heterodense mass in the left gluteal region measuring 199*188m, presenting the same characteristics as the hepatic masses and presenting an endopelvic extension

DISCUSSION

For the non-diabetic patient, hypoglycemia is defined as a venous glucose level below 2.75 mmol/L (50 mg/dL). A low capillary blood glucose reading requires confirmation by venous blood glucose [4].

Hypoglycemia can be secondary to a variety of etiologies; however, it is most commonly found in diabetic patients on insulin or secretagogues [5].

Paraneoplastic hypoglycemia is now known as NICTH (Non-islet cell tumor hypoglycemia) since it is due to an extra-pancreatic tumor. It is a rare cause of hypoglycemia, the first case of which was identified in 1929 (Doege-Potter syndrome). Initially attributed to excess glucose consumption by the tumor and subsequently to tumor secretion of an "insulin-like" factor which would correspond to a high molecular weight precursor of IGF-2, called Big-IGF-2 (the overproduction of pre-pro-IGF-2 exceeding the capacity of the enzymes which metabolize it and leading to an excess of Big-IGF-2 compared to IGF-2) Note that somatostatin or IGF1 secretion can also be the cause for that.

IGF-2 is a hormone secreted mainly by the liver, where it acts on cell proliferation, differentiation and apoptosis. This molecule as well as its precursor are able to bind to the insulin and IGF receptor and thus to cause hypoglycemia [6], (by decreasing glucose production by the liver and increasing glucose utilization by muscles and peripheral tissues) [7], seborrheic keratosis, rhinophyma and acromegaloid syndrome [6].

Regarding our patient, he suffered from severe recurrent hypoglycemia without signs of seborrheic keratosis, rhinophyma, or acromegaloid syndrome.

Frequently found tumors are large hepatic and mesenchymal (solitary fibrous pleural) tumors [6]. Benign or malignant solid tumors of the mesenchyme, epithelial, hematopoietic and rarely neuroendocrine tumors [7]. In our case the histological origin of the tumor could not be determined.

Hypoglycemia is a revealing symptom in half of the cases that lead to the search for an etiology, as it can be, as in our case, a sign in the course of an already known tumor pathology whose neuroglycopenic symptoms lead to the realization of cerebral imagery in search of tumor metastasis or stroke explaining the symptomatology (an episode of confusion, a fall in the elderly individual, focal neurological signs)

Any behavioral or mental change in a patient with a tumor requires screening for hypoglycemia [6]. In our case, the tumor syndrome preceded the hypoglycemia, which was manifested by repeated discomfort but not identified as such until after a loss of consciousness, which led to the measurement of capillary blood glucose with recovery of consciousness after a serum glucose infusion.

Hypoglycemia is suspected when two types of clinical signs are observed:

- **Adrenergic signs:** are related to sympathetic neuronal activation rather than adrenal gland activation. They are not specific to hypoglycemia and can be seen regardless of the cause of hypoglycemia;
- **Neuroglycopenic signs:** reflect cerebral glucose deprivation. These symptoms appear when the blood glucose level falls below 2.75 mmol/l (50 mg/dl) and are reversible by correction of the hypoglycemia. They are observed during organic hypoglycemia and their occurrence requires a thorough etiological check-up [5].

The adrenergic signs of hypoglycemia may appear at blood glucose levels between 2.75 and 3 mmol/L (50 and 55 mg/L), but the sensory threshold may be lowered with repeated episodes of hypoglycemia, and the sensation of hypoglycemia may

even disappear completely (hypoglycemia unawareness) [5].

The threshold value used to define hypoglycemia remains a matter of debate: inferior to 3 mmol/l (55 mg/dl) for the American Endocrine Society [8], inferior to 2.75 mmol/l (50 mg/dl) in venous blood for the French Society of Endocrinology (SFE) [9].

Hypoglycemia should be suspected when the signs of Whipple's triad are present during malaise [4]:

- The presence of symptoms suggestive of hypoglycemia;
- Venous blood glucose below 2.75mmol/l (50 mg/dl)
- Rapid correction of symptoms by unresuscitation.

A detailed history is essential to evaluate any systemic disease or medications that may cause hypoglycemia. [10].

In this case, the threshold of hypoglycemia causing neuroglycopenic signs became lower as the episodes recurred, with a totally asymptomatic patient for capillary glycemia up to 35 mg/l and signs during hypoglycemia < 21mg/l.

In order to confirm the neoplastic origin of the hypoglycemia, blood insulin, C-peptide, proinsulin and beta-hydroxybutyrate should be collected at the time of hypoglycemia. NICTH corresponds to low levels of insulin, C-peptide, proinsulin and beta-hydroxybutyrate.

Further evaluation of NICTH involves measuring IGF-1 and IGF-2 levels. IGF-1 usually equals zero, whereas IGF-2 levels may be normal or elevated. An IGF-2/IGF-1 ratio greater than 10 confirms NICTH (normal value < 3).

However, it is important to keep in mind that the IGF-2/IGF-1 ratio can be >10 in malnutrition and sepsis; nevertheless, in these cases, both IGF-2 and IGF-1 are low [11, 12].

It should also be noted that the IGF-2/IGF-1 ratio is influenced by the IGFBP-3 level, which is abnormally reduced in renal failure, therefore, we may have a falsely negative IGF-2/IGF-1 ratio in the renal failure patient.

In our case, the insulin and C-peptide measurement performed at the time of the hypoglycemia revealed a low insulin level < 0.1 mIU/l and a collapsed C-peptide < 0.15ng/ml during an episode of symptomatic hypoglycemia at 18mg/dl measured on capillary blood with concomitant venous glycemia at 21 mg/dl. This made it possible to eliminate hyperinsulinism as the etiology of the hypoglycemia and to retain the diagnosis of paraneoplastic hypoglycemia given the neoplastic context of the patient.

From a therapeutic point of view, surgical resection of the tumor is the preferred treatment for NICTH, resulting in immediate resolution of hypoglycemia. When complete resection is impossible, reduction of the tumor mass can be proposed [14-16] and Embolization remains an alternative for unresectable tumors [7].

Glucocorticoids are an effective therapy in the treatment of NICTH. They prevent hypoglycemia by increasing hepatic gluconeogenesis, inhibiting peripheral glucose utilization and promoting lipolysis. The dose should be adjusted to better manage hypoglycemia. (30-60 mg prednisone/day)[14].

Glucagon can prevent hypoglycemia by increasing glycogenolysis and gluconeogenesis. Hoff and al. used pump infusions of glucagon to treat NICTH in a patient with meningeal sarcoma. However, the effects are not long lasting; therefore, it is only a short-term treatment [17].

Somatostatin analogues have been used successfully in some cases, while in other cases there has been no improvement in glycemic numbers probably due to the fact that these tumors do not have somatostatin receptors [7].

Recombinant growth hormone (rGH) can alleviate hypoglycemia by increasing neoglucogenesis and peripheral glucose uptake. Additionally, it modifies IGF-2 production by increasing 150 kDa complexes and decreasing 50 kDa complexes. It is used in cases of NICTH that did not respond to glucocorticoids [18].

Since NICTH results from the interaction between the large IGF-2 and the insulin receptor, therapies aimed at disrupting this interaction would be potentially useful in the treatment of NICTH [19].

Administration of intravenous glucose and frequent carbohydrate snacks may also help reduce the frequency and symptoms of hypoglycemia [7].

In our situation, surgical resection was not possible due to the advanced stage of the tumor. Nevertheless, oral corticosteroid therapy (prednisolone 60 mg/d) associated with dietary rules allowed the disappearance of hypoglycemic episodes even after stopping the infusion of glucose serum.

CONCLUSION

The paraneoplastic origin of severe hypoglycemia must be evoked in the context of advanced neoplasia. Tumor removal is the treatment of choice for such hypoglycemia. In cases where this treatment is not possible, corticosteroid therapy appears

to be the first-line alternative, with recourse to other therapies being considered in the event of failure of corticosteroid therapy.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

- Benkacem marieme: corresponding author.
- M. Smouni, H. Lahbib: residents undergoing training in the endocrinology department.
- Fatimzahra al Mrabet: oncologist who follows the patient for his neoplastic disease.
- Siham al Alaoui Rachidi: radiologist who interpreted the CT scan.
- All authors have read and approved the final version of the manuscript.

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