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CASE REPORT

Hemangiopericytoma-associated hypoglycemia improved by glucocorticoid therapy: a case report

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Abstract A 59-year-old man was admitted because of recurrent, severe hypoglycemia. He had multiple metastases from a meningeal hemangiopericytoma, which had been operated on 12 years earlier. The results of laboratory testing at the time of hypoglycemia showed very low serum levels of insulin, C-peptide, and growth hormone, with slightly high levels of insulin-like growth factor-II, and a normal level of insulin-like growth factor-I. The diagnosis of hemangiopericytoma-associated hypoglycemia was proposed. The patient was given corticosteroid therapy, which ameliorated symptoms of hypoglycemia.

Keywords Hemangiopericytoma · IGF-II · Nonislet cell tumor-induced hypoglycemia · Hypoglycemia

Introduction

Hemangiopericytoma is a soft-tissue sarcoma arising from contractile pericapillary pericytes. Pericytes are contractile cells that are arranged along capillaries and venules [1]; they were first reported by Stout and Murray in 1942 [2]. In 1959, Howard and Davis defined hemangiopericytoma as *a nonislet cell tumor hypoglycemia tumor* [3]. The hypoglycemia related to hemangiopericytoma is associated with high levels of insulin-like growth factor-II (IGF-II). The IGF-II gene is expressed in tumor tissue [4]. Surgery for nonislet cell tumor hypoglycemia tumors involves complete removal of the tumor or reduction of the tumor mass [5]. When curative resection is not possible, various approaches to relieve the hypoglycemia have been tried. Here, we report a case of hemangiopericytoma, complicated by severe hypoglycemia, treated with corticosteroids.

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Case report

A 59-year-old man was admitted because of recurrent, severe hypoglycemia. His history included surgery in 1996 for a falx meningeal hemangiopericytoma, followed by frontal radiotherapy. Ten years later, he was diagnosed with multiple pulmonary and bone metastases. Owing to the size of the tumors, surgical removal, chemotherapy, and radiotherapy were not suitable. The patient received interferon alfa for 1 year as an experimental therapy, which failed to decrease the size of the tumors. He was apparently well thereafter.

Two weeks before admission, he was brought to the emergency room twice, in a state of unconsciousness, with serum glucose levels of 25 mg/dl and 24 mg/dl, respectively. Each time, he was given intravenous dextrose and recovered. Episodes of hypoglycemia without unconsciousness became more frequent, especially at night and in the morning. The hypoglycemia resolved after food intake. He was referred to the endocrinology clinic and was subsequently hospitalized because of severe hypoglycemia.

After admission, the patient was given 10% dextrose infusion during the night. The fasting serum glucose levels

Table 1 Laboratory results of the patient

	Patient	Normal range
Glucose (mg/dl)	23	60–115
Insulin (μIU/ml)	0.2	2.6–24.9
C-peptide (ng/ml)	0.066	1.1–4.4
Growth hormone (ng/ml)	0.046	0.004–1.406
IGF-1 (ng/ml)	80	70–197
IGFBP-3 (ng/ml)	3900	2020–3990
IGF-2 (ng/ml)	1155	459–1123
IGF-2/IGF-1	14.4	

IGF insulin-like growth factor, *IGFBP* insulin-like growth factor binding protein

were very low, ranging from 23 to 33 mg/dl, and accompanied by very low insulin, C-peptide, and growth hormone levels. Concentrations of serum IGF-I, IGF-II, and insulin-like growth factor binding protein-3 (IGFBP-3) were normal; however, the ratio of serum IGF-II to IGF-I was elevated (Table 1). A computer tomography (CT) scan showed numerous pulmonary masses of different sizes (Fig. 1). No metastases were detected with cranial and abdominal CT scanning. A diagnosis of a nonislet cell tumor hypoglycemia tumor was proposed. Therapy with prednisone (60 mg/day; 3 times/day, in equal doses) was started. After the dextrose infusion was stopped and the prednisone had been tapered to 15 mg/day (10 mg in the morning and 5 mg in the evening), hypoglycemia did not recur. No further episodes of hypoglycemia occurred in the following 7 days, and the patient was discharged from the hospital with instructions for blood glucose self-monitoring with glucagon for use in the case of severe hypoglycemia.

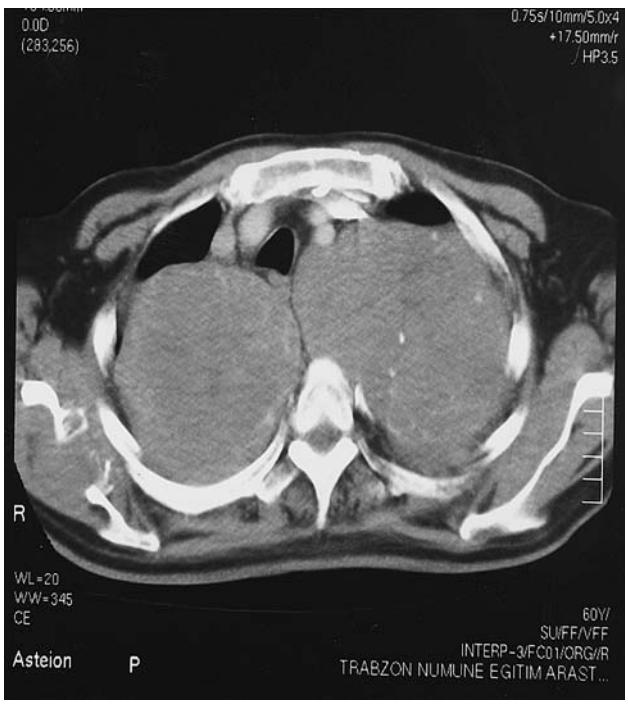

Fig. 1 Multiple lung metastases

One month after discharge, he was admitted for episodes of morning hypoglycemia. The steroid dose was increased to 20 mg (10 mg in the morning and 10 mg in the evening). After 3 months of this therapy, he has not had a hypoglycemic episode.

Discussion

In patients with cancer and severe hypoglycemia, a nonislet cell tumor hypoglycemia should be considered, especially when symptoms of hypoglycemia occur between meals and in the morning. Rarely, hypoglycemia may be the presenting symptom in patients with nonislet cell tumors, although it is more common for hypoglycemia to develop in a patient with a known malignant tumor [5]. Fukuda and associates analyzed the final diagnosis in 44 patients with hypoglycemia [6]. A hypoglycemic episode was the initial sign that led to a diagnosis of a nonislet cell tumor hypoglycemia tumor in one-half of the patients, and a tumor was known before the hypoglycemia in the remaining patients. In our patient, the disease was already known before the hypoglycemia.

The pathogenesis of nonislet cell tumor hypoglycemia is complex, and multiple factors may be involved. These tumors are usually large. The tumor itself uses large amounts of glucose; however, glucose uptake by peripheral tissues is also increased, and hepatic glucose production is inhibited, suggesting insulin-like activity [4, 5, 7]. Levels of proinsulin and C-peptide during hypoglycemia are suppressed, as we encountered in our case [5]; for this reason, an insulin-like factor is probably responsible for hypoglycemia [5, 7]. Mesenchymal tumors that cause hypoglycemia often secrete IGF-II, a protein with high homology to proinsulin. In IGF-II-producing tumors, the majority of circulating IGF-II is a high molecular weight form of 11–18 kDa, designated as *big IGF-II*. Big IGF-II is generated by abnormal processing of the IGF-II precursor in tumors [5, 7].

Most IGF is normally bound to a heterotrimeric 150-kDa complex consisting of IGF, the binding protein IGFBP-3, and an acid-labile glycoprotein. The large complex is retained in the circulation, and, as a result, the half-life of the IGF-II complex is relatively long, 12–15 h. This complex can cross the capillary barrier and gain easy access to target tissues [7]. It is, therefore, possible that the turnover and bioavailability of big IGF-II may be accelerated considerably, thereby leading to hypoglycemia.

A minority of IGF circulates in a smaller 50-kDa complex that contains mainly IGF and a different binding protein, IGFBP-2. The small complex can cross capillaries and deliver IGF to tissue receptors, and IGF-II bound to this complex has a half-life of only about 30 min [5].

Oversecretion of big IGF-II suppresses the secretion of insulin, GH, and IGF-I [5]. In turn, suppression of GH and IGF-I downregulates the synthesis of IGFBP-3 and the acid-labile subunits, both of which are GH dependent, and upregulates the synthesis of IGFBP-2 [5, 7]. Consistent with this proposal regarding the role of GH is the response of a patient to GH therapy. Thus, IGF-II oversecretion leads to altered binding and increased bioactivity of IGF-II, and can cause hypoglycemia even when total IGF-II levels are normal. The level of free IGF-II in serum is also increased [5]. The GH response can be corrected by the removal of the tumor, indicating that IGF-II may suppress GH secretion at the pituitary level [5, 6]. This may lead to a reduction in circulating IGF-I levels as well as a GH counterregulatory response for hypoglycemia. Although the concentration of IGF-II in the patients' blood can be within the normal range, the proportion of big IGF-II may be increased as a consequence of altered processing and increased bioavailability [5–7].

Investigators have reported different results regarding IGF-II levels. Hizuka and Fukuda showed that rather than high levels of IGF-II, normal or high levels of IGF-II with low levels of IGF-I and a high ratio of IGF-II to IGF-I in patients are more indicative of a nonislet cell tumor hypoglycemia tumor [6, 8]. In our case, the IGF-II level was slightly elevated, but the subunits of IGF-II could not be measured because of technical difficulties. Although the IGF-I level was normal, the ratio of IGF-II to IGF-I was relatively high. Circulating levels of big IGF-II decrease significantly following successful removal of the tumor, leading to the resolution of hypoglycemia [6, 8]. However, as the tumor in our patient was not suitable for an operation, decreased IGF-II levels were not expected.

In clinical practice, it is important to distinguish fasting hypoglycemia (occurring more than 5 h after food intake, which usually indicates underlying disease) from reactive or postprandial hypoglycemia (2–5 h after food intake). Drugs, either sulfonylurea or insulin, account for the most common causes of hypoglycemia in adults. Other causes of fasting hypoglycemia include insulinoma, Addison disease, GH deficiency, hypopituitarism, autoimmune causes, organ failure, and starvation [9]. The association of increased insulin levels (greater than 6 μIU/ml) with either low glucose levels or serum glucose to insulin ratio greater than 0.3 supports the diagnosis of insulinoma [10]. Very low insulin and C-peptide levels accompanying very low serum glucose levels, with the other findings, pointed to a nonislet cell tumor hypoglycemia tumor in our case.

Treatment is aimed toward the primary tumor, with supportive therapy of frequent meals for the patient. The most effective treatment of a nonislet cell tumor hypoglycemia tumor is surgical removal or debulking of the tumor [5, 11]. When tumor load reduction with surgery is not possible, various modalities have been used with variable and limited success to relieve hypoglycemic symptoms [5]. Selective tumor embolization may alleviate symptoms [5]. Diazoxide and chlorothiazide have been used to improve symptoms [5, 11]. Glucagon, which corrects serum glucose by increasing hepatic glucose output, may be used to acutely raise glucose levels [5]. Somatostatin analogs have been used with variable and limited success [5, 7]. Corticosteroids may, in addition to their antihypoglycemic action, also suppress IGF-II production by tumor tissue [5]. Moreover, shrinkage of the tumor has been demonstrated with moderate to high doses of corticosteroids [4, 11]. Growth hormone may reduce IGF-II availability to tissues by increasing levels of IGFBP-3 and the acid-labile subunit. The combination of low doses of prednisone and GH has been proposed for long-term therapy to alleviate symptoms of hypoglycemia [5].

In the present case, we chose corticosteroids because of low cost and convenience in practice. It is difficult to anticipate whether corticosteroids will be enough to control symptoms in the future.

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