IGF-II Producing Hepatic Fibrosarcoma Associated with Hypoglycemia

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A 67-year-old male was admitted with the complaint of weakness at hunger early in the morning, when blood glucose was less than 40 mg/dl. The abdominal ultrasonogram and computerized tomogram demonstrated a huge tumor in the right liver lobe. Hypoglycemia disappeared after transcatheter arterial embolization. Then hepatic lobectomy was performed. The tumor was histologically shown to be a fibrosarcoma. Insulin-like growth factor-II was intensely stained in the Golgi area of the tumor cells, suggesting its role in the mechanism of hypoglycemia.

(Key words: hepatic fibrosarcoma, hypoglycemia, insulin-like growth factor-II (IGF-II), transcatheter arterial embolization (TAE))

Introduction

Reports of patients with primary hepatic fibrosarcoma are rare, while 20% of these patients are associated with hypoglycemia as a paraneoplastic syndrome (1-6). The insulin-like growth factor-II (IGF-II) produced by certain mesenchymal or epithelial tumors is thought to be responsible for the development of hypoglycemia in some cases (7, 8). Transcatheter arterial embolization (TAE) has been frequently used in the management of hypervascular tumors, but it has seldom been performed for treatment of hormone-secreting tumors because of hormone release at embolization (9, 10). Here we report a case of primary hepatic fibrosarcoma, in which hypoglycemia was controlled safely by TAE and IGF-II was demonstrated in the Golgi area of the tumor cells.

Case Report

A 67-year-old man, who had suffered from weakness at hunger early in the morning for two months, visited Itami City Hospital. An ultrasonogram (US) revealed a hepatic tumor. He was admitted on January 8, 1991. On physical examination he appeared lucid, was 164 cm in height and 67.8 kg in weight. The conjunctivae were neither anemic nor icteric. No superficial lymph node was swollen. The liver, smooth and elastic hard, was palpable 3 cm below the right costal margin. The spleen was not palpable. There were no abnormal neurological findings. The laboratory data were as follows: Urinalysis results and blood cell count were normal. The levels of GOT (72 IU/L), GPT (61 IU/L), ALP (446 IU/L) and γ-GTP (387.5 IU/L) were elevated, while the total bilirubin level was normal. The prothrombin time and heparplastin test results were normal. Serum creatinine, BUN, and electrolyte values were also normal. The fasting blood glucose (FBG) level was as low as 36 mg/dl. Plasma insulin by radioimmunoassay (IRI) and glucagon levels were 5.0 (lU/ml (normal 3-15) and 131 pg/ml (normal 40-140) respectively. Serological tests for hepatitis virus B and C were negative. 17-hydroxycorticoid and 17-ketosteroids in the urine were 3.7 mg/day (normal 2.1-11.5) and 3.35 mg/day (normal 3.0-9.0) respectively. Alfa-fetoprotein (AFP), carcinoembryonic antigen (CEA) and protein induced by vitamin K absence-II were normal although pancreatic cancer-associated antigen (DU-PAN-2) slightly increased to 174 U/ml (normal <159). After admission, he often suffered from restlessness, confusion and amnesia early in the morning, when then blood glucose was between 20 and 40 mg/dl. The symptoms were improved after administration of dextrose. On January 18, 1991, the response to a 75 g oral glucose tolerance test (OGTT) was abnormal. Blood glucose, IRI and C-peptide levels were 42 mg/dl, 5.3 μU/ml and lower than 0.3 ng/ml (normal 1.5-3.0) before; 149 mg/dl, 29.4 μU/ml and 3.5 ng/ml at 30 min; 166 mg/dl, 58.7 μU/ml and 7.5 ng/ml at 60 min; 64

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mg/dl, 7.9 μU/ml and 1.9 ng/ml at 120 min; and 36 mg/dl, 5.3 μU/ml and 0.5 ng/ml at 180 min respectively (Fig. 1a). On intravenous administration of 1 mg glucagon, IRI remained at a low level with a poor response, when the blood glucose level increased from 54 mg/dl at the beginning to 93 mg/dl at 30 min after stimulation (Fig. 1b). US demonstrated a space occupying lesion in the right liver lobe, which was 11 cm in diameter and showed a mixed echoic pattern including an iso-echoic region in part. The tumor pressed the right hepatic vein and the right branch of the portal vein. The abdominal computed tomogram (CT) showed a huge tumor with uneven density and irregular enhancement after contrast medium injection (Fig. 2).

On January 21, the selective celiac angiogram revealed a hypervascular huge tumor fed by the right hepatic artery (Fig. 3). TAE using small cubes of Spongel (Yamanouchi Pharmaceutical Co., Ltd., Tokyo) was performed. During and after embolization, no hypoglycemic attack occurred. The next morning FBG increased to 95 mg/dl and hypoglycemic symptoms disappeared. On January 28, blood glucose and IRI levels on a 75 g OGTT were improved as follows: 100 mg/dl and 5.7 μU/ml before; 177 mg/dl and 56.6 μU/ml at 30 min; 186 mg/dl and 82.1 μU/ml at 60 min; 107 mg/dl and 41.4 μU/ml at 120 min; and 63 mg/dl and 13.2 μU/ml at 180 min, respectively (Fig. 1a).

No tumor was found in other organs by gallium scintigram, abdominal CT or magnetic resonance imaging.

Thirty seven days after TAE, the right liver lobe including the tumor was resected. The resected liver weighed 1,060 g. The cut section showed a yellowish white tumor of 11 cm in diameter with more than 90% central necrosis. It was well demarcated from the hepatic parenchyma. There was a small daughter nodule 1 cm in diameter adjacent to the main tumor (Fig. 4). Hematoxylin-eosin staining revealed that the tumor was composed of spindle-shaped cells arranged in a storiform pattern. Mitotic figures and mild atypia were observed (Fig. 5). Polypkaryocytes and histiocytes were not observed. Azan-
Fig. 4. Cut section of the segmental hepatectomy specimen: A well-demarcated tumor mass is noted.

Mallory and Masson-trichrome stains demonstrated abundant collagen fibers intermingled with the individual cells. Silver staining revealed argyrophile fibers surrounding each of the tumor cells. Immunohistochemistry was performed. The tumor cells were positive for vimentin, which was a stromal marker, but negative for the following: keratin, CEA, epithelial membrane antigen, lysozyme and α1-antichymotrypsine, which were epithelial markers; factor-VIII related antigen which was a marker of vascular endothelial cells; actin, myoglobin and desmins, which were markers of muscle cells; S-100 protein which was a marker of nerve cells; AFP and albumin. Therefore, the patient was diagnosed as having a primary hepatic fibrosarcoma. The hepatic parenchyma surrounding the tumor was normal and not cirrhotic. The tumor and the hepatic parenchyma were examined by immunohistochemistry for insulin (Dakopatts: rabbit polyclonal antibody used), insulin-like growth factor-I (IGF-I) (rabbit polyclonal antibody used (11)) and IGF-II (Amano Pharmaceutical Co., Nagoya, mouse monoclonal antibody) using the avidin-biotin-peroxidase complex method (12). IGF-II was strongly stained in the Golgi area of the spindle-shaped tumor cells but not in the hepatic parenchymal cells (Fig. 6). Insulin and IGF-I were stained in neither the neoplasm nor the hepatic parenchyma.

Fig. 5. Light microscopy (HE stain, x230): The tumor is composed of spindle-shaped cells arranged in storiform pattern.

Discussion

It has been well recognized that hepatic tumors, especially hepatocellular carcinoma (HCC), are frequently associated with hypoglycemia (13). Since HCC sometimes exhibits a sarcomatous change (14), care is required in the diagnosis of hepatic fibrosarcoma.

In the present case, the results of immunohistochemical staining for AFP and albumin were negative and no suggestive feature of HCC was found. Existence of collagen fibers and argyrophile fibers suggested a mesenchymal tumor. Furthermore, there were abundant collagen fibers in the interstitium embedding individual cells. Therefore, either fibrosarcoma or malignant fibrous histiocytoma (MFH) was suspected. Histological findings specific to MFH, such as polykaryocyte, inflammatory cell infiltration, myxosarcoma and hematoma, were not observed. According to these histopathological studies, the present patient was diagnosed as having a fibrosarcoma.

Primary hepatic fibrosarcoma is rare. Ito et al reported that there have been only 34 cases in the literature since Jaffe described the first case in 1924 (15, 16). There were 7 cases associated with hypoglycemia (1–6). The patients were between 45 and 71 years old, and the sex ratio was 5:2 with male predominancy.

The blood glucose level at the hypoglycemic attacks was between 20 and 40 mg/dl, but IRI did not show a high level in any of these 7 cases. In the present case, fasting C-peptide was suppressed below the limit of detection of the assay with some discrepancy of IRI levels. The following mechanisms have been proposed for the etiology of hypoglycemia: 1) secretion of insulin and/or insulin-like substances by the tumor (10), 2) inhibition of gluconeogenesis and glycogenolysis (15), 3) ex-
cessive utilization of glucose by the tumor (16) and 4) interference with sympathetic impulses to the liver by pressure on the right splanchnic nerve and the celiac ganglion (17). At the time of diagnosis, the hepatic fibrosarcoma which induced hypoglycemia was usually massive. One tumor was as large as a football (2), another occupied the entire right lobe (6) and the tumor in the present patient was 11 cm in diameter. Thus, the fibrosarcoma was not noticed until the patient complained of an upper abdominal tumor mass or upper abdominal pain other than the hypoglycemic symptoms. The huge tumor must be a prerequisite to the development of hypoglycemia. Hypoglycemia is usually seen in acute liver failure due to reduction in hepatic glucose release, but there was no evidence of liver failure in the present case.

Nonislet cell tumor hypoglycemia (NICTH) has been attributed to production of IGF-II (18). The suggested functions of IGF-II are suppression of splanchnic glucose production, stimulation of peripheral glucose utilization and functional growth hormone deficiency (19). In the present case, the Golgi area of the tumor cells was intensely stained for IGF-II. There have been reports of extrapancreatic tumors associated with hypoglycemia in which positive staining for IGF-II was observed in the Golgi area of the tumor cells (20). Unfortunately, the serum IGF-II level presenting with hypoglycemia before TAE could not be measured and the frozen tumor tissue failed to be obtained for analysis. However both the symptoms of hypoglycemia and the tumor recurred after a ten-month remission, at which time the serum IGF-II level was elevated to 991 ng/ml (normal range 374 to 804) and the IGF-I level was lower than 22 ng/ml (normal range 88 to 240). The size heterogeneity of serum IGF-II was investigated by Western immunoblot (Fig. 7). In normal subjects, most IGF-II was detected at 7.5 kDa. However, in the present patient, most IGF-II was detected at ~15 kDa, as well as in other patients with NICTH (21). These findings indicated that the tumors associated with hypoglycemia not only produced but also secreted an excessively large form of IGF-II which resulted in feedback inhibition of IGF-I.

Two of the seven reported cases of hepatic fibrosarcoma accompanied by hypoglycemia were treated with radiation (1, 2), and in one case the tumor was surgically resected (6). In the present case, the tumor was extirpated after TAE. TAE has been commonly used for treatment of hypervascular tumors, but it has been used rarely in dealing with hormone-secreting tumors because of hormonal crisis. Although the serum IGF-II could not be measured, hypoglycemia caused by secretion of IGF-II after TAE did not occur in the present case. Therefore, TAE seemed to be safe and effective in ameliorating the hypoglycemic symptoms with hepatic fibrosarcoma.

In the present case, positive staining for IGF-II in the Golgi area of the tumor cells, disappearance of hypoglycemic symptoms after TAE and the elevation of a large form of IGF-II in the serum suggested that IGF-II secreted by the tumor plays a role in the mechanism of hypoglycemia.

![Western immunoblot of serum IGF-II](image-url)

Fig. 7. Western immunoblot of serum IGF-II. Acid-ethanol extracted serum samples were electrophoresed on 16% SDS-acrylamide gel under non-reduction condition. The size-fractionated proteins were electroblotted onto a nitrocellulose sheet. The sheet was incubated with anti-IGF-II antibody (Amano Pharmaceutical Co.), washed, and then incubated with HRP-conjugated anti-mouse IgG. IGF-II-anti-IGF-II antibody complexes were detected with the ECL system. Lanes 1 and 6: IGF-II; 5: the present patient; 2, 3: nonislet cell tumor hypoglycemia; 4: after a successful removal of tumor in the patient (lane 3), 7 and 8: normal subjects.

**References**

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