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Hypoglyceamia due to Paranoeplastic Secretion of Insulin in a Patient with Metastasizing Colon Cancer

Nadia Charfi, Lilia Affes, Mouna Elleuch*, Wafa Ben Saada, Nabila Rkik, Faten Hadj Kacem, Mouna Mnif, Fatma Mnif, Mohamed Abid

Departement of Endocrinology, Diabetolgy, Hedi Chaker Hospital, Sfax, Tunisia
*Corresponding author: elleuch_mouna@yahoo.fr

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Abstract Paraneoplastic hypoglycemia by insulin secreting is rarely described in literature. We review rare cases of paraneoplastic hypoglycemia due to insulin secreting non islet cell tumor diagnosed in a 51 years old patient. This man has an advanced colon cancer with hepatic metastasize. He was admitted in our department for frequent, severe, organic hypoglycemia. Hormonal finding showed elevated serum levels of insulin and c peptide associated with normal serum levels of IGF1 and IGF2. The patient was treated by diet, prednisolone, diazoxid and the metastasize was surgically removed. So that, Hypoglycemia disappeared quickly after the treatment.

Keywords: *Paraneoplastic hypoglycemia, colon cancer, insulin, metastasize, IGF1, IGF2*

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1. Introduction

Paraneoplastic hypoglycemia is rare and the first case was reported in 1930. It is called a doege and Potter syndrome or non-islet cell tumor hypoglycemia (NICTH) [1,2]. It is four times less frequent than insulinoma. Until our day, only a few hundred cases were reported around the world. Paraneoplastic hypoglycemia was usually reported in large tumors (weighting more than 500 g), well differentiated and slow growing [1]. It can be benign or malignant. It is described in 50% of mesenchymatosis tumors (fibrosarcoma, leiomosarcoma, hemangiopericytoma, (gastro intestinal stromal tumors(GIST)) [3]. Few cases were reported in epithelial tumors (hepatic carcinoma, adrenal carcinoma) and rarely hematopoietic tumors [4]. In some cases the diagnosis is difficult mainly when hypoglycemia is the first symptom.

2. Case Report

A 51 years old man was admitted to the emergency room in the early hours of the morning in February 2014 for confusion then loss of consciousness. On the admission, the capillary blood glucose was low (0.3g/l) confirming hypoglycemia. He recovered quickly after parenteral glucose 30% administration. Several tests were made in order to find other causes for this unconsciousness. There were no baseline laboratory neither ionic abnormalities. The electrocardiogram was normal as well as echocardiography and echo-Doppler of the supra aortic trunk. The CT brain scan was normal. During his admission, the patient suffered from recurrent bouts of hypoglycemia. So he was commenced on a continuous infusion of 10% dextrose for adequate control. Therefore the patient was admitted in the hospital for further examination.

With further questioning, the patient reported in the last week similar episodes of dizziness and blurred vision especially in the early hours of the morning. In fact, he had a history of a sigmoid cancer without metastasis for which he was treated by surgery two years ago. The primary tumor was, completely, surgically removed. The pathohistological study showed an adenocarcinoma T3N0M0. After one year, the patient had a peritoneal carcinomatosis for which he was given chemotherapy and led to the disappearance of the metastasis. Then hepatic metastasis appeared and chemotherapy began with infusion FOLFOX (Folinic acid-Fluoroucil-Oxaliplatin) regimen led to normalization of the level of ACE and CA19-9. The last cure was one month ago when serum levels of CA 19-9 and ACE were 11.93 UI/ml (<37UI/ml) and 1.31ng/ml (<5 ng/ml) respectively. His medical history revealed also paraneoplastic thrombosis of superior vena cava.

Physical examination was unremarkable; the patient had a weight of 93 kg with a body mass index of 23 Kg/m². There was no hepato- splenomegaly neither lymphadenopathy. A more complete laboratory work-up was made. Liver and kidney function was normal (ASAT=24, ALAT=23, creatinine=68 µmol/l, clearance of creatinine=140ml/min). Thyroid disease and adrenal insufficiency were excluded (TSH=2.63 UI/ml, FT4= 16.3 pmol/l and cortisol 8H=93 µg/l and cortisol 16H=100 µg/l, ACTH=10pg/ml). During

spontaneous hypoglycemia blood was taken to measure levels of insulin, c peptide, proinsulin and growth factors 1 and 2 (IGF1-IGF2). Serum levels of insulin and c peptide were elevated, at respectively 60000 MUI/l (VN <27) and 27 µg/l (1.1-4.4) with concomitant hypoglycemia at 3mmol/l. Serum levels of insulin-like growth factor 1(IGF1) was at 15.6 ng/ml (NV: 77-224 ng/ml) and insulin-like growth factor 2 (IGF2) was at 654 ng/ml (NV: 396-1049 ng/ml) excluding the diagnosis of IGF1 and IGF2 secreting non islet cell tumor. Unfortunately insulin antibodies were not searched. The diagnosis of paraneoplastic hypoglycemia was made after excluding the diagnosis of insulinoma. In fact, octreoscan was normal. Positron emission tomography with 18 FDG (TEP-TDM with 18 FDG) showed a peritoneal thickening without any anomalies in pancreatic parenchyma. The treatment was based on high glycaemic index nutriment and initially a continuous 10% glucose intravenous infusion. The use of diazoxide to inhibit the secretion of insulin at the dose of 5 to 10 ng/ml was effective within sides' 63effects. Prednisolone 20 mg twice daily was very successful to avoid hypoglycemia and enabling the intravenous glucose infusion to be stopped. Therefore the patient state was quickly improved and he presents no more hypoglycemia. The etiological treatment was the surgical resection of the hepatic metastasis. Then, he received capecitabine (Xeloda®) which is used to treat colorectal stage III. The serum levels of insulin were quickly depressed. Diazoxide and corticosteroid therapy were progressively degreased. Actually, the patient received low doses of prednisolone and he is doing well. Therefore the diagnosis of paraneoplastic hypoglycemia by insulin secreting non islet cell tumor hypoglycemia was established.

3. Discussion

Paraneoplastic hypoglycemia is rare. Diagnosed in patients having tumor with abnormal or ectopic secretion of insulin, insulin like growth factor (IGF1, IGF2) or carrier proteins IGF. This mechanism seems the most common and the most characteristic of patients with typical NICTH [5]. These different mechanisms cause a more important effect of insulin that increase the glucose intake in peripheral tissue, decrease the hepatic glucose production due to the decrease of glycogenolysis and gluconeogenesis and the decrease of lipolysis in adipose tissue [6]. Three types of secretion were found in paraneoplastic hypoglycemia:

The most frequent is the secretion of Big IGF2 [7]. The serum level of IGF2 (Big IGF2) is high. Serum levels of insulinemia, poinsulinemia, IGF1 and hormone growth are suppressed. This secretion results from the excessive production of incomplete IGF2 called "big" IGF2. This molecule is called BigIGF2 that decreases the formation of a 150 Kd heterodimer called IGF binding protein (IGFBP) including IGF1, IGF2, IGFBP-3 and the acid-labile subunit (ASL). In normal subjects, most of circulating IGFs (80-90%) are related to the complex where their insulin like action is decreased. But when the complex of IGFBP is reduced [8], IGFs are divided into complexes with IGFBP3 with a low molecular weight (50 kD) [9]. The Big IGF2 has a higher hypoglycemic effect. They can reach the capillary wall then they can reach more easily insulin receptors [10] and insulin-like potential is exposed which leads to an increased peripheral glucose consumption [7] and inhibition of hepatic glucose production [11].

In this type of secretion, the rate of IGF2, IGFBP-1, IGFBP-2 and Big IGF2 are high whereas, IGFBP3 and ALS are decreased [12].The lack of symptoms of acromegaly in these patients may be explained by the absence of combined elevation of GH and IGF, the half-life of short paraneoplastic hormones and the increased insulin sensitivity [13].

Paraneoplastic hypoglycemia can also be due to the secretion of IGF1, as far as we know only a few cases were described in the literature such as a case of metastazing large cell carcinoma [13]. In this type of secretion, serum levels of insulin, proinsulin, IGF2, are low, and the serum levels of IGF1 are considerably elevated.

The secretion of insulin in non-islet cell tumor hypoglycemia was exceptional. It was especially described in lung tumor, ovarian carcinoma and cervical uterine carcinoma [14]. Paraneoplastic hypoglycemia with hyperinsulinism was also described in advanced metastazing colon cancer as in our case [15]. In this type of secretion, serum levels of Insulin, proinsulin were considerably elevated as well as C peptide. However levels of IGF1, IGF2 were suppressed [13]. Generally, symptoms of hypoglycemia started progressively. At first, the patient had adrenergic symptoms that happened in the first hours of the morning. Then appeared the neuroglycopenic symptoms.

NICTH has many differential diagnoses that should be eliminated, like kidney failure, liver failure, adrenal insufficiency, pancreatic tumor and factice hypoglycemia (using drugs like insulin or sulfonylureas [15,16,17].

The treatment of paraneoplastic hypoglycemia is difficult and it is based on symptomatic and etiological treatment.

Symptomatic treatment is essential. It is based on the dietetic rules with a hypercaloric diet and serum glucose infusion if it is necessary [2,16]. The Diazoxide can be used. It is a sulfamide that inhibits the secretion of insulin. It is taken at the dose of 5 to 10 mg/kg/day [18,19]. This treatment has many side effects such as sodium and water retention, gastro-intestinal disorders such as nausea, vomiting especially if the doses are rapidly increased. Rarely, it may induce skin rash, thrombocytopenia, neutropenia, hyperosmolarity. Our patient presented no disorders related to this treatment. The long-term corticosteroid therapy may be given at the dose of 20 mg twice daily [16,20]. Corticosteroid therapy has several mechanisms such as the gluconeogenesis stimulation and decreasing of the tumor size [21,22]. It induces the decline of IGF2 production, the increase of IGFB3 rates and ALS and the correction of abnormality in GH-IGF2 axe [2]. The benefits of corticotherapy are dose dependent and reversible [2,19,20,23].

Etiological treatment is the main step and based on surgery. In fact, the complete resection of the tumor is very effective and decreases the frequency of hypoglyceamia [2,15,16]. Many authors reported that, even, the partial resection of tumor called also Debulking tumor, was effective in the decrease of the frequency of hypoglycemia [5,18].

In case of paraneoplastic secretion of Big IGF2, somatostatin analogue (octreotide) can be used, an improvement of hypoglycemia is seen in many cases [24]. But it is unnecessary to use this treatment because receptors in the tumor are non functional [25].

The treatment by GH can be used also in case of secretion of Big IGF2. In fact, GH increases the production of IGFBP3, ALS and ameliorates the gluconeogenesis and glycogenolysis [2]. This treatment is insufficient for two reasons. First, the production of IGFBP3 and ALS is not sufficiently high. Second, the concentration of Big IGF2 is very high. So that, the formation of the complex remains decreased [2].

4. Conclusion

Paraneoplastic hypoglycemia should be considered in front of every patient who has a malignant tumor with hypoglycemia after elimination of other causes of organic hypoglycemia.

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