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Case Report

Prompt Resolution of Hypoglycemia by Hepatic Transarterial Embolization for Malignant Insulinoma with Multiple Liver Metastases

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A 45–year-old female who presented with loss of consciousness and a cold sweat was found to have a pancreatic tumor and multiple liver metastases. Laboratory studies showed marked hypoglycemia and inappropriately elevated serum insulin, C-peptide, and serum tumor markers. Fine needle aspiration revealed Grade 3 small-cell type primary pancreatic neuroendocrine carcinoma. Consequently, the diagnosis of malignant insulinoma was made. Transarterial embolization (TAE) for hepatic metastases resulted in the reduction of tumor volume and prompt resolution of hypoglycemic attacks, whereas diazoxide and systemic chemotherapy had been ineffective for controlling blood glucose levels, and octreotide was unavailable due to the allergic effect. This case report highlights the potential usefulness of TAE for malignant insulinomas in the management of hypoglycemia.

Key words: malignant insulinoma, hypoglycemia, liver metastases, transarterial embolization, neuroendocrine tumor

Insulinomas, arising from β cells in the islets of Langerhans, induce hypoglycemia by secreting excessive insulin. The majority of cases present with a solitary pancreatic tumor, the surgical resection of which is curative. On the other hand, malignant insulinoma, which presents with multiple hepatic metastases or recurrence after surgical resection, is refractory to surgery and/or systemic chemotherapy. The metastasis rate of insulinoma is reported to be 5.4% [1]. In the management of malignant insulinoma, controlling blood glucose levels is particularly vital, because hypoglycemia adversely affects quality of life and is sometimes life-threatening. We herein report a case of malignant insulinoma with hepatic metastases, in which hepatic transarterial embolization (TAE) was effective for volume reduction of the metastatic tumors and subsequent prompt resolution of hypoglycemia. Strategies for the prevention of hypoglycemia in insulinoma patients are discussed.

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Case Report

A 45–year-old female presented with 2-month duration of left hypochondrial pain, occasional loss of consciousness, and cold sweats. She was emergently admitted given her loss of consciousness and a blood

glucose level of 20 mg/dl. After the admission, she frequently developed hypoglycemic attacks even during meals or while receiving an intravenous dextrose solution. She was transferred to our hospital for further treatment. The patient had no family history of neuroendocrine tumors or other endocrine tumors. Physical examination revealed no abnormality. Laboratory examination showed hypoglycemia (54 mg/dL) and inappropriately high serum immunoreactive insulin (IRI) (67.5 μU/mL) and C-peptide (6.3 ng/mL) levels. Tumor markers including CA19–9 (53.7 U/mL), NSE (169.9 ng/mL), DUPAN-2 (235 U/mL), and SPAN-1 (36.1 U/mL) were elevated. Complete blood count and chemistries were otherwise normal.

Abdominal computed tomography (CT) scans showed a solitary pancreatic tumor having clear enhancement with contrast media. Portal infiltration by the tumor and enlarged lymph nodes around the pancreas head were also noted. In addition, multiple tumors were detected in the liver (Fig. 1). Fine-needle aspiration biopsy performed for the hepatic and pancreatic tumors revealed atypical cells with oval-shaped eccentric nuclei, deeply stained chromatin, and eosinophilic cytoplasm. Immunohistochemical staining was positive for chromogranin A, synaptophysin and CD56. The Ki-67 index was 27%. Thus, a diagnosis of Grade 3 small-cell type primary pancreatic neuroendocrine carcinoma was made (Fig. 2).

Although high-calorie infusion was initiated, hypoglycemic episodes occurred and administration of glucose was required orally or intravenously to treat each episode. Diazoxide was orally administered, but it was not effective to prevent hypoglycemia. Subcutaneous infusion of octreotide was also tried, but had to be stopped due to allergic reactions. To prevent the hypoglycemic episodes, TAE using Embozene® was performed on the right and left hepatic lobes on days 12 and 22, respectively. Glucose levels were normalized after the next day of the first TAE, and no hypoglycemia was observed during days 13 to 61 (Fig. 3). The levels of CA19–9, NSE, IRI and C-peptide decreased (Fig. 4), and contrast CT scans performed 4 weeks after the TAE (Fig. 5) showed a clear decrease of hepatic metastases. On day 41, systemic chemotherapy with etoposide and cisplatin was initiated. Despite 3 courses of the chemotherapy, hepatic metastases increased and hypoglycemic attacks recurred. The patient deteriorated due to a catheter-associated fungal infection and died on day 157.

Discussion

Diazoxide, a non-diuretic benzothiazine derivative, has affinity for the sulfonylurea receptor and blocks opening of ATP-sensitive potassium channels [2]. Based on this chemical property, diazoxide inhibits insulin secretion from pancreatic β cells [3]. Therefore, diazoxide is effective for controlling blood glucose levels in patients with malignant insulinoma [4]. Octreotide, a somatostatin derivative, is another drug that is able to prevent hypoglycemia in insulinoma patients. Octreotide inhibits insulin secretion by competitively blocking cyclic AMP production. However, 70–80% of insulinomas do not express somatostatin receptors [5], and thus somatostatin antagonists are ineffective in such cases. Moreover,

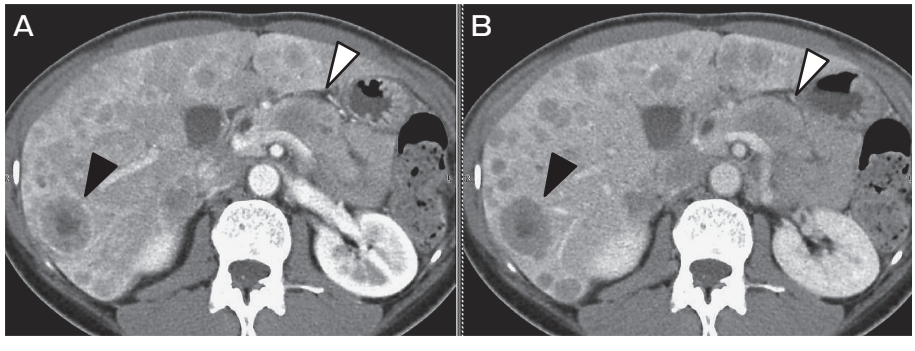

Fig. 1 Contrast-enhanced CT scans on admission. Arterial phase (A) and portal phase (B) of the CT scans showed a 2.7-cm tumor with diminished contrast effect and an ill-defined border in the pancreatic body (white arrows), in addition to dilation of the main pancreatic duct in the caudal portion. Multiple tumors were also detected in the liver, showing ring-shaped enhancement in the early phase and washout in the late phase (black arrows).

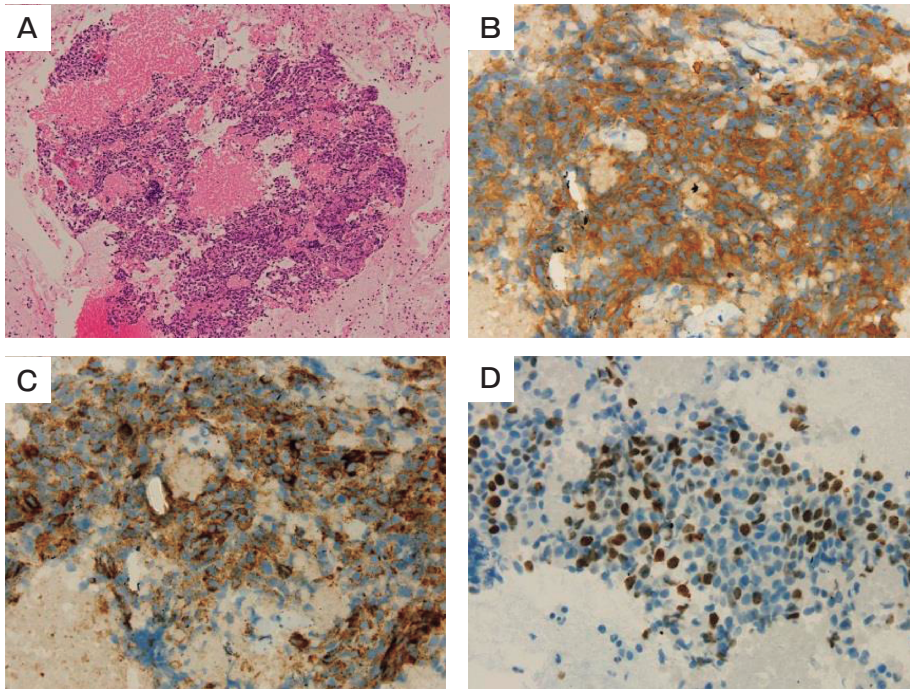

Fig. 2 Histopathological findings. In hematoxylin-eosin staining (**A**), atypical cells exhibiting oval-shaped eccentric nuclei with deeply stained chromatin and eosinophilic cytoplasm were observed. Immunostaining for synaptophysin (**B**) and chromogranin A (**C**) were positive. The Ki-67 index (**D**) was 27%. The tumor was thus diagnosed as G3 small-cell neuroendocrine carcinoma according to the WHO classification.

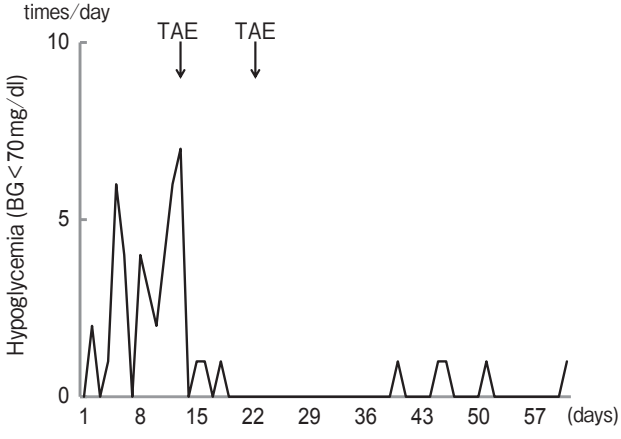

Fig. 3 Clinical course. Glucose levels were normalized after TAE.

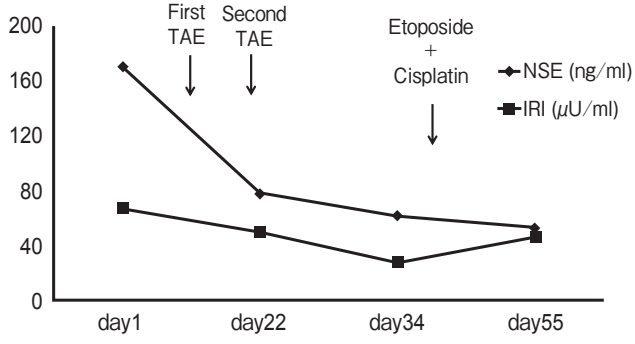

Fig. 4 Clinical course. Serum tumor markers tended to decrease after TAE.

octreotide may aggravate hypoglycemia in patients with insulinomas, because it might also inhibit glucagon secretion.

Physicians from only 2 institutions have reported four cases in which TAE has been performed for hepatic metastases of malignant insulinomas [6, 7]; to the best of our knowledge, our case is the 5th. As the initial therapy, the 4 cases were administered interferon, diazoxide, or combination therapy with adrimycin and streptozocin, but these treatments were abandoned because of strong side effects or lack of therapeutic effect. But a survival time of 14 to 31 months or more was achieved by performing TAE after these initial therapies. In each of the three cases

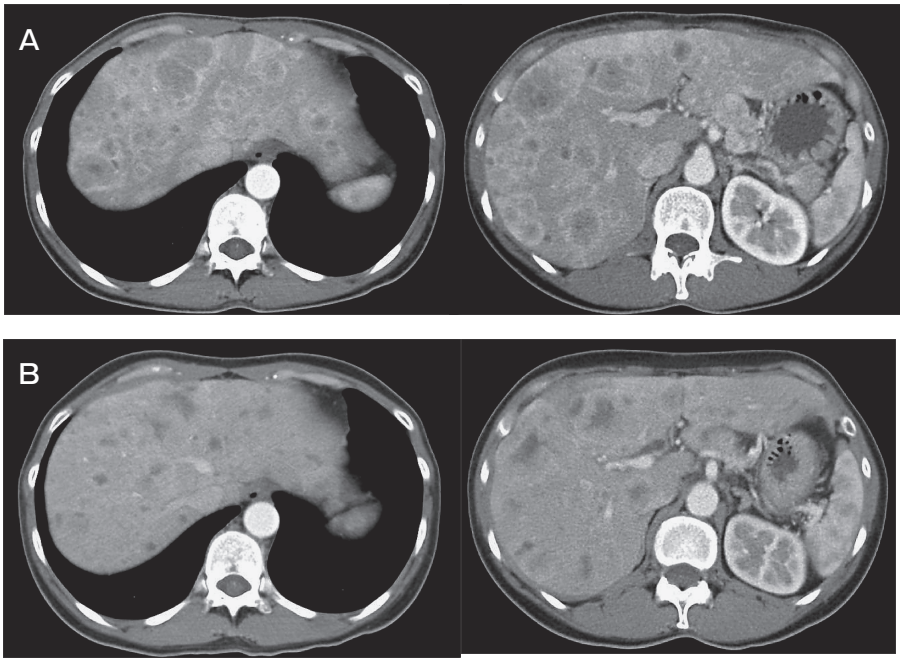

Fig. 5 Contrast CT scans before TAE (**A**) after TAE (**B**). Reduction of the tumor volume and necrosis was observed in most of the multiple liver metastatic nodules.

reported in detail, TAE was performed 2–3 times during the observation period and no exacerbation of symptoms or increase of serum glucose or insulin levels or tumor size was observed. In the present case, TAE was performed because of the ineffectiveness of octreotide and diazoxide, which were administered to improve the hypoglycemic attack; after TAE, temporary improvement of serum glucose and insulin levels, abdominal symptoms and tumor size was observed. On the other hand, the survival time was short, about 4 months, probably because the proliferative potency was significantly high, with a Ki-67 index of 27%. The Ki-67 indexes of the 4 other cases are unknown; hence, it is not clear whether the malignancy grades were the same as the present case.

Hepatic metastases of neuroendocrine tumor (NET) in 80–90% of the cases are already too difficult to excise at the time of diagnosis. The standards of local treatment for hepatic metastases are TAE and transarterial chemoembolization (TACE) [8], although at present there are not many case reports of TAE or TACE for hepatic metastases of NET that have ended well [9]. In cases where the number of unresectable liver metastases is limited, sometimes tumor ablation is useful.

In the current case, we performed TAE for hepatic metastases to decrease the tumor bulk and to prevent hypoglycemic attacks, since diazoxide was ineffective and octreotide was not available due to the allergic reaction. Reduction of symptoms by TAE treatment have been reported in 64–93% of neuroendocrine carcinoma patients with hepatic metastasis for a period varying between 1 and 18 months [8]. Radiological response (*i.e.*, partial response and complete response) was reportedly 37–74%, the 5-year survival rate for TAE is 40–54%. Kress *et al.* reported that prognosis was improved when the number of liver metastases is small and sufficient lipiodol accumulation was obtained [10]. In the presented patient, the blood glucose levels promptly improved after the initial TAE, and hypoglycemic attacks disappeared. Furthermore, CT scans revealed significant decreases of the tumor volume. Decreases in levels of tumor markers (*e.g.*, CA19-9 and NSE) in addition to IRI and C-peptide, were also noted.

Systemic chemotherapies have also been used for pancreatic neuroendocrine carcinomas. Prior reports suggest comparatively favorable effects of combination therapy with etoposide and cisplatin, or with irinotecan and cisplatin [11, 12]. However, no randomized

controlled trial of chemotherapies for this disease has been conducted, and no survival benefit has been demonstrated. Moreover, generally it takes more than 2–3 weeks to obtain considerable reduction of tumor volume by systemic chemotherapy; consequently, immediate improvement of glucose levels is unlikely to occur by chemotherapy alone. In the present patient, we administered 3 courses of etoposide and cisplatin [13], but the size of tumors increased and the patient continued to suffer from multiple episodes of hypoglycemia.

In conclusion, prompt resolution of hypoglycemia was achieved by TAE in a malignant insulinoma patient with hepatic metastases. This case indicates that TAE is useful in the management of malignant insulinomas for prevention of hypoglycemic attacks, particularly for cases in which drugs such as diazoxide and octreotide are ineffective or unavailable.

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