Hypoglycemia Associated with Big Insulin-Like Growth Factor II Produced during Development of Malignant Fibrous Histiocytoma

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Abstract. We describe a rare case of hypoglycemia associated with a high molecular weight form of insulin-like growth factor II (big IGF-II) produced during the development of malignant fibrous histiocytoma (MFH). A 66-year-old man was referred to our department for further evaluation of hypoglycemia. At the age of 59, he had been diagnosed as having a MFH in the retroperitoneum, and underwent incomplete resection of the tumor. He had no symptoms of hypoglycemia at that time. Within the last few years, he developed symptoms of hypoglycemia in the early morning. Computerized tomography scans of the abdomen showed multiple tumors around the peritoneum and the liver. Serum insulin levels were decreased although no other hormonal deficiencies were observed. Serum IGF-II levels were elevated as a result of big IGF-II production. Taken together, these results indicated that hypoglycemia in this patient was associated with the production of big IGF-II by the MFH. The most effective therapeutic modality in patients with non-islet cell tumor hypoglycemia is resection of the tumor. In our case, as complete resection was impossible, dexamethasone and glucagon were administered and proved to be effective for preventing hypoglycemia.

Key word: Insulin-like growth factor II, Malignant fibrous histiocytoma, Growth hormone, Glucocorticoid, Insulin, Extrapancreatic tumor

NON-ISLET cell tumor hypoglycemia (NICTH) is one of the major causes of fasting hypoglycemia. NICTH is a syndrome that produces fasting hypoglycemia via an insulin-independent pathway as a consequence of an extrapancreatic tumor [1]. Fibrosarcomas, rhabdomyosarcomas, leiomyosarcomas, mesotheliomas, and hemangiopericytomas account for more than half of the cases of NICTH [1]. A small number of cases of hypoglycemia associated with a retroperitoneal malignant fibrous histiocytoma (MFH) have been reported in the literature [2]. Insulin-like growth factor II (IGF-II) produced by and secreted from these non-islet cell tumors would cause hypoglycemia, although the mechanism of this action is still unclear. Interestingly, in our case, hypoglycemia was associated with a high molecular weight form of IGF-II (big IGF-II) that was produced during the development of the MFH. We report that treatment with dexamethasone was effective in preventing hypoglycemia in this patient.

Case report

Clinical summary

In November 2002, a 66-year-old man was referred to our department for further evaluation of hypo-
glycemia. At the age of 59 he had been diagnosed in a nearby hospital as having MFH in the retroperitoneum, and had undergone incomplete resection of the tumor (Fig. 1). He had no symptoms of hypoglycemia at that time. Recently, he complained of progressing hypoglycemia from midnight until morning that had developed over the last few years. On admission to our hospital, his height was 166 cm, body weight 73 kg, with a body mass index of 26.5 kg/m$^2$. He was not taking any anti-hypertensive drug and was normotensive with a blood pressure of 100/65 mmHg.

Reddish brown verrucae of various sizes were present on his face. His hypoglycemia was so severe that it required administration of up to 5 mg/day of oral prednisolone and supplementation of food during the night to maintain a fasting plasma glucose level of 60 mg/dl. He had not been taking any hypoglycemic agents.

Laboratory and endocrinology data on admission are shown in Tables 1 and 2, respectively. Treatment with 5 mg of prednisolone per day resulted in a decrease in both plasma ACTH and cortisol levels,

![Fig. 1. Hematoxylin-eosin stained sections of the retroperitoneal tumors, which were obtained from the earlier operation, show a pleomorphic storiform appearance containing spindle-shaped cells with oval nuclei and a fine granular eosinophilic cytoplasm, undifferentiated cells, and fibrotic material. The cells form a cartwheel pattern. (Original magnification, 100 × and 400 ×.)](image)

### Table 1. Laboratory data on admission

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th></th>
<th>Blood biochemistry</th>
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</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>11570/μl (3500–9000)</td>
<td>Blood urea nitrogen</td>
<td>14 mg/dl (8–20)</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>467 × 10$^6$/μl (380–500 × 10$^6$)</td>
<td>Creatinine</td>
<td>0.7 mg/dl (0.4–0.7)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>15.8 g/dl (11.1–15.0)</td>
<td>Uric acid</td>
<td>3.0 mg/dl (2.6–6.0)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>46.7% (33.3–45.0)</td>
<td>Sodium</td>
<td>144 mmol/l (138–149)</td>
</tr>
<tr>
<td>Platelets</td>
<td>129 × 10$^9$/l (150–350 × 10$^9$)</td>
<td>Chloride</td>
<td>108 mmol/l (99–110)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potassium</td>
<td>3.5 mmol/l (3.5–5.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium</td>
<td>8.5 mg/dl (8.2–10.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phosphorus</td>
<td>2.9 mg/dl (2.5–4.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma glucose (fasting)</td>
<td>59 mg/dl (70–110)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemoglobin A1c</td>
<td>4.9% (4.3–5.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine clearance</td>
<td>93 ml/min (70–130)</td>
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</tbody>
</table>

Normal basal ranges are indicated in parentheses.
while serum thyroid-stimulating hormone (TSH), thyroid hormone, and age-matched luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were within normal limits. At admission, his plasma glucagon level was within the normal limit (Table 2), although this increased to 200 pg/ml in association with more severe hypoglycemia (i.e. 48 mg/dl). Serum growth hormone (GH), insulin-like growth factor (IGF)-I, and IGF-binding protein-3 (IGF-BP3) levels were all within normal limits, while IGF-II level was elevated. Insulin (IRI) was undetectable in the serum with no insulin antibodies being present. The C-peptide (CPR) levels in both serum and urine were also decreased with no urinary ketone bodies being detected during the periods of hypoglycemia. As shown in Table 2, plasma glucose levels increased for up to three hours in response to subcutaneous administration of glucagon. Computerized tomography (CT) scanning of the abdomen showed multiple tumors around the peritoneum and the liver that were not enhanced (Fig. 2). Western immunoblotting revealed the presence of big IGF-II in the patient’s serum (Fig. 3).

On the basis of the diagnosis of inoperable MFH, intensive therapy was initiated and involved the administration of potent and long-acting glucocorticoids (i.e. dexamethasone 0.8 mg/day: 0.3 mg in the morning and 0.5 mg at night). With this treatment, the patient’s plasma glucose levels were controlled easily throughout the night without any food supplementation, resulting in a fasting plasma glucose level of 100 mg/dl.

**Pathological findings**

The light microscopic findings of hematoxylin-eosin (HE) stained sections, prepared from the retroperitoneal tumors removed in the earlier operation, are shown in Fig. 1. These sections revealed a pleomorphic storiform appearance containing spindle-shaped cells with oval nuclei and a fine granular eosinophilic cytoplasm, undifferentiated cells, and fibrotic material. The cells were observed to form a cartwheel pattern.

**Discussion**

In this case, severe hypoglycemia was presented during the fasting state despite the patient not having taken any hypoglycemic agents. No symptoms of adrenal crisis were observed to account for this hypoglycemia. Although his ACTH and cortisol levels were low, the patient was administered glucocorticoids

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**Table 2.** Summary of the endocrinological examinations with normal basal ranges indicated in parentheses. ACTH, adrenocorticotropic hormone; GH, growth hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; PRL, prolactin; DHEA-S, dehydroepiandrosterone sulfate; IGF, insulin-like growth factor; IGF-BP3, insulin-like growth factor binding protein 3; IRI, insulin; CPR, C-peptide; PG, plasma glucose.

<table>
<thead>
<tr>
<th>Hormonal data</th>
<th>ACTH &lt;5 pg/ml (&lt;60)</th>
<th>GH 0.7 ng/ml (&lt;3.1)</th>
<th>LH 13.9 mIU/ml (0.3–7.1)</th>
<th>FSH 43.0 mIU/ml (1.6–10.6)</th>
<th>TSH 1.14 μIU/ml (0.38–0.64)</th>
<th>PRL 12.3 ng/ml (3.4–16.2)</th>
<th>Cortisol 0.9 μg/dl (4.5–21.1)</th>
<th>DHEA-S 18 μg/dl (13–264)</th>
<th>IGF-I 99 ng/ml (42–250)</th>
<th>IGF-II 927 ng/ml (429–896)</th>
<th>IGF-BP3 2.70 μg/ml (2.17–4.05)</th>
<th>Free T&lt;sub&gt;3&lt;/sub&gt; 2.65 pg/ml (2.13–4.07)</th>
<th>Free T&lt;sub&gt;4&lt;/sub&gt; 1.29 ng/dl (0.95–1.74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRI</td>
<td>&lt;1 μU/ml (1–17)</td>
<td>Insulin Ab 3.7% (&lt;7)</td>
<td>CPR 0.1 ng/ml (1.0–2.0)</td>
<td>CPR (U) 33 μg/day (42–79)</td>
<td>Glucagon 120 pg/ml (40–180)</td>
<td>Adrenaline 0.01 ng/ml (&lt;0.17)</td>
<td>Noradrenaline 0.32 ng/ml (0.15–0.57)</td>
<td>Dopamine 0.03 ng/ml (&lt;0.03)</td>
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</tbody>
</table>

**Glucagon test**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>PG (mg/dl)</th>
<th>IRI (μU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>99</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>116</td>
<td>24</td>
</tr>
<tr>
<td>20</td>
<td>140</td>
<td>33</td>
</tr>
<tr>
<td>30</td>
<td>155</td>
<td>42</td>
</tr>
<tr>
<td>60</td>
<td>175</td>
<td>56</td>
</tr>
<tr>
<td>120</td>
<td>107</td>
<td>19</td>
</tr>
<tr>
<td>180</td>
<td>63</td>
<td>5</td>
</tr>
</tbody>
</table>

Glucagon test (glucagon 1mg, subcutaneously).
to prevent hypoglycemia. We observed that the level of plasma glucagon was increased during periods of severe hypoglycemia. A deficiency in adult GH alone would not be expected to cause fasting hypoglycemia, although it is possible that GH level may be suppressed by IGF-II. On the basis of these findings, we concluded that fasting hypoglycemia in our patient was not caused by any hormonal deficiencies elevating glucose levels. Serum IRI, and serum and urine CPR levels were all decreased, whereas serum IGF-II levels were slightly increased, with big IGF-II being detected in the serum by the Western immunoblotting method. Additionally, abdominal CT scans revealed multiple tumors around the peritoneum and the liver, confirming the pathological findings of the previous operation that had indicated a MFH. Taken together, the clinical information indicated that hypoglycemia in this patient was associated with the production of big IGF-II produced during the development of MFH.

The etiology of NICTH has now been determined. Initially, it was considered that tumor-derived IGF-II was the main factor inducing hypoglycemia [3], although other studies found that serum IGF-II levels were not elevated in the majority of cases [2, 4]. It has, however, been reported that the level of big IGF-II, an incompletely-processed IGF-II, is increased in the sera and tumors of patients with NICTH [2, 5]. The potential of big IGF-II to cause hypoglycemia is now recognized and accordingly in our case, Western immunoblotting confirmed the presence of big IGF-II in the serum.

The mechanism by which big IGF-II causes hypoglycemia has been widely discussed. As the insulin-like bioactivity of big IGF-II is similar to that of normal IGF-II [5], the intrinsic bioactivity of big IGF-II would not be expected to have a major impact on the development of hypoglycemia. Normal IGF-II, but not big IGF-II, creates a heterotrimeric 150-kd complex, composed of the binding protein IGFBP-3 and an acid-labile subunit (ALS). It has been suggested that the increased bioavailability of big IGF-II may be due to impaired formation of the 150-kd complex, and that this difference is the key factor for
the resulting hypoglycemia [5, 6]. While it is possible
that impaired formation of the 150-kd complex may be
caused by decreased production of IGF-BP3 and ALS,
Baxter et al. [7] demonstrated that big IGF-II inhibited
ALS binding to IGFBP-3 in vitro. This suggested that
the intrinsic inability of big IGF-II to form the com-
plex may be the major reason for the impaired forma-
tion of the 150-kDa complex.

In our case, while hypoglycemia was associated
with the presence of an MFH, the mechanism of develop-
ment to NICTH remains unknown. Bertherat et al.
[8] reported that dysregulation of imprinting of the
chromosome 11p15 region leads to IGF-II overex-
pression in NICTH. In their patient, recurrence of the
tumor four years later was not associated with
hypoglycemia, suggesting that a large volume of tumor
or high levels of big IGF-II are required to cause
hypoglycemia. The mechanism involved in the devel-
opment of NICTH therefore remains to be elucidated.

The most effective therapeutic modality in patients
with hypoglycemia due to NICTH is complete resec-
tion of the tumor [1]. In our case, as complete resec-
tion was impossible, we considered that it was
important to prevent hypoglycemia. Therapy with
either GH, glucagon, glucocorticoids or somatostatin
has been shown to be effective in individual patients
with unresectable tumors. The use of recombinant
human GH has been reported to alleviate hypo-
glycemia in NICTH [9], by increasing serum levels of
IGFBP-3, and thereby reducing the bioavailability of
IGF-II.

Glucocorticoids enhance the activity of hepatic glu-
coneogenic enzymes and also mobilize gluconeogenic
precursors to the liver, thereby increasing gluconeo-
genesis [10]. Glucocorticoids also suppress big IGF-II
permitting re-establishment of normal IGF and IGF-
BP patterns [11]. Corticoids may therefore inhibit
tumor growth [7], as IGF-II acts as an autocrine
growth factor for tumors [12]. Patients treated with
glucocorticoids should therefore have long-term follow-
up of tumor growth as well as of the hypoglycemia. In
our case, treatment with dexamethasone (0.8 mg/day)
was more effective than prednisolone (5 mg/day) for
preventing hypoglycemia, despite the two agents
having similar glucocorticoidal activity. While the
reason for the greater efficacy of dexamethasone is un-
clear, it is possible that this may be attributable to its
longer-acting effect, producing a more potent and con-
tinuous gluconeogenesis or inhibition of big IGF-II.

Glucagon was injected subcutaneously in our pa-
tient in order to test both the duration and the extent
to which it elevated plasma glucose levels. We found
that administration of glucagon increased plasma
glucose for up to three hours. This result confirmed
that glucagon treatment is beneficial for preventing
hypoglycemia [13], and in addition suggested that
NICTH may be related to an increase in hepatic glyco-
gen stores. We consider that subcutaneous injection
of glucagon should be used as an adjuvant therapy,
due to limitations of subcutaneous or intravenous
administration with a combination of these therapies
being required to treat more severe hypoglycemia.

In summary, we report a rare case of hypoglycemia
that occurred during the development of MFH. Hypo-
glycemia in this patient was associated with the
production of big IGF-II by his tumor. In this case,
as complete resection of the tumor was impossible,
treatment with dexamethasone was introduced result-
ing in improvement in fasting hypoglycemia.

Acknowledgments

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