Severe Hypoglycemia and Hypokalemia in Association with Liver Metastases of Gastric Cancer

Akihiko Kato, Etsuro Bando*, Shingo Shinozaki, Yutaka Yonemura*, Motohiko Aiba***, Izumi Fukuda****, Naomi Hizuka**** and Toru Kameya**

Abstract

We report an 80-year-old man who presented with non-islet cell tumor hypoglycemia (NICTH) in association with hepatic recurrence of gastric cancer. His serum potassium was reduced from 3.9 to 3.1 mmol/l 5 weeks after gastrectomy, and he subsequently developed hypoglycemic coma. He was diagnosed as having NICTH because of the presence of serum big IGF-II and positive staining for IGF-II in gastric cancer cells obtained at surgery. A computed tomography showed multiple liver metastases. His hypoglycemia was refractory to steroid therapy. This case suggested that NICTH could develop in association with hepatic metastases of gastric cancer. Unexpected hypokalemia may be a manifestation of occult NICTH.

Key words: NICTH, hypokalemia, big IGF-II, liver metastasis, gastric cancer

Introduction

Hypoglycemia is one of the most common endocrine emergencies that occurs in 0.9% of hospitalized patients (1). The causes of low blood sugar are mostly related to diabetic treatments and endocrine deficiencies (1). Non-islet cell tumor hypoglycemia (NICTH) is a rare cause of hypoglycemia, and it is most commonly associated with large, slow-growing, mesenchymal tumors located in the retroperitoneum or the thorax (2). Hypoglycemia associated with gastric cancer is rarely noted (3–6), but its clinical manifestations remain to be explored. Here, we report a case of gastric cancer that first presented with hypokalemia, and subsequently developed uncontrollable hypoglycemia in association with multiple liver metastases.

Case Report

An 80-year-old man was admitted to Shizuoka Cancer Center Hospital for the treatment of advanced gastric cancer. At admission, his fasting blood sugar and potassium were 6.1 mmol/l (normal, 3.9–6.1 mmol/l) and 4.2 mmol/l (normal, 3.6–5.0 mmol/l). Gastric fiber examination revealed an irregular surfaced tumor 8 cm in width, macroscopically Borrmann’s type I, in the cardia. Abdominal computed tomography (CT) showed metastases in regional multiple lymph nodes (Fig. 1). He underwent subtotal gastrectomy with lymphadenectomy, splenectomy and partial hepatectomy. He was discharged from hospital with 6.0 mmol/l of fasting plasma glucose and 3.9 mmol/l of potassium 3 weeks after the surgery.

Two weeks after the discharge, his serum potassium was decreased to 3.1 mmol/l without any clinical symptoms. He soon complained of syncope and neuroglycopenic symptoms such as blurred vision and cortical blindness. Four weeks after the discharge, he was emergently admitted to our hospital due to hypoglycemic coma. At admission, his blood glucose and potassium were markedly reduced to 1.0 mmol/l and 2.4 mmol/l. He also had metabolic alkalosis (pH 7.53) with 29.9 mmol/l of plasma bicarbonate. Blood hemoglobin A1c was decreased to 4.1% (normal: 4.3–5.8%). Endocrinological examination yielded a low plasma insulin of below 3 pmol/l (normal, 36–72 pmol/l), a plasma C-peptide level of 0.14 nmol/l (normal: 0.31–0.93 pmol/l) and a suppressed somatostatin concentration of below 1.0 pg/ml (normal: 1.0–12.0 pg/ml). Plasma growth hormone was 0.70 ng/ml. Circulating glucagon was not increased, and anti-human in-
sulin antibody was negative. Blood cortisol and ACTH were within normal ranges. Plasma renin activity and aldosterone were slightly suppressed to 0.2 ng/ml/h (normal, 0.3–2.9 ng/ml/h) and 0.08 nmol/l (normal, 0.08–0.44 nmol/l). Thyroid function was normal. Serum insulin-like growth factor-I (IGF-I) was decreased to 30 ng/ml (normal: 75–218 ng/ml), while serum IGF-II was within normal range (480 ng/ml, normal: 459–873 ng/ml). IGF-II/IGF-I ratio was 16.0. Serum IGF binding protein (IGFBP)-3 was reduced to 0.84 g/ml (normal: 1.99–3.89 g/ml). Because blood insulin and C-peptide were suppressed at a hypoglycemic episode, and blood IGF-II/IGF-I ratio exceeded over 10, an upper limit of control values (2), we diagnosed as having non insulin-mediated hypoglycemia in association with gastric cancer in this case.

He became fully oriented following continuous infusion of 17% dextrose solution, and his blood glucose was transiently elevated to 7.8–8.9 mmol/l. However, he again suffered from frequent and severe episodes of hypoglycemia despite the use of 20% dextrose infusion. His serum potassium was suppressed to 3.3 mmol/l. Abdominal CT scans disclosed multiple hepatic metastases with portal vein invasion and lymph node swelling around abdominal aorta (Fig. 1). Treatment with prednisolone, maximally 40 mg/day, failed to improve his hypoglycemia (Fig. 2). His blood insulin also remained below 0.4 µU/ml. He finally died of pneumonia and heart failure. Permission for autopsy was denied.

**Immunohistological and Immunoblot Examination**

Immunohistological studies using monoclonal anti-IGF-II antibody (Amano Pharmaceutical Co., Nagoya, Japan) demonstrated a positive staining of IGF-II in the Goldi area near the nuclei in most tumor cells obtained from surgically excised gastric tumor samples (Fig. 3). In contrast, only a few cells became positive for pro-IGF-II in gastric tumor tissues (Fig. 3). Western blot analysis of IGF-II in sera obtained at hypoglycemia disclosed a 3-fold higher molecular IGF-II (20.9 kDa) when compared with normal serum, or recombinant human IGF-II (7.5 kDa) (Fig. 4).

**Discussion**

Recently, tumor-associated hypoglycemia has been demonstrated to be mediated through IGF-II (molecular weight, 7.5-kDa) (7, 8), a substance that exhibits a high degree of structural homology to proinsulin. In normal serum, IGF-II exists in three different forms: free IGF-II is less than 1% with a short half-life of approximately 10 minutes, 20–30% of total IGF-II is bound to a 50-kDa IGFBPs with a half-life of about 30 minutes, and 70–80% of total IGF-II is formed ternary 150 kDa complex, which has a half-life of 12 hour. In NICTH, about 70% of the patients have big IGF-II (11–18 kDa) despite the normal range of total IGF-II (2). Since big IGF-II fails to form the normal ternary 150-kDa complex and instead forms binary complexes with IGFBPs, these small complexes can easily pass the capillaries and deliver IGF-II to insulin target organs, consequently inhibiting
hepatic gluconeogenesis and increasing glucose uptake in the skeletal tissue (9, 10).

Hizuka et al (2) demonstrated that IGF-II/IGF-I ratio in sera is useful to more sensitively detect NICTH with big IGF-II. The mean ratio of IGF-II/IGF-I ratio was 35.0±2.2 [16.4–64.2] in patients with big IGF-II, which was significantly higher than NICTH without big IGF-II (11.5±2.4) or normal subjects (3.3±0.2). They found that 29 (94%) out of 31 patients with IGF-II/IGF-I ratios more than 20 had a big IGF-II in blood. In contrast, 12 (92%) of 13 patients without big IGF-II had IGF-II/IGF-I ratios less than 20. In the present case, the serum IGF-II/IGF-I ratio was slightly increased to 16.0. However, immunohistological examination revealed a strong staining of IGF-II in gastric tumor cells. Western blot analysis also disclosed the presence of serum big IGF-II. These findings collectively suggested that hypoglycemia was related to big IGF-II production from cancer cells in this case.

Macdougall et al (5) reviewed the previously published 10 cases of gastric cancer that presented with hypoglycemia. Hepatic metastases were uniformly present, although invasion of the liver was minimal in 2 cases. The prognosis was poor, and few patients survived for more than 3 months without operation, and death can occur within a few days of presentation. In the present case, hypoglycemia and hypokalemia were absent at operation, while these were first evident when the liver was mostly replaced by metastatic tumors. Thus, hepatic invasion is closely related to the development of hypoglycemia in gastric cancer. Marked hepatic structural destruction may further worsen hypoglycemia by blocking compensatory mechanisms to stimulate glycogenolysis in the liver.

IGF-II is a potent mitogen for many cell types in the autocrine, paracrine and endocrine fashions. Recently, overexpression of IGF-II was found in cultured human gastric cancer cell lines (11). Increased expression of IGF-II mRNA was also noted in human gastric cancer tissues, especially in the case of infiltration types with lymphatic permeation (12). In this case, metastases to liver and lymph node rapidly occurred shortly after operation, possibly indicating that overproduction of IGF-II from residual tumor cells may play a role for facilitated tumor growth. Interestingly, a recent study demonstrated that high expression of IGF-II gene is closely associated with a reduction of H19, a tumor suppressor gene regulating IGF-II imprinting, and p57Kip2, a cyclin-dependent kinase inhibitor, in chromosome 11p15 region of tumor DNA obtained from a NICTH patient (13). So, abnormal imprinting of the IGF-II region may be related to rapid tumor metastases as well as IGF-II production.

Insulin is well known to acutely decrease blood potassium...
by moving extracellular potassium into the cells (14). A single subcutaneous injection of recombinant human IGF also can reduce blood potassium in short-term (15). In NICHT, however, hypokalemia was not generally recognized as a clinical symptom (6). In the present case, the reduction of blood potassium was closely related to the development of hypoglycemia. Our patient had no clinical symptom such as vomiting, diarrhea, or wound discharge that causes extrarenal potassium loss. Intravenous potassium loading failed to restore his blood potassium to normal range. Plasma aldosterone was rather suppressed. In addition, urinary potassium excretion was not fully enhanced (43.9 mEq/l) despite the venous administration of 70 mEq/day of potassium for 5 days. Thus, this hypokalemia seems more likely to be caused by big IGF-II-induced intracellular shift than renal or nonrenal potassium loss. A close association between big IGF-II and hypokalemia was also reported in a NICHT patient with adrenal cancer (16).

In summary, we encountered a case of NICHT with multiple liver metastases in gastric cancer. Hypoglycemia was closely associated with hepatic involvement in our patient. Reduced blood potassium was first noted in association with hypoglycemia, suggesting that unexpected hypokalemia may be a manifestation of occult NICHT in cancer patients.
References


Figure 4. Western immunoblot of serum IGF-II. Western blot analysis of IGF-II in the patient’s sera disclosed a big IGF-II (20.9 kDa) (lane 2 and 3) when compared with recombinant IGF-II (7.5 kDa) (lane 1) and normal serum (lane 6). The molecular weight of serum IGF-II in our case was almost identical to those in other NICTH patients (lane 4 and 5).