Recurrent Solitary Fibrous Tumor of the Pleura with Malignant Transformation and Non-islet Cell Tumor-induced Hypoglycemia due to Paraneoplastic Overexpression and Secretion of High-molecular-weight Insulin-like Growth Factor II

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Abstract

A 41-year-old man was diagnosed with a solitary fibrous tumor (SFT) of the pleura in the posterior mediastinum. Despite two surgeries for excision, the SFT recurred and progressed with direct invasion of the chest wall and bone metastases. He was hospitalized because of cerebral infarction and presented with recurrent severe hypoglycemia fourteen years later. High-molecular-weight (HMW) insulin-like growth factor II (IGF-II) was identified in the serum and tumor using Western blotting and immunohistochemistry. These findings suggested that the cause of the recurrent severe hypoglycemia was SFT production of HMW IGF-II, a mediator of non-islet cell tumor-induced hypoglycemia (NICTH).

Key words: solitary fibrous tumor of the pleura, non-islet cell tumor hypoglycemia, high-molecular-weight insulin-like growth factor II, platelet-derived growth factor receptor tyrosine kinase

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Introduction

A solitary fibrous tumor (SFT) is a rare tumor of the pleura that arises from mesenchymal cells and has an estimated age-standardized incidence of 1.4 per million population (1). The majority of SFTs have a benign clinical course, but the tumor may recur and metastasize after surgical resection, and 10 to 20% of SFTs are classified as malignant and eventually lead to death (2, 3). Complete radical surgical resection of all benign and malignant SFTs is the single most important indicator of clinical outcome; however, surgical excision is not feasible for some invasive and metastatic cases. Furthermore, there is no effective treatment other than surgery available for SFT. Approximately 4-6% of SFT patients also develop non-islet cell tumor-induced hypoglycemia (NICTH) (2, 3), which is a cause of recurrent hypoglycemia observed with several rare non-beta-cell tumors.

Case Report

The patient was a 41-year-old man with a large tumor in the right posterior mediastinum that was found on a chest radiograph during a medical examination in 1992. Surgical excision was performed by thoracotomy. He had no history of smoking or asbestos exposure. A 6.0×6.0×6.0 cm, circumscribed, firm mediastinal mass was present with no direct cardiac or pulmonary involvement. The tumor contained

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predominantly oval or spindle cells organized in a haphazard growth pattern (a so-called “patternless pattern”) with a few mitoses observed in 10 high-power fields. The tumor cells were immunoreactive for CD34 and vimentin (Fig. 1A-C), but not for desmin, actin, neurofilament (NF), S-100, myoglobin, neuron-specific enolase (NSE) and factor VIII (data not shown). These findings were consistent with a benign SFT of the pleura in the posterior mediastinum.

An abnormal shadow was identified on a chest radiograph in 2000, 8 years after the surgical procedure, but the patient was not admitted to hospital. He developed a severe pain in his right back in 2002. A tumor of about 10 cm in diameter was located in the right hemithorax (Fig. 2A) and a computed tomography (CT)-guided Tru-cut biopsy was performed at a hospital. Many tumor cells were immunohistochemically positive for vimentin, but negative for desmin, smooth muscle actin, CD45RO, CD20 and CD34. MIB-1 (Ki-67)-positive nuclei were found in about 1-5% of the tumor cells (data not shown). Surgery revealed the tumor to have directly invaded the third and fourth ribs and then grown toward the right lung. Therefore, tumor resection combined with right upper pulmonary lobectomy was performed for a recurrent lesion. The specimens of resected tissues showed wide necrosis, but were negative for CD34, c-KIT and ALK-1 in an immunohistochemical analysis. The tumor cells were positive at the cut ends of the resected tissues. Recurrence of SFT was diagnosed based on these results.

The patient presented with severe and intolerable lumbago in 2003. Magnetic resonance imaging (MRI) revealed an abnormal intensity in L2, which led to suspicion of a metastatic lesion. There is no established effective treatment for this tumor, thus imatinib mesilate was administered orally at 400 mg/day as a possible inhibitor of the platelet-derived growth factor receptor (PDGFR) pathway in tumor cells, after written informed consent was provided. Follow-up MRI revealed no apparent growth of the metastatic lesion, and thus administration of imatinib mesilate was discontinued in August 2004.

Both the recurrence of the primary lesion and multiple bone metastases were discovered six months later, in 2005 (Fig. 2B). Imatinib mesilate was restarted and administered for about 6 months. However, symptoms of canal stenosis due to metastasis to the lumbar spine appeared and gradually worsened. The patient was referred to the orthopedics department and palliative surgery for spinal fusion and tumor excision was performed. The tumor cells from the L2 specimen were the same as those of the primary lesion, indicating that the lumbar lesions were metastases of the SFT of the pleura.

The patient was hospitalized for left cerebral infarction and a hypoglycemic episode in 2006. Hypoglycemia occurred in the clinical course after admission; despite a normal appetite in the early morning. He had been given no medication that caused hypoglycemia in his medicine. Laboratory data at the time of hypoglycemic attack are shown in Table. Immunoreactive insulin (IRI) and C-peptide immunoreactivity (CPR) were below their detectable limits.
(≤0.6 μU/mL and ≤0.03 ng/mL, respectively), with hypoglycemia of 14 mg/dL glucose, and the concentrations of insulin-like growth factor (IGF)-I, IGF-II and IGFBP-3 were 23 ng/mL, 409 ng/mL and 1.01 μg/mL, respectively. IGF-II was measured using a commercially available immunoradiometric assay kit (DSL, Webster, TX, USA). Plasma growth hormone was 0.29 ng/mL and anti-insulin antibody was negative. The levels of other hormones were within normal ranges, except for a slightly high level dopamine and cortisol, those. Enhanced CT demonstrated both growth of the tumor and multiple metastases to contralateral costal, vertebral and left iliac bones (Fig. 2C, D), whereas no metastasis to the liver and adrenal glands was observed.

The cause of the persistent severe hypoglycemia seemed to be NICTH caused by SFT production of high-molecular-weight (HMW) IGF-II. Authentic and HMW IGF-II in serum were analyzed by Western blotting. Locally recurrent

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**Figure 2.** Chest computed tomography scan. (A) A tumor of diameter about 10 cm with a heterogeneous area due to hemorrhage or necrosis was present in the right hemithorax in 2002. (B) Recurrence of the primary lesion and invasion of the muscle and ribs occurred in 2005. (C) Invasion of the primary lesion in the thorax. (D) Metastatic lesion in the left iliac bone.

**Figure 3.** Western blot of serum IGF-II in the patient and in a normal subject. Lane 1: patient serum; lane 2: normal serum. High-molecular-weight IGF-II and authentic IGF-II were detected in the patient’s serum.
Figure 4. Immunohistochemical staining of IGF-II and Pro-IGF-II in locally recurrent tissues of the right chest wall. (A) Patternless proliferation of oval or spindle cells (Hematoxylin and Eosin staining). (B) IGF-II immunoreactivity localized in the Golgi area of the tumor cells. (C) Pro-IGF-II immunoreactivity localized with the same pattern as IGF-II in the tumor cells, thus suggesting that a high-molecular-weight IGF-II may be present in these cells.

Discussion

SFT is a rare neoplasm that typically develops in the pleural space, but has been reported in various locations. It accounts for less than 5% of all pleural neoplasms (2, 4-8). SFT was first described by Klemperer and Rabin in 1931 and was initially termed localized mesothelioma, since the tumor was believed to originate from mesothelial cells. However, immunohistochemical evidence has emerged, thus indicating that these fibromas are derived from the mesenchyme, rather than the mesothelium (9-12). SFTs of the pleura express vimentin, a marker of mesenchymal cells, and do not express cytoplasmic keratins, which are found in mesotheliomas. Staining for CD34, initially characterized as a hematopoietic progenitor cell antigen, is helpful for identifying SFT and distinguishing SFT from mesothelioma (13-15).

SFTs of the pleura are generally slow-growing neoplasms that have a favorable prognosis, but some cases have a malignant outcome. SFTs with local or distant recurrences are often larger than 10 cm on presentation (3, 6). Benign SFT of the pleura has a high cure rate and an 8% local recurrence rate that is usually amenable to curative re-excision, often with chest wall resection because of the propensity for local recurrence (16). England et al. considered neoplasms to be malignant if one or more of the following histologic features are present: 1) high cellularity, 2) high mitotic activity (more than 4 mitotic figures per 10 high-power fields), 3) pleomorphism, 4) hemorrhage, and 5) necrosis (3). Pathological findings are not always predictive of the clinical outcome of SFTs and the tumor occasionally can transform into malignant variants after several years (2, 3, 17). A negative immunohistochemical finding for CD34 has been suggested to indicate a poor prognosis (18-20) and it has been proposed that this phenomenon is associated with dedifferentiation in SFT (18, 21). The tumor in the current patient initially showed pathologically benign features; however, it
then transformed to a malignant tumor clinically with conversion from a CD34-positive tumor to a CD34-negative lesion associated with malignant transformation over 10 years.

IGF-II accounts for 10-20% of the total caused by a combination of cachexia and glucose consumption in this case. In addition, hypoglycemia may have been suggested that paraneoplastic overexpression and secretion of HMW IGF-II associated with SFT caused lethal hypoglycemia by direct interactions with IGF and insulin receptors (24, 27-30).

The benefit of adjuvant therapy for SFT of the pleura remains unclear because of the rarity of these tumors (8, 31). Metastasis to L2 was found a year after the second radical resection of the tumor in the current case, and no clear therapeutic options were available at that point. The MRI findings showed no apparent growth of the metastatic lesion after administration of imatinib mesilate, as well as Bcr-Abl and kit, and is effective for treatment of chronic myeloid leukemia (CML), Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) and gastrointestinal stromal tumor (GIST).

Prunotto et al. examined the in vitro effects of imatinib mesilate as a possible inhibitor of the PDGFR pathway in cells derived from a recurrence of a pleural malignant SFT. Western blotting showed that PDGFR-beta was highly expressed and phosphorylated in SFT-derived cells, and that imatinib mesilate reduced PDGFR-beta phosphorylation and SMA expression (32). De Pas et al. found clinical evidence for the efficacy of imatinib mesilate in a symptomatic patient with a chemo- and radioresistant advanced malignant SFT, with a 21-month lasting major clinical benefit and a consistent reduction in tumor metabolism (33). This suggests that the tumor cells strongly expressed PDGFR, since there were no findings of c-KIT expression in the immunohistochemistry.

In summary, this report presented a case of NICHT with a recurrent solitary fibrous tumor of the pleura with malignant transformation. The hypoglycemic condition may have been caused by HMW IGF-II generated in the tumor. Imatinib mesilate may therefore be useful as adjuvant therapy for unresectable solitary fibrous tumors.

The authors state that they have no Conflict of Interest (COI).

References


