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Malignant Solitary Fibrous Tumor of the Pleura Causing Recurrent Hypoglycemia; Immunohistochemical Stain of Insulin-Like Growth Factor I Receptor in Three Cases

We present three cases of malignant solitary fibrous tumors of the pleura (SFTP) that produced recurrent hypoglycemia. Removal of the tumors produced normoglycemia. The tumors were well circumscribed and lobulated, and consisted of firm masses weighing 1,150 g to 1,450 g with the greatest diameter of 15 to 20 cm. The tumors were composed of spindle cells in fascicles or in a haphazard arrangement and were highly cellular and mitotically active (3-8 mitoses/10 high-power fields), showing histologically malignant features. Ultrastructurally, fibroblastic features of the tumor cells were present. Insulin-like growth factors (IGF) have been implicated in the presentation of hypoglycemia. The serum insulin and C-peptide levels were not elevated. Serum IGF-I levels were also low with values of 97.4, 157.1 and 51.9 ng/mL (ref. 125-317 ng/mL), respectively. However, tumor cells were strongly positive for IGF-I receptor on immunohistochemical analysis. It is tempting to speculate that IGF-I contributes to the hypoglycemia, even though the circulating levels were low.

Key Words: *Pleura; Neoplasms; Insulin-Like Growth Factor I (IGF I); Blood Glucose*

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INTRODUCTION

Solitary fibrous tumors of the pleura (SFTP) are uncommon spindle cell neoplasms with diverse clinical and pathologic features. They are usually benign, but can be malignant, especially if they grow to a large size (1). For many years there has been an ongoing debate as to whether these tumors originate from mesothelial or mesenchymal cells. It is now accepted that the proliferating cells of SFTP are likely to develop from submesothelial connective tissue cells (2). Ultrastructural studies have indicated that these tumors are probably derived from submesothelial connective tissue cells rather than from mesothelial cells (1, 2). Patients with these tumors have frequently suffered from hypoglycemia (2).

We were interested in finding cases of patients associated with recurrent symptomatic hypoglycemia. Hypoglycemia is more commonly associated with large SFTP (3). Often, hypoglycemia is the first manifestation of the illness. The presence of an intrathoracic tumor is usually discovered subsequent to the initial examination for hypoglycemia, which is usually resolved after removal of the tumor. Immunohistochemical studies have revealed immunoreactivities for the IGF-I receptor. Although most of these tumors are benign, SFTP may be locally aggressive and the nature is not always predictable from morphologic examination (3, 4).

We report three cases of malignant SFTP that produced recurrent hypoglycemia.

CASE REPORT

Case 1

A 71-yr-old man was admitted to the hospital with profound hypoglycemic episodes that occurred every night. His blood glucose level was 21 mg/dL. The patient recovered after administration of dextrose. Serum insulin and C-peptide levels were 4.6 μU/mL (2-25 μU/mL) and 0.3 ng/mL (0.3-3.8 ng/mL), respectively. Serum obtained during hypoglycemia showed an IGF-I level of 97.4 ng/mL (115-313 ng/mL) (Table 1). The IGF-II level was not evaluated.

The patient had visited a local clinic 10 months prior to his initial hospital examination with cough, dyspnea,

Table 1. Clinical summary of the patients

Case	Sex	Age (yr)	Symptoms	Glucose (mg/dL)	Insulin (2-25 μU/mL)	IGF I (125-317 ng/mL)
Case 1	M	71	hypoglycemia, cough, dyspnea, night sweat, dizziness	21	4.6	97.4
Case 2	F	55	hypoglycemia, dizziness	17	8.9	157.1
Case 3	F	73	loss of consciousness	33	7.1	51.9

night sweat, and dizziness. A large pleural based mass was demonstrated by chest radiography, for which a sono-guided biopsy was obtained. The tumor was reported as "localized fibrous tumor of the pleura", but it was considered to be inaccessible for radical surgery. The patient suffered relapsing hypoglycemia which improved after glucose administration. A CT scan of the thorax showed a large, mixed, attentuated mass in the left hemithorax. During the subsequent thoracotomy, the tumor was found to be encapsulated and partially adherent to the chest wall and rib. Because of high vascularity, even limited trauma to the surface resulted in profuse bleeding. The tumor was completely removed.

The excised tumor weighed 1,450 g and measured 20 ×17×10 cm. It was encapsulated with a grayish white cut surface and partly lobulated with areas of hemorrhage and necrosis (Fig. 1).

The patient had a good recovery with no further hypoglycemic episodes. Repeat biochemistry showed a serum glucose level of 107 mg/dL, an insulin level of 5.6 μU (2-25 μU/mL), and a C-peptide level of 0.9 ng/mL (0.4-4.0 ng/mL). The IGF-I level had risen to 297.1 ng/mL (115-313 ng/mL). Five months after the operation the patient was fit and well.

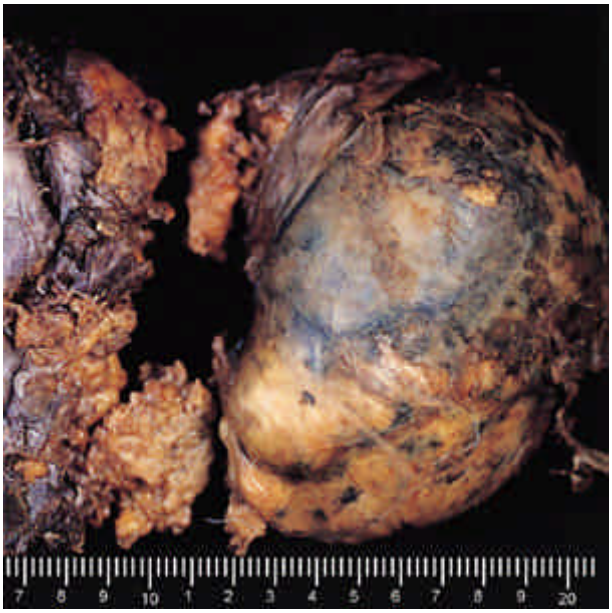

Fig. 1. A large, ovoid, bosselated, well-circumscribed encapsulated tumor measuring 20×17×10 cm and weighing 1,450 g. It is surrounded by a thin translucent, glistening membrane containing a reticulated vascular network in case 1.

Case 2

A 55-yr-old female suffered a sudden attack of dizziness. On admission for investigation she was found to have profound hypoglycemic episodes every night. A dextrose infusion was started. Investigation revealed an apparently homogenous, large, soft extrapleural mass on a chest radiograph. Biochemical analyses revealed a serum glucose level of 17 mg/dL, an insulin level of 8.9 μU/mL (2-25 μU/mL), and IGF-I level of 157.1 ng/mL (78-258 ng/mL) (Table 1).

At surgery, a large, smooth, encapsulated tumor was found in the right hemithorax that arose from the pleura by a narrow stalk and was attached to the adjacent lung and pericardium. It was highly vascular. The tumor weighed 1,150 g and measured 20×17×4 cm. After surgical removal the hypoglycemia was resolved and the patient was clinically and biochemically normal.

Case 3

A previously healthy 73-yr-old woman was admitted with a 2-week history of transient episodes of loss of consciousness and mild dementia associated with sweating and dysarthria. The results of blood biochemical and hematologic studies were normal except for a blood glucose level of 33 mg/dL, and insulin and IGF-I level were 7.1 μU/mL (2-25 μU/mL) and 51.9 ng/mL (125-317 ng/mL) (Table 1). Chest radiography showed a large, well-circumscribed, space-occupying lesion in the right hemithorax causing the right lung to collapse and displacing the mediastinum to the left.

There was no invasion into the mediastinal structures. The tumor was dissected freely and removed from the thorax en masse. Postoperative blood sugar measurements were normal. The tumor was a 15×15×9 cm, lobulated, rubbery mass weighing 1,183 g. The cut surface had a grayish-yellow firm consistency with focal hemorrhage, necrosis, and small cystic spaces.

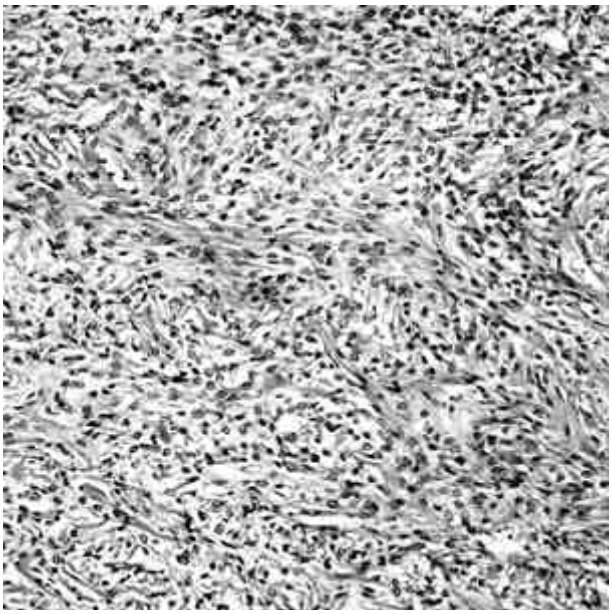

Fig. 2. Elongated tumor cells are arranged in interwoven bundles or haphazardly with scanty collagenous stroma in case 2 (H&E, ×100).

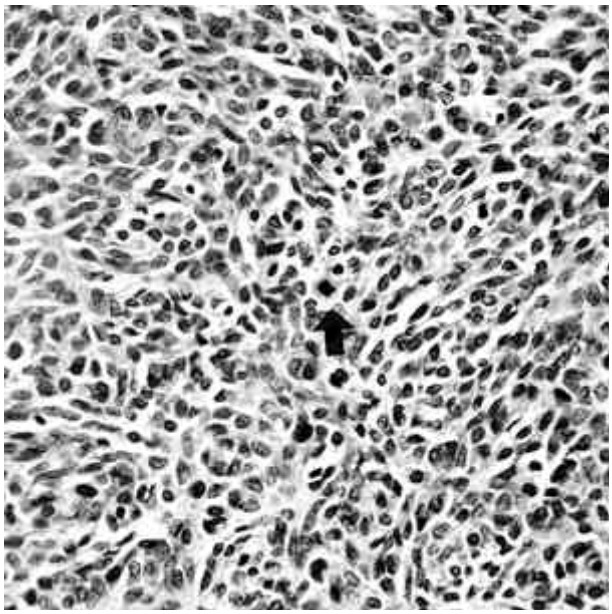

Fig. 3. The tumor is highly cellular and shows diffuse growth of haphazardly arranged short spindle cells with slightly pleomorphic nuclei and scanty cytoplasm with occasional mitotic figures in case 3 (arrow) (H&E, ×200).

Microscopic findings

The tumors were principally composed of spindle or plump ovoid cells with hypercellularity and mild nuclear pleomorphism with foci of necrosis and increased mitotic activity (3-5/10 high-power fields). Uniform spindle cells in interlacing fascicles or in a haphazard arrangement were present (Fig. 2). In the cell-rich areas there was a mitotic count of up to 8 per 10 high-power fields in case 1 (Fig. 3).

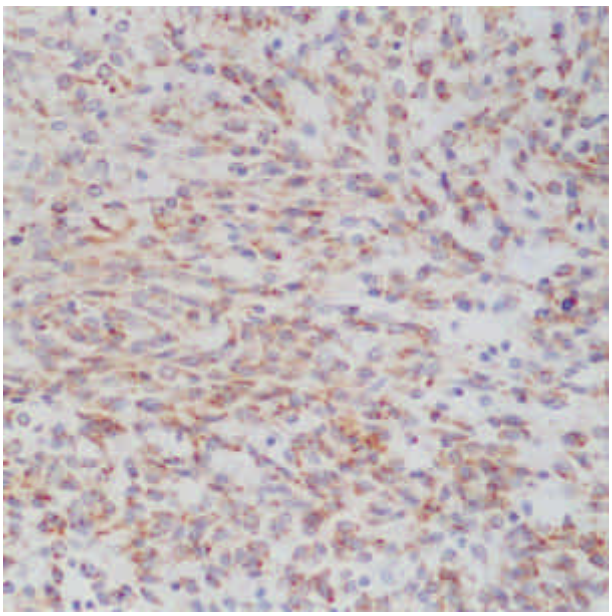

Fig. 4. Immunostaining for IGF-I receptor displays a strong positive reaction in tumor cells in case 3 (AEC, ×200).

Immunohistochemical findings

All three tumors were immunoreactive for vimentin and CD-34 with no staining for cytokeratin, smooth muscle actin, or S100 protein. All of the tumor cells demonstrated immunoreactivity for IGF-I receptor (Fig. 4).

Ultrastructural findings

The tumors were composed of spindled mesenchymal cells with well-developed granular endoplasmic reticulum and indistinct cell borders, often joined together by tight junctions. The cells were separated by a loose collagen-rich matrix. Cells lacked epithelial or mesothelial features (Fig. 5).

DISCUSSION

SFTP is uncommon spindle cell neoplasm occurring most often in the visceral pleura. This tumor has been the subject of much debate regarding its mesothelial versus nonmesothelial nature, although most investigators favor the nonmesothelial origin (3, 5). Mediastinal SFT has no pathogenetic relationship to asbestos expo-

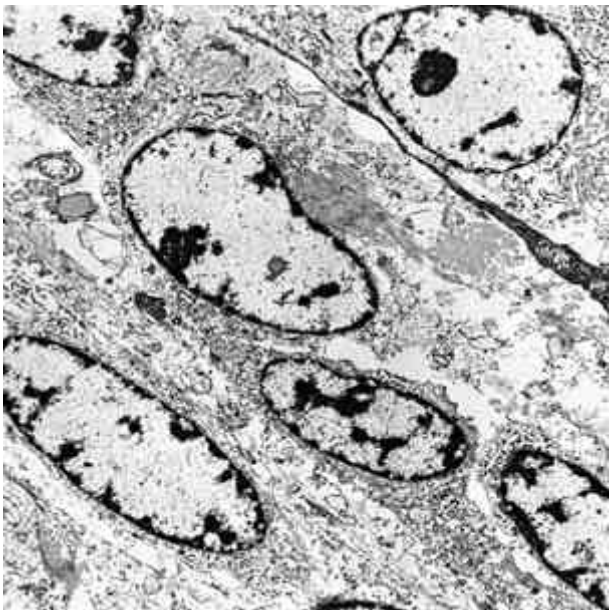

Fig. 5. Tumor shows spindled mesenchymal cells with well-developed granular endoplasmic reticulum and indistinct cell borders in close apposition to focal or abundant collagen in case 1 (×7,200).

sure (3).

SFTP is predominantly a tumor of adult life, most commonly in the sixth to seventh decades, and is evenly distributed between the sexes (3). Hypoglycemia is three times as frequent in females as in males (1). Tumors associated with hypoglycemia were typically located in the right hemithorax (1). In our cases, two of three patients were females with tumors located on the right side.

These tumors are often discovered incidentally on a chest radiograph. Commonly presenting symptoms include cough, chest pain, dyspnea and fever (1, 3). Extrathoracic manifestations of SFTP, which are more often associated with large tumors, include osteoarthropathy, clubbing, and, less frequently, hypoglycemia (1-3, 6, 7). If hypoglycemia is demonstrated in connection with a solitary fibrous tumor, it is referred to as Doege-Potter syndrome (8). Briselli et al. (4) showed that 4% of solitary fibrous tumors are associated with hypoglycemia, more commonly in large, slow-growing tumors with a high mitotic rate.

The mechanism by which large tumors, such as SFTP, induce hypoglycemia has been widely discussed (2, 9). Among possible causes, mechanical pressure on autonomic nerves, increased consumption of glucose by the tumor, inhibition of gluconeogenesis, and secretion of an insulin-like substance by the tumor have been mentioned (2, 9). Insulin-like growth factors I and II are obvious contenders for this role. IGF-I and IGF-II share some of the biologic effects of insulin with a reduced potency (2, 9). However, IGF-I does not appear to mediate tumor-induced hypoglycemia since circulating levels of the peptide are low in patients with this syndrome. In our patients, serum insulin and IGF-I levels were low, as they were in other reports (2, 7), but tumor cells were strongly positive for IGF-I receptor on immunohistochemical stain. It is tempting to speculate that IGF-I contributes to the hypoglycemia, even though the circulating levels were low in our patients.

IGF-II may be produced by the tumor, or it may be produced as a larger precursor (big IGF-II) by the tumor (6, 9, 10). Alternatively, the insulin and IGF-I can be suppressed by IGF-II (6, 7). It now appears that the increased production of an insulin-like substance, IGF-II, leads to the increased use of glucose by peripheral tissues and, perhaps, by the tumor with a concomitant impairment of the counter-regulatory response mediated by the growth hormone (6). An acquired growth hormone deficiency may contribute to the pathogenesis of hypoglycemia by decreasing hepatic glucose output (9). In our patients, IGF-II levels were not evaluated.

The gross neoplasms in our study were large, circumscribed, lobulated masses encapsulated by a thin, translucent, glistening membrane containing a reticulated vascular network. The external surfaces were smooth, bosselated, or lobulated. Neoplasms found in patients with hypoglycemia are usually larger than 10 cm (1). Malignant forms were larger than 10 cm in diameter, and they were usually hemorrhagic and necrotic (1).

In this study, neoplasms were composed of plump to spindled cells in a collagenous background. The tumor cells were cytologically bland, but these areas blended with more hypercellular, mitotically active regions. Blood vessels were prominent and often thick-walled. Necrosis was prominent in cases 1 and 3. High mitotic rates were associated with hemorrhage and necrosis.

Microscopic features that separate benign from malignant tumors have been described (1). England et al. (1) considered neoplasms to be malignant if one or more of the following histologic features are present: 1) high cellularity, 2) mitotic activity (more than four mitotic figures per 10 high-power fields), 3) pleomorphism, 4) hemorrhage, and 5) necrosis. All three tumors herein were considered to be histologically malignant. They also possessed characteristic features of benign localized fibrous tumor of the pleura. Fibroblast-like tumor cells were arranged in bundles in cellular areas or between collagen bundles by dense fibrous stroma.

Tumor cells were negative for cytokeratin, smooth muscle actin, and S100 protein. They were positive for vimentin, CD-34, and IGF-I receptor. The CD-34 reaction is diagnostic because it is consistently positive in

SFTP, but absent in malignant mesothelioma (4, 11).

Ultrastructural studies have supported the fibroblastic nature of SFT in that they show spindle cells with notable profiles of rough endoplasmic reticulum and focal intrareticular collagen fibers (1). Myofibroblasts or myogenous cells have not been observed.

Surgical removal of the tumor is the treatment of choice, if possible, especially as the tumors are more likely to undergo malignant change if they grow to a large size (6). All our patients were treated with wide, local excision. None of the tumors had metastasized and none recurred. Histologic malignancy alone does not always forecast an unfavorable clinical course (1, 5). The single most important indicator of clinical outcome is whether the tumor can be initially and completely excised (1).

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