Case Report

Non-Islet Cell Tumor Hypoglycemia Manifested as Recurrent Hypoglycemia - A Case Report

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Abstract

Hypoglycemia is a complication in diabetic patients with insulin replacement therapy but rarely happened in subjects without diabetes mellitus except factitious hypoglycemia. Solitary fibrous tumor of pleura, an uncommon mesenchymal originated neoplasm, is occasionally associated with persistent hypoglycemia and tumor size usually been huge when discovered. An incompletely processed insulin-like growth factor II (IGF-II) produced by the mesenchymal tumor is considered to be the cause of hypoglycemia. Here we reported a 50-year-old woman, without any systemic disease before, was presented to local hospital due to repeated episodes of conscious change due to hypoglycemia. Huge right lung mass noted incidentally by the chest radiographs. Computed tomography indicated a huge extrapulmonary, intrathoracic mass. Hypoglycemia repeated during hospitalization, non-islet cell tumor hypoglycemia was thought to be the cause. We performed complete tumor excision and wedge resection of the right middle lung. Pathological report revealed malignant solitary fibrous tumor of the pleura. No more hypoglycemia episode developed in the next few months follow up after tumor removal. (Formos J Endocrin Metab 2010; 1(5): 9-13)

Key words: hypoglycemia, non-islet cell tumor hypoglycemia, solitary fibrous tumor, insulin-like growth factor

Introduction

Non-islet cell tumor hypoglycemia (NICTH) is an uncommon but critical complication of neoplasm. Solitary fibrous tumor of the pleura (SFTP), one of the diverse tumors related to NICTH, causes hypoglycemia without producing insulin but through the effect of tumor secreted insulin-like growth factor II which was known as Doege-Potter syndrome. SFTP is rare, arises from the visceral pleura with mesenchymal origin. About 800 cases with SFTP have been reported in the medical literatures.¹² SFTP is a slow growing tumor with 12-13% rate of malignancy. Symptomatic hypoglycemia has been observed in about 4% of SFTP cases and SFTP related hypoglycemic coma is rarely lethal.³ In this patient, without immunohistochemical evidence of tumor producing high molecular IGF-II, the excellent result after tumor excision and low serum insulin, C-peptide, and IGF-I level leading to the diagnosis of hypoglycemia induced by IGF-II secreting malignant SFTP.
Case Report

A 50-year-old woman presented to local hospital with conscious change due to hypoglycemia more than two times. She had no systemic disease before. Intermittent palpitation, cold sweating, panic attack and body weight loss developed during the past three months. A huge mass with lobulated opacity in right lower lung field was discovered incidentally by chest radiographs (Figure 1). Computed tomography indicated a extrapulmonary, intrathoracic lobulated mass (Figure 2). Therefore, the patient was admitted to our hospital.

On admission, her consciousness was clear and respiration was not labored. No digital clubbing nor cyanosis was presented. She had no history of smoking and denied any exposure to hazardous materials. Physical examination revealed decreased breath sound at right inferior lung field. No cervical, supraclavicular lymadenopathies. The liver and renal functions were normal. The levels of tumor markers were all within the normal limits. The serum level of insulin, C-peptide and IGF-I were 1.82 μIU/ml (reference range: fasting <30.00 μIU/ml), 0.38ng/ml(reference range: 1.10-3.20 ng/mL) and 63.90 ng/mL(reference range:106-398 ng/ml), respectively. Simultaneous serum sugar level was 49 mg/dl. No significant lesion in liver, pancreas and biliary system detected by abdominal echo. Whole body bone scan revealed negative findings. Frequent hypoglycemia episodes occurred in the morning and between meals, recovered by intravenous infusion of 50% dextrose.

Echo-guide pleural biopsy was done through right lower lung, no cellular atypia or increased mitotic figures were seen. The cells are CD34(++), CD117(+), vimentin(+++), S-100(-), and smooth muscle actin(-). These profiles support the diagnosis of solitary fibrous tumor. The tumor cells are strongly immunoreactive with CD99 (MIC-2) that also supports solitary fibrous tumor. Due to above findings, insulinoma related hypoglycemia was ruled out and NICTH was suspected.

Wedge resection of the right lung and complete tumor excision were performed. Gorrysly, the tumor was 17x11x11 cm in size with grayish white appearance, just located over the interlobar fissure between

![Fig. 1 Chest roentgenogram in August 2009 showing a large mass in the right inferior lung field](image)

![Fig. 2 Computed tomographic scan of the chest showing a giant heterogenous mass (10x11x15cm) in the right thoracic cavity with mass effect to the adjacent lung](image)
Recurrence hypoglycemia & solitary fibrous tumor

Fig. 3 The cut section of the well-capsulated tumor originated from the visceral pleura of right lung

Fig. 4 Highly cellular tumor with elongated spindle-shaped cells arranged in a storiform pattern on Hematoxylin and eosin stain (100X)

The right upper lobe and right lower lobe. The tumor reveals a solid firm whorled cut surface(Figure 3). Microscopically, the pleural mass shows a malignant solitary fibrous tumor (MSFT) with a pushing border and focally attached to the visceral pleura of adjacent lung tissue. The tumor cells are hypercellular in most areas and focally hypocellular. There are round to spindle-shaped cells with mild to moderate nuclear atypia(Figure 4). Mitotic figures are increased in focal areas (more than ten mitotic figures per 10 high-power fields). Tumor necrosis is not present. The neoplastic cells are CD34+, Bcl2+, calretinin-, CK-, and S100- that supports the diagnosis. Sections of the rib bone and the lung parenchyma appear unremarkable. The resection margin of the subsequent specimen is focally involved by the MSFT.

The postoperative course was smooth except for post-operative wound pain. Hypoglycemia resolved after the tumor excision. No more hypoglycemia related symptoms occurred after patient discharge. Intensity-modulated radiation therapy(IMRT) 60 Gy in 30 fractions to tumor bed was arranged as post surgery adjuvant therapy. No signs of recurrence during 5 months post operation.

Discussion

Hypoglycemia is a medical emergency with manifold causes. Consider of the clinical symptoms and signs with levels of serum insulin, C peptide, sulfonylureas may differentiate insulin or sulfonylureas related hypoglycemia. Acquired severe liver disease, renal insufficiency, sepsis, congestive heart failure, and starvation should also be taken in to account as predisposing factors. If above conditions are excluded, tumor-associated hypoglycemia may be considered next. There are two major causes of tumor-induced hypoglycemia, including insulinoma and non-beta cell tumors.4-5 Non-islet cell tumor hypoglycemia (NICTH), a rare paraneoplastic phenomenon, often causes fasting hypoglycemia. Hypoglycemia associated non-islet cell tumors are composed of diverse tumor types, including adrenocortical carcinoma, lymphoma, hepatoma, hemangiopericytoma, fibrosarcoma, mesothelioma, malignant pheochromocytoma, leiomyosarcoma and miscellaneous tumors.6 Most tumors with NICTH are large.7,8

In NICTH, IGF-II mRNA overexpressed tumor cells cause the synthesis of incompletely processed IGF-II (Big-IGF-II). Normally, most of IGFBPs forms a 150 kDa ternary complex with IGF binding proteins, but Big-IGF-II primarily forms a 40-50 kDa binary complexes with IGF binding proteins. The binary complexes have a higher biological activity to interact with insulin receptors in the liver, adipocytes and muscle, lead to the inhibition of gluconeogenesis and more glucose uptake by skeletal muscle.9 The
binary complexes also have a greater capillary permeability and thus cause a strong insulin-like effect through the insulin receptors, profound hypoglycemia thereupon developed.\(^7\) When the incompletely processed IGF-II binds to the IGF-I receptors in the pituitary gland, growth hormone production will be suppressed by a feedback inhibition, results in serum IGF-I concentration decreasing.\(^7\) In our patient, the circulating level of insulin, C-peptide and IGF-I is low, implies that the mechanism of hypoglycemia is not mediated by insulin and IGF-I. Tumor-derived IGF-II plays a crucial role in non-islet cell tumor related hypoglycemia.

Solitary fibrous tumor of pleura (SFTP) was first classified as methothelial origin but now immunohistochemical evidence indicate that this tumor originate from mesenchyma.\(^11\) Solitary fibrous tumors tend to affect serosal surface with an intrathoracic growth, most commonly seen attaching to visceral pleura, but also have been reported in parietal pleura or rare extrapleural sites, including orbit, salivary glands, thyroid, retroperitoneum, and abdominal cavity (liver, GI tract, urinary bladder).\(^12\) SFTP distributed equally in both sexes and peak in the sixth to seventh decades of life. About half of these cases were asymptomatic when tumor discovered. Most common symptoms including non-productive cough, dyspnea and chest pain, more frequently observed in patients with a malignant tumor. Unspecific signs such as hypoglycemia, clubbed digits, pulmonary osteoarthropathy can be found in patient with either benign or malignant SFTP.\(^1,3,8\) SFTP with malignant histologic signs may present one or more of these features: High cellularity with crowded overlapping nuclei (more than four mitotic figures per 10 high-power fields), nuclear atypia, pleomorphic giant cells, necrosis, and hemorrhage.\(^2,8\)

In 1981, Briselli and colleagues\(^3\) studied eight new cases and reviewed 360 cases in the literature, they concluded that the best indicator of a good prognosis is the presence of a pedicle supporting the tumor. Extensive sessile intrathoracic growth and unresectable recurrence are responsible for patient’s death. Tumor growth pattern has more powerful impact to the prognosis than histologic characteristics dose.\(^2,3\)

Complete en bloc surgical resection is the only possible way of cure for both benign and malignant SFTP. Resectability is the single most important indicator of clinical outcome.\(^2,8\) Benign predunculated SFTP has a highest cure rate up to 98%. An 6% local recurrence rate has been observed in patients with benign sessile SFTP that is usually curable after reexcision. Malignant SFTP, especially the sessile type, has a 63% recurrence rate even with complete resection. Half of patients with recurrent disease die of the tumor within 24 months. The overall long-term cure rate after complete resection for all patients is above 80% to 92%.\(^1,2\) In our patient, she has a huge well-capsulated malignant tumor, sessile type, the recurrence of disease after complete surgical resection may be high. Intensity-modulated radiation therapy(IMRT) 60 Gy in 30 fractions to tumor bed was arranged as post surgery adjuvant therapy. Adjuvant therapy, though remains controversial in SFTP due to the limited experience, is recommended after resection of malignant sessile tumors and if tumors recurrent.\(^2\)

In conclusion, SFPT induced NICTH is a rare paraneoplastic syndrome, complete resection of the tumor usually brings good resolution of profound hypoglycemia. Though serum IGF-II measurement is available in limited institutions, low serum insulin, C-peptide, and IGF-I level still provide strong information for the differential diagnosis of tumor-induced hypoglycemia.

References

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