Malignant Insulinoma which Expressed a Unique Creatine Kinase Isoenzyme: Clinical Value of Arterial Embolization as a Palliative Therapy

Michio Hayashi, Kenmei Takaichi, Toshitsugu Kariya*, Hiroki Kanbe*, Naoto Hayashi**, Masako Honsei, Shuhei Hayashi, Hiroshi Yasuda, Tomoko Ueno and Toshiro Fujita

Abstract

A 76-year-old man with hypoglycemic coma was diagnosed as malignant insulinoma with multiple hepatic metastases. Embolization was done for two-thirds of the hepatic mass and it rapidly lowered the serum immunoreactive insulin. He was discharged without medication and has been free from hypoglycemia. After the embolization, the serum creatine kinase (CK) level increased transiently although there was no evidence of myocardial infarction. On electrophoresis, the CK activity showed an abnormal peak, suggesting mitochondrial CK. CK release after embolization has been reported in only a few cases with endocrine tumors, which might indicate some relationship between active energy metabolism and mitochondrial CK.

Key words: mitochondrial CK, hyperparathyroidism, MEN1

Introduction

Insulinoma arises from pancreatic islets and is characterized by unregulated insulin secretion which causes hypoglycemia. In many cases, insulinoma is a solitary pancreatic tumor and can be cured by surgical operation. On the other hand, “malignant” insulinoma, which presents multiple/bulky hepatic metastases or recurrence after surgical resection, is refractory to usual surgery or systemic chemotherapy. Multidisciplinary approach, including mass reductive surgery, diazoxide, which suppresses insulin secretion, or arterial embolization, is required for these “malignant” insulinoma (1).

Arterial embolization for hepatocellular carcinoma or metastatic liver tumor is effective in reducing tumor mass and improving patients’ survival rates. It can be performed repetitively with relatively low risk. In the management of malignant insulinoma, arterial embolization is a useful therapeutic option (2, 3). Here we report a case of malignant insulinoma. Arterial embolization was dramatically effective in reducing serum immunoreactive insulin (IRI) level, even though only two-thirds of the liver metastatic tumors were embolized. In addition, this insulinoma expressed mitochondrial creatine kinase (m-CK) isoenzyme and serum CK activity increased transiently after embolization. CK release after embolization for hepatic tumor is not common and has been reported in only five cases (4, 5). These cases and the present case are all endocrine tumors and the m-CK isoenzyme was demonstrated in three cases. We propose an association between m-CK activity and active energy metabolism.

Case Report

A 76-year-old man, who was managed with furosemide and beta adrenergic blocker for congestive heart failure since 1988 in an outpatient clinic, was admitted to the hospital because of consciousness disturbance on December 23, 1998. He was 150 cm in height and weighed 55 kg. The physical examination findings were normal except for consciousness disturbance and hepatomegaly. Laboratory findings showed remarkable hypoglycemia (38 mg/dl) and inappropriately high serum IRI (16 μIU/ml) (Fig. 1), therefore he was diagnosed as insulinoma. Ultrasonography, computed tomography, and angiography revealed multiple hypervascular masses in the pancreas head and liver (Fig. 2A, Fig. 3). Plasma glucagon and gastrin levels were normal. Primary hyperparathyroidism was diagnosed based on the findings of hypercalcemia (12.0 mg/dl), elevated serum PTH level (78 pg/ml), undetectable serum PTHrP, and parathyroid adenoma detected by ultrasonography. Pituitary hormones were all normal and magnetic resonance imaging showed no pituitary tumor. Serum calcium levels of his son and daughter were normal and none of his relatives had urolithiasis, thus the pa-
Arterial Embolization for Insulinoma

Figure 1. Plasma glucose (PG, mg/dl) and serum IRI (µU/ml) of the patient. Arterial embolization was done on February 16, 1999 (arrow).

Figure 2. A) Computed tomography enhanced with intravenous contrast medium (January 6, 1999). Multiple hepatic metastases are demonstrated. The image is in the late enhanced phase (portal phase), thus the tumors are less enhanced compared with normal liver tissue. B) Computed tomography two weeks after the embolization (March 1, 1999). Lipiodol stains are demonstrated in two-thirds of the liver tumors. The pancreas head tumor remained unchanged (not shown in the figure).

Figure 3. Abdominal angiography (January 19, 1999). Multiple hypervascular tumors (two large masses and multiple tumors in the liver, and a pancreas head tumor) are demonstrated.

The patient was clinically diagnosed as sporadic multiple endocrine neoplasia (MEN) I. Other laboratory data, including blood cell counts, hepatic function tests, coagulation function tests, were all normal.

The patient suffered a hypoglycemic attack even under hyperalimentation with glucose infusion of 180 g/day. Selective arterial embolization was performed into the left hepatic artery with lipiodol and farmorubicine 20 mg on February 16, 1999. The right hepatic area was not embolized because of the vascular anomaly (anomalous right hepatic artery originated from the superior mesenteric artery). Following the embolization, the serum IRI decreased rapidly and hypoglycemic attack was resolved (Fig. 1). Serum AST/ALT/LDH and CK level increased transiently (Fig. 4). The CK activity was apparently in CK-MB by routine immunoinhibition method, but electrocardiogram showed no evidence of myocardial infarction. Electrophoresis showed the CK activity was in CK-MM, CK-BB, and cathodically migrating abnormal CK-MiMi peak (Fig. 5). Serum activity of mitochondrial enzymes also increased immediately after the embolization, and gradually decreased in
parallel with the change of the CK activity (Fig. 4). Two weeks after embolization, computed tomography showed lipiodol stain in two-thirds of the liver tumors (Fig. 2B). No intervention was done to the parathyroid adenoma, because of the moderate disease activity of hyperparathyroidism. The patient was discharged without any medications or intravenous nutritional support, and has been without any signs or symptoms of hypoglycemia for six months after the embolization.

**Comments**

Malignant islet tumors are usually slowly growing and have high endocrinological activity which causes many annoying symptoms. Therefore tumor mass reduction is, though not curative, beneficial in managing these tumors (2, 3). Arterial embolization can safely reduce the hepatic metastatic tumor mass. In the case reported here, the hepatic metastatic tumor mass was large and surgical resection was apparently impossible. The use of a beta adrenergic blocker was possibly the reason why the patient had been asymptomatic until the tumor grew so huge. His age and the history of congestive heart failure rendered us to choose arterial embolization, rather than a chemotherapy with streptozotocine and doxorubicin (6), as a therapeutic modality. Serum IRI decreased rapidly after the embolization and patient has been free from hypoglycemic symptoms. Endocrine tumor is often heterogeneous in the hormone secreting activity. We speculate this heterogeneity is the reason why IRI decreased so rapidly though one-third of the hepatic tumor remained intact. Embolization was not curative, but beneficial for the patient. This demonstrates the clinical value of arterial embolization as a palliative therapy for malignant insulinoma.
Another unique point of this case is the transient rise of serum CK activity after embolization. The elevated CK activity was mainly in the anomalous peak. This electrophoretic pattern and the transient rise of the mitochondrial enzymes, which indicates degradation of mitochondria, suggest that the elevated CK activity was derived from mitochondria of the insulinoma.

There is a negligible amount of CK in liver tissue, and total CK activity is very low in most tumor tissues (7). Some malignant tumors, especially advanced adenocarcinomas, are known to express m-CK (8–10). However, CK activity in hepatocellular carcinoma is low and mainly BB-CK isoenzyme (11). In our hospital, sixteen embolizations were performed in twelve hepatocellular carcinoma patients from March 1999 to November 1999. Serum CK levels were checked after twelve embolizations. There was a slight rise of CK not exceeding 300 IU/L in seven cases and all of these CK activities were revealed to be MM-CK by a routine immunoinhibition method (unpublished data). From these findings we think that embolization for hepatocellular carcinoma does not raise the serum m-CK activity. CK release from tumors after embolization has been hitherto reported in only five cases (4, 5), and they were all endocrine tumors (one insulinoma, four carcinoids). In two cases, the CK isoenzyme patterns were determined as m-CK by electrophoresis (4). The present finding and the previously reported cases suggest that in addition to advanced adenocarcinomas some endocrine tumors also express m-CK at a high level. Though the significance of m-CK in the endocrine tumors is still to be elucidated, it is likely that m-CK represents the active energy metabolism in these tumors.

Reference