Gastric Neuroendocrine Carcinoma with Non-islet Cell Tumor Hypoglycemia Associated with Enhanced Production of Insulin-like Growth Factor II

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Abstract

A 75-year-old man was admitted to the hospital with a loss of consciousness. His blood glucose level was 24 mg/dL. Abdominal computed tomography revealed multiple metastatic lesions in the liver, while upper endoscopy disclosed advanced gastric cancer. The hypoglycemia was refractory despite the administration of glucose and steroid therapy. The patient died within one month of admission. An autopsy revealed neuroendocrine-type gastric cancer, which, on examination with immunohistochemistry, was found to be negative for insulin and insulin-like growth factor I and positive for insulin-like growth factor II (IGF-II). The patient was diagnosed as having gastric cancer with non-islet cell tumor hypoglycemia (NICTH) caused by IGF-II.

Key words: non-islet cell tumor hypoglycemia, gastric neuroendocrine carcinoma, insulin-like growth factor II

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Introduction

Hypoglycemia is one of the most common endocrine emergencies, estimated to occur in 0.9% of all hospitalized patients. In most cases, the hypoglycemia is related to the treatment of diabetes and endocrine deficiencies (1). However, there are also reported cases of non-islet cell tumor hypoglycemia (NICTH) as a rare cause of hypoglycemia, which is generally associated with large, slow-growing, mesenchymal tumors arising from the retroperitoneum or the thorax (2). Hypoglycemia associated with gastric cancer has rarely been reported (3-6); however, its clinical manifestations remain to be explored. We herein report the case of a patient with gastric cancer with multiple liver metastases who presented with severe hypoglycemia in which an immunohistochemical analysis confirmed the expression of insulin-like growth factor II (IGF-II) in gastric cancer cells.

Case Report

A 75-year-old man with a two-month history of epigastric discomfort was admitted emergently to the Omori Red Cross Hospital with loss of consciousness. The initial Glasgow Coma Scale assessment revealed scores of E3, M4 and V3. On admission, the blood glucose level was found to be in the range of severe hypoglycemia (24 mg/dL). Abdominal computed tomography revealed multiple metastatic tumors in the liver and thickening of the stomach wall with no lesions detected in the pancreas or other organs (Fig. 1). Upper gastrointestinal endoscopy revealed a large, hemorrhagic, protruberant tumor in the pylorus of the stomach (Fig. 2), and a gastric biopsy revealed poorly differentiated adenocarcinoma. Therefore, the patient was diagnosed to have advanced gastric cancer with multiple liver metastases. On admission, the blood sodium level was 139 mEq/L (normal: 135-145), the blood potassium level was 2.8 mEq/L (normal: 3.6-4.9) and the chloride level was 102 mEq/L (nor-
Figure 1. Abdominal computed tomography revealed multiple liver metastases and a thickened stomach wall; however, no lesions were detected in the pancreas or other organs.

Figure 2. An endoscopic examination revealed a friable, ulcerated and circumferential mass in the pylorus, suggestive of advanced gastric cancer.

were strongly positive for synaptophysin, chromogranin A and IGF-II (Fig. 3). The histopathological findings of the metastatic lesions of the liver were similar to those of the gastric tumor. Based on these findings, the gastric tumor was considered to be a neuroendocrine carcinoma (NEC) expressing IGF-II, thereby causing NICTH.

Discussion

Tumor-associated hypoglycemia is well known to be associated with the secretion of IGF-II (molecular weight: 7.5 kDa) (7, 8). Structurally, IGF-II exhibits a high degree of homology to proinsulin. In normal serum, IGF-II exists in three different forms: free IGF-II, accounting for less than 1% and having a short half-life of approximately 10 minutes, bound IGF-II, accounting for 20-30% of total IGF-II and it is bound to 50-kDa IGFBPs, with a half-life of approximately 30 minutes, and a ternary 150-kDa complex, accounting for 70-80% of the total IGF-II, with a half-life of 12 hours. Not all tumors that overexpress the IGF-II gene cause NICTH; however, most cases of NICTH are caused by tumors. It is not clear whether the serum pro-IGF-II levels in patients with these tumors are already elevated prior to the appearance of the first signs of hypoglycemia (1). In our present case, the patient was diagnosed as having hypoglycemic coma on admission with no previous history of diabetes. Due to the presence of upper abdominal symptoms (epigastric discomfort lasting for two months), we conducted gastrointestinal endoscopy and diagnosed the gastric tumor.

In patients with NICTH, serum IGF-II usually occurs in the high-molecular-weight form with a high proportion (usually >60%) of IGF-II being non-glycosylated and consisting primarily of IGF-II with a 21-amino acid extension of the E-domain [pro-IGF-IIIE (66-88); ‘big’-IGF-II] (7, 9, 10). ‘Big’-IGF-II is biologically active and present in relatively high amounts in the sera of patients with NICTH. In most previously reported cases of NICTH, no elevations in the serum levels of total IGF-II were observed. Therefore, ‘big’-IGF-II is considered to have specific biochemical properties
Figure 3. (a) [low-power view (×40)] and (b) [high-power view (×400)] of Hematoxylin and Eosin-stained sections revealed features consistent with gastric cancer. The tumor was composed of relatively small cells with pyknotic nuclei and eosinophilic cytoplasm forming small microtubular structures and small solid nests. (c) [low-power view (×100)] and (d) [high-power view (×400)] show the results of immunohistochemical staining of the gastric tumor using rabbit polyclonal anti-IGF-II antibodies. (e) Immunopositivity for IGF-II was diffusely observed in many tumor cells. (d) IGF II was recognized in the cytoplasm of the tumor cells. (e) [high-power view (×400)] and (f) [high-power view (×400)] show the results of the immunohistochemical expression for neuroendocrine markers in the gastric tumor. Immunohistochemical staining using (e) mouse monoclonal anti-synaptophysin antibodies and (f) rabbit polyclonal anti-chromogranin A antibodies (DakoCytomation) exhibited positive immunoreactivity for each marker.

and is different from mature IGF-II, resulting in enhancement of its bioavailability and consequent increases in its insulin-like activity in the body (11, 12). Since ‘big’-IGF-II fails to form the normal ternary 150-kDa complex and instead forms binary complexes, it can easily pass into the capillaries and deliver IGF-II to target organs of insulin, consequently inhibiting hepatic gluconeogenesis and increasing glucose uptake in skeletal tissue (13, 14).

In the present case, immunohistochemistry demonstrated a positive reaction for IGF-II in the cancer cells in the stomach and liver. The anti-IGF II antibody used for the test in this case was a rabbit polyclonal antibody that is not specific to ‘big’-IGF-II proteins. However, considering the positivity of the tumor cells for IGF II antibodies, as well as the existence of hypoglycemia on admission, the hypoglycemia observed in the present case is suggested to be associated
with the expression of ‘big’-IGF-II in the cancer cells, although we did not detect ‘big’-IGF-II in the serum using a Western immunoblot analysis.

Neuroendocrine carcinoma (NEC) of the stomach is rare; however, particular attention must be paid to this tumor due to its aggressiveness and poor prognosis. Furthermore, liver metastasis is also closely related to the development of hypoglycemia in patients with gastric cancer. Marked hepatic structural destruction may further worsen hypoglycemia by blocking compensatory mechanisms that stimulate glycogenolysis in the liver. Therefore, overproduction of ‘big’-IGF-II by tumors in combination with decreased hepatic glucose output associated with the destruction of hepatic tissue by tumor metastasis play a role in the onset of hypoglycemia in patients with liver metastasis. In addition, in this case, abdominal computed tomography performed on admission revealed multiple tumor metastases.

IGF-II is involved in fetal development, cell proliferation and apoptosis (15-17), and overproduction of IGF-II plays a role in the facilitation of tumor growth (18). In addition, an increased expression of IGF-II mRNA has been noted in human gastric cancer tissue, especially in infiltrative types of cancer with lymphatic invasion (19). Therefore, abnormal imprinting of the IGF-II region may be related to rapid tumor metastasis as well as IGF-II production.

de Groot et al. reported that NICTH can arise in virtually every benign or malignant tumor and that 8% of cases of NICTH occur in the stomach (12). According to a search of the MEDLINE database up to December 2012 using the terms “non-islet cell tumor hypoglycemia” and “gastric neuroendocrine carcinoma” and a search of the reference lists of published articles, there are no case reports describing gastric neuroendocrine carcinoma exhibiting NICTH. Therefore, we herein reported the first case of gastric neuroendocrine carcinoma that developed into NICTH.

In summary, we encountered a case of NICTH in a patient with gastric cancer associated with multiple liver metastases. Gastric cancer associated with NICTH caused by enhanced production of IGF-II is rare, but important condition for medical physicians.

The authors state that they have no Conflict of Interest (COI).

References


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