Hypoglycemia Induced by Secretion of High Molecular Weight Insulin-like Growth Factor-II from a Malignant Solitary Fibrous Tumor of the Pleura

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Abstract

A 49-year-old woman with a malignant solitary fibrous tumor of the pleura presented with hypoglycemia. Most of the serum insulin-like growth factor II (IGF-II) existed as high molecular weight IGF-II. Furthermore, there were larger amounts of high molecular weight IGF-II found in the tumor cystic fluid than in the serum. After surgical resection of the tumor, high molecular weight IGF-II was not detected in the serum and the hypoglycemia resolved. Immunohistochemically, IGF-II was localized in the so-called Golgi area of the tumor cell. These findings suggest that hypoglycemia in this patient was caused by the high molecular weight IGF-II produced by the tumor.

Key words: non-islet cell tumor hypoglycemia, IGF-II

Case Report

A 49-year-old woman visited our hospital because of a pleural mass detected on chest radiography in November 1997. She had no history of smoking or asbestos exposure. A chest CT scan showed a large mass measuring 12x7x7 cm in the right thorax associated with a moderate pleural effusion and paraaortic lymph node enlargement. The microscopic appearance of a biopsied specimen of the mass showed fibrous mesothelioma suggestive of malignancy. The patient received two cycles of chemotherapy with methotrexate, vindesine and cisplatin, with no reduction in the size of the mass. The serum fasting glucose levels in November 1997 and August 1998 were 105 and 103 mg/dl, respectively. In December 1998, the patient was admitted for the second time because of hypoglycemic coma. One month before admission she complained of unpleasant dreams. The serum glucose level at the time of admission was 26 mg/dl (normal range: 70 to 110 mg/dl). Subsequently, the levels of serum insulin, C-peptide and growth hormone on admission were reported to be 3.9 μU/ml (normal range: 3 to 12 μU/ml), 0.16 ng/ml (normal range: 0.5 to 3 ng/ml) and 2.80 ng/ml (normal range: <5 ng/ml). The patient’s level of consciousness improved immediately after intravenous infusion of 50% dextrose. Physical examination showed silent breath sounds with decreased vocal fremitus on the right chest. She had no clubbing or bone tenderness. Chest radiography showed complete opacification of the right lung field with mediastinal shift to the left. Chest CT scan of the thorax revealed cystic lesions in a huge mass which were separated by thin membranous walls associated with an enlarged paraaortic lymph node measuring 4x2 cm in diameter (Fig. 1).

Although the patient received a continuous infusion of 10% dextrose, hypoglycemic episodes still occurred at night and in the early morning. Serum glucose levels during the day receiving intravenous 10% dextrose were 48 (8 am), 94 (11 am), 78 (4 pm), 88 (8 pm), 132 (11 pm) and 34 mg/dl (3 am). The
serum and tumor fluid levels of IGF-II were 558.4 and 1,588.3 ng/ml (normal range: 459 to 873 ng/ml).

The patient underwent a right thoracotomy, with most of the tumor being resected, because the hypoglycemia was suspected to be related to the large tumor. The appearance of the tumor revealed multiloculated cystic lesions, containing serous fluid with adhesion to the adjacent lung. The tumor was 22.5×16.0×12.5 cm in size and 780 g in weight after removing the fluid in the tumor. Macroscopic appearance of the cut surface of the resected tumor showed a grayish-white solid portion and a thin membranous portion. Microscopic examination revealed interlacing fascicles of spindle tumor cells interspersed with thick bundles of collagen in a solid portion and small tumor cells with high cellularity and a paucity of collagen in a membranous portion, showing histological malignant features (Fig. 2). Immunohistochemically, most of the tumor cells stained positive for CD34 and vimentin, but negative for keratin. Based on these findings, the tumor was diagnosed as malignant SFT of the pleura. The serum glucose level in the patient returned to normal immediately after the excision of the tumor. The serum IGF-I levels before and after surgery were 49.9 and 205.9 ng/ml (normal range: 37–466 ng/ml), respectively.

Size heterogeneity of IGF-II in serum and in cystic fluid of the tumor was investigated by Western immunoblot analysis (6) (Fig. 3). Serum IGF-II in a normal control was detected at the expected size of 7.5 kDa, whereas most of the serum IGF-II in the patient was detected at 19.8 kDa, and designated as high molecular weight IGF-II. High molecular weight IGF-II was also detected in the cystic fluid. Additionally, after surgical resection of the tumor high molecular weight IGF-II was not detected in the patient’s serum. Immunohistochemical localization of IGF-II was analyzed on paraffin sections of the tumor by the labeled streptavidin biotin method. The antibody used was mouse monoclonal antiserum for human IGF-II (Amano Pharmaceutical Co., Nagoya). The so-called Golgi area of tumor cells stained positive for IGF-II (Fig. 4).
IGF-II Producing Malignant SFT

Discussion

Non-islet cell tumor hypoglycemia (NICTH) is one of the major causes of fasting hypoglycemia. Most of these tumors, including SFT, fibrosarcoma, mesothelioma, leiomyosarcoma, hemangiopericytoma and hepatoma (7), are mesenchymal or epithelial in origin. Because SFT shows a wide spectrum of histological features, the surgical resection of the tumor is usually required to make a final diagnosis by histological typing. The detection of CD34-positive cells has been reported to be useful to diagnose SFT (2). In the present patient, microscopic analysis showed two different histological patterns in the tumor. Part of the tumor showed interlacing fascicles of spindle cells, and another part showed small tumor cells with high cellularity. These histological features of the tumor are consistent with those previously reported for SFT (1). The positive immunoreactivity for CD34 in this tumor confirmed the diagnosis as SFT. SFT is graded as benign or malignant according to histological features that include high cellularity, mitotic activity, pleomorphism, hemorrhage, and necrosis (8). The present tumor was diagnosed as malignant based on this criteria and evidence of mediastinal lymph node metastasis.

The mechanism of NICTH has been widely discussed. In some patients with NICTH, tumor-derived IGF-II is thought to be a hypoglycemic agent. However, serum IGF-II levels are not always elevated in these patients. It has been recognized that NICTH could be explained by secretion of high molecular weight IGF-II, an incompletely processed IGF-II (6).

In normal individuals, IGF-II forms an inactive ternary complex with IGF binding protein (IGFBP)-3 and an acid-labile subunit. High molecular weight IGF-II fails to form a complete complex and is preferentially bound to IGFBP-2 in an abnormal binary complex that can cross capillary membranes and cause hypoglycemia by direct interaction with IGF and insulin receptors (9–11).

In the present case, preoperative levels of serum insulin, C-peptide and growth hormone were low. However, the total serum IGF-II level was within the normal range, and most of the serum IGF-II circulated as high molecular weight IGF-II preoperatively. Furthermore, there were larger amounts of high molecular weight IGF-II found in the tumor cystic fluid than in the serum. In the present case, the so-called Golgi area of the tumor cells stained positive for IGF-II. Aiba et al (12) and Kotani et al (13) showed that high molecular weight IGF-II was observed in the Golgi area of the tumor cells in NICTH. According to these findings, high molecular weight IGF-II produced by and secreted from the tumor could be related to hypoglycemia in the present case. To our knowledge, high molecular weight IGF-II has not been demonstrated in a malignant SFT.

The most effective therapeutic modality in patients with SFT is resection or debulking of the tumor. Although complete resection was impossible in this case due to contralateral mediastinal metastasis, excision of the right-sided large tumor successfully corrected the life-threatening hypoglycemia.

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References

4) Fukasawa F, Takada A, Tateno M, et al. Solitary fibrous tumor of the