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Solitary Fibrous Tumor of the Pleura: An Analysis of 13 Cases

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Abstract
Background Solitary fibrous tumor of the pleura is a rare soft-tissue tumor. In search of appropriate diagnosis and treatment methods, we present our experience with 13 patients.
Methods The medical charts of 13 patients treated during the last 5 years were reviewed, as well as pathological records, including immunohistochemical stains. Follow-up data were obtained. In addition, a literature review with regard to treatment and clinical outcome was performed.
Results Our series consisted of four men and nine women with a mean age of 47 years. Two were diagnosed before operation with ultrasonography-guided core needle biopsy. All patients underwent primary surgical treatment, and four of them were resected by video-assisted thoracic surgery. Seven tumors were malignant and the other six were benign. Immunohistochemical staining showed nestin was positive in three malignant solitary fibrous tumors of pleura (3/7), which were negative for CD34. Except for one, all patients were followed-up for 3 to 35 (mean, 14.5) months. Among them, one patient experienced a recurrence and one patient died of brain metastasis.
Conclusion Ultrasonography-guided core needle biopsy combined with immunohistochemical analysis might be a safe and rapid method to provide a confirmatory diagnosis before resection. For smaller, pedunculated tumors, video-assisted thoracic surgery could be a powerful and useful approach. We speculate that CD34-negative and nestin-positive might be a malignant marker for solitary fibrous tumor of pleura.

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Introduction

Solitary fibrous tumor (SFT) is a rare mesenchymal neoplasm that most commonly involves the pleura, which probably derives from fibroblast [1, 2]. Approximately 800 cases of solitary fibrous tumor of the pleura (SFTP) have been reported in the literature [3]. SFTP often is asymptomatic, and compared with other mesenchymal neoplasms, it has no characteristics in radiology. Resection is mandatory for all the tumors and the final diagnosis should be based on histopathology. In search of appropriate diagnosis and treatment methods, we present our experience with 13 patients.

Patients and methods

Between January 2002 and January 2007, 13 patients of a SFTP were treated in Department of Thoracic Surgery, Zhongshan Hospital, Fudan University. All clinical, surgical, and pathological records were reviewed and complete follow-up was assured. Chest x-rays and CT scans were reviewed to determine site, size, and number of primary pleura tumors, as well as the presence of vascular invasion

and distant metastases. Three patients underwent an ultrasonography-guided core needle biopsy (16G needle, BARD). All the tumors were removed surgically through thoracotomy or video-assisted thoracic surgery (VATS).

Tissue specimens were fixed in formalin and embedded in paraffin. Deparaffinized sections were stained with hematoxylin and eosin (H&E). From all cases, one or two tissue blocks were analyzed immunohistochemically by using the primary antisera (DAKO, Carpinteria, CA) on consecutive slides with the EnVision (DAKO, Carpinteria, CA) procedure. Primary antibodies included cytokeratin, vimentin, CD34, nestin, Bcl-2, EMA, SMA, and S100.

All the slides were re-examined; tumors were classified as benign or malignant according to criteria reported by England et al [4]: 1) high mitotic activity (>4 mitosis/10 high-power fields); 2) high cellularity with crowding and overlapping of nuclei; 3) presence of necrosis; 4) pleomorphism.

Results

Clinical features

The clinical features of the 13 patients are presented in Table 1. Four patients were male and nine were female (mean age, 47 (range, 27–72) years). Cough ($n = 3$), dyspnea ($n = 2$), chest distress ($n = 4$) were common symptoms. Clubbed fingers presented in one patient (case 12). Six tumors were incidental findings. Neither symptomatic hypoglycemia nor abnormal blood glucose was observed before operation. A smoking history was present in three male patients and no patient had asbestos exposure.

Chest X-ray showed a solitary opacity in hemithorax (Fig. 1A). Preoperative CT scan was performed in all the patients. A single, well-demarcated, round or ovoid mass was found in all cases (Fig. 1B), which was heterogeneous in four (case 2, 9, 10, 13) and homogeneous in nine. The density of mass was lower than the musculature. Calcification and pleural effusion were also found in CT (case 12, case 13). MRI was carried out only in one patient, which displayed a single ovoid mass with high intensity on T2-weighted images (Fig. 1C). For case 9, middle lobe bronchus of right lung was occluded by a mass in bronchoscopy, indicating the invasion of bronchus.

The ultrasonography-guided core needle biopsy was performed in three patients. Two of them showed at least one feature of high cellularity, necrosis or hemorrhage. Both of them were diagnosed as malignant SFTP before operation. No complications, such as bleeding, pneumothorax, happened during this procedure.

At surgical exploration, a single lesion was detected in all the cases, 2 cm to 24 cm in diameter (Table 1). The tumor arose from the visceral pleura in 10 patients; among them, a pedicle was present in four (Fig 1D) (case 5, 6, 8, 11). One of the non-pedicle tumors (case 9) invaded the lung parenchyma and also infiltrated the middle and the inferior lobar arteries; the other one (case 13) adhered to the left inferior lobe. In the other three patients, tumors arose from the mediastinal pleura; all were sessile and two (case 3, 10) adhered to the adjacent tissues.

Table 1 Clinical features of 13 patients with SFTP

Case	Age (yr)/sex	Location/ side	Tumor size(cm)/ capsule	Surgery method	Hospital stay (day)	Follow-up (mo)
1	58/M	LP/L	7/Yes	T	14	7 m/DFA
2	29/F	MP/L	6/Yes	T	12	lost
3	47/F	MP/L	13/No	T	22	35 m/ DFA
4	56/F	LP/L	17/Yes	T	17	28 m/ DFA
5	61/M	LP/L	2.5/Yes	VATS	7	26 m/ DFA
6	72/F	LP/L	3/Yes	VATS	7	17 m/ DFA
7	44/F	RP/R	13Yes	T	12	17 m/ DFA
8	37/M	RP/R	7/Yes	VATS + ST	11	10 m/ DFA
9	33/F	RP/R	11/No	T	18	6 m/D
10	27/F	MP/R	15/No	T	18	10 m/Re
11	39/F	RP/R	6/Yes	VATS	6	7 m/DFA
12	52/M	LP/L	24/Yes	T	10	8 m/DFA
13	60/F	LP/L	9/Yes	T	9	3 m/DFA

D die, *DFA* disease-free alive, *F* female, *L* left, *LP* left pleura, *M* male, *MP* mediastinal pleura, R = right, *Ra* radiotherapy, *Re* recurrence, *RP* right pleura, *T* thoracotomy, *VATS* video-assisted thoracoscopic surgery, *VATS + ST* video-assisted thoracoscic surgery plus a small thoracotomy

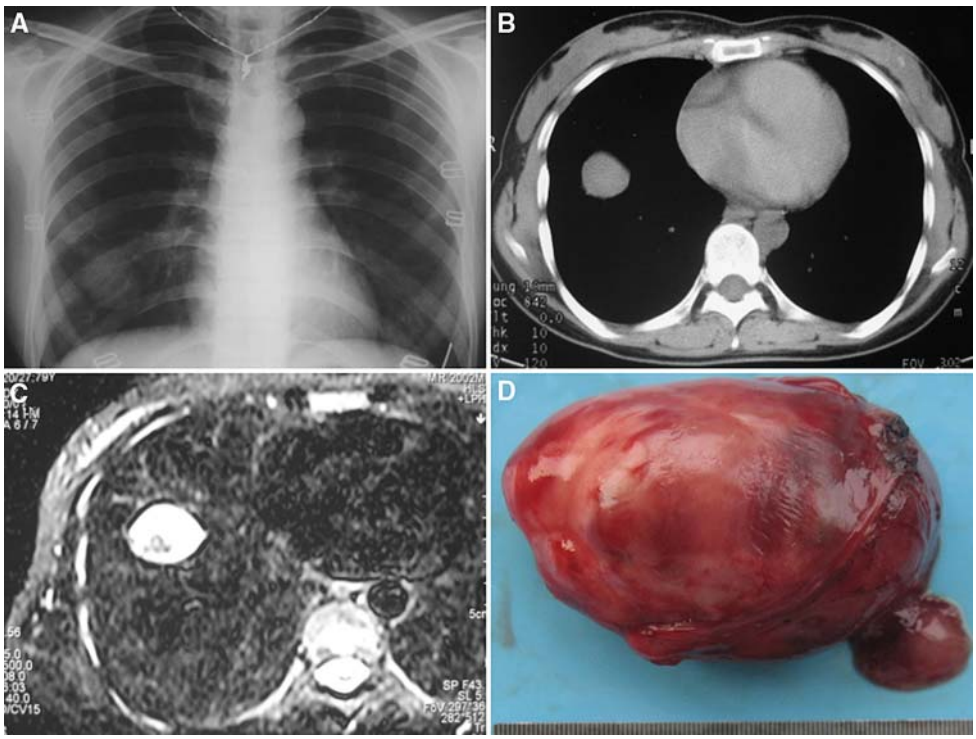

Fig. 1 Chest x-ray of case 11 showed a solitary opacity in her right lower hemithorax (**A**); an ovoid, sharply delineated and homogeneous mass was displayed in CT scan (**B**); in MRI, the signal intensity of the tumor was high on T2-weighted images (**C**); in gross, the tumor is an encapsulated mass with a pedicle (**D**)

In our series, nine tumors were resected by a thoracotomy and four by VATS (including VATS plus a small thoracotomy in one patient). Two tumors (case 3, 10) in mediastinum were resected combining with a partial lung and a partial thymus resection, respectively. A left inferior lobectomy was performed on case13. The tumor with lung invasion (case 9) was partially resected with combination of a right middle lobectomy.

For all the patients, the postoperative course was uneventful. The mean hospital stay time was 12.5 days. Four patients treated by VATS had a shorter mean hospital stay time than those undergoing thoracotomy (7.8 vs. 14.7 days; Table 1).

All cases except for one (case 2) were followed-up for 3 to 35 (mean, 14.5) months. Ten patients had no recurrence and metastasis. Diffuse metastases of parietal, visceral pleura, and lung in the same hemithorax occurred 10 months after operation in one patient (case 10), who presented with breathlessness and cough. Reoperation was performed but the metastatic tumors were irresectable completely. She is still alive with residual tumors. Radiotherapy was administered in one patient (case 9) for a brain metastasis, which was found 1 month after incomplete resection. However, it had no valid effect. Progressive brain metastasis contributed to her death 5 months later.

Pathologic examination

Seven tumors were malignant and the other six were benign. All tumors except for two (case 9, case 10) had complete capsules and free margin in macroscopy. Microscopically, they showed predominantly fibrous lesions containing large collagenized areas and thick/hyalinized-walled vessels (Fig. 2A). In seven malignant cases, cellular areas often were present and showed nuclear overlapping, clumping of chromatin, and brisk mitotic activity. No atypical mitosis was detected. In two cases, a prominent hemangiopericytic arrangement of tumor cells around a rich vascular framework could be noticed. Besides these, four malignant tumors showed obvious hemorrhage in microscopy (Table 2).

In immunohistochemical analysis, all cases were positive for vimentin but negative for cytokeratin, EMA, SMA, or S100. Malignant SFTP (4/7) was less frequently positive for CD34. When positive, the staining was usually less strong than in benign SFTP (6/6) and often focal (Fig. 2B). Nestin was only detected in malignancies (3/7) that were negative for CD34 (Fig. 2C). Bcl-2 (11/13) was focally expressed (Table 2).

Electron microscopic examination was performed in three tumors (cases 8, 12, and 13). Ultrastructurally, the tumor cell displayed the features of fibroblast (Fig. 2D).

Discussion

Solitary fibrous tumor of pleura is a rare mesenchymal cell tumor, which has gained increasing recognition during the last two decades as a discrete pathologic entity. Its presentation is nonspecific, although the selection of

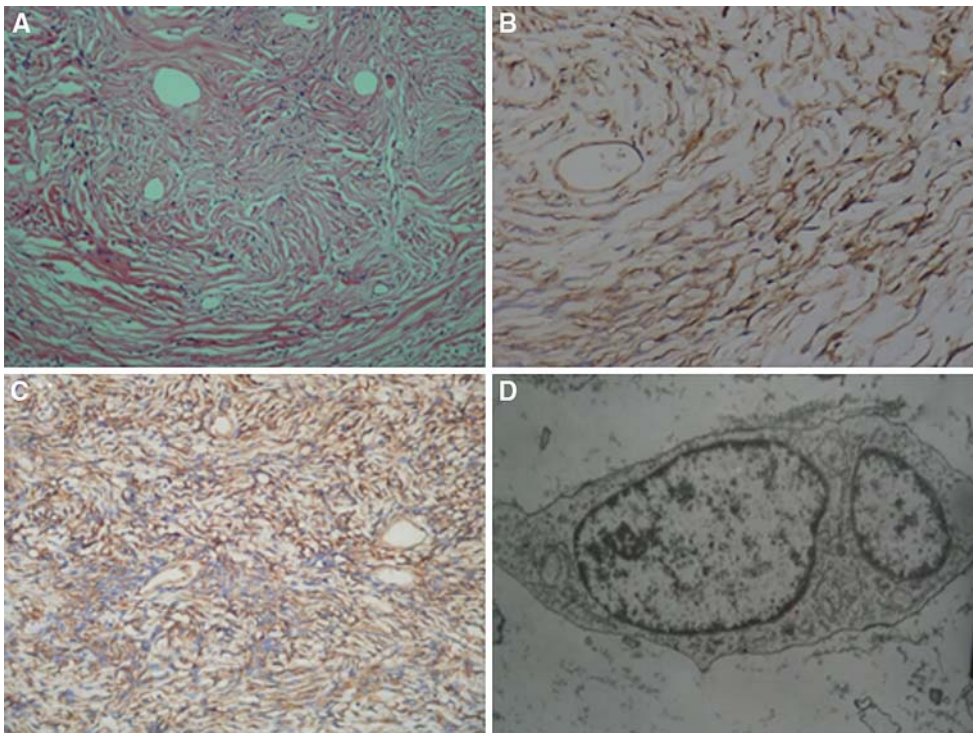

Fig. 2 Solitary fibrous tumor component showing haphazard spindle cells growing among dense collagen bundles (hematoxylin-eosin, original magnification *100) (**A**); diffuse positive staining in benign solitary fibrous tumor component (CD34 immunohistochemistry, original magnification *200) (**B**); focal staining in malignant components (nestin, immunohistochemistry, original magnification *200) (**C**); electromicroscopy reveals fibroblast-like tumor cells with irregular-shaped nuclear, well-developed, rough endoplasmic reticulum and scattered collagen in the cytoplasm (EM*6500) (**D**)

Table 2 Pathologic features of SFTP

Case	Pleomorphism	High cellularity	Necrosis	Mitoses, No/10 HPFs	Hemorrhage	Benign/ malignant	CD34	Nestin	Bcl-2
1	Yes	Yes	Yes	4	No	M	++	−	+
2	No	Yes	No	2	Yes	M	+	−	+
3	No	No	No	3	No	B	++	−	+
4	No	No	No	1	No	B	++	−	+
5	No	No	No	0	No	B	++	−	+
6	No	No	No	0	No	B	++	−	+
7	Yes	Yes	No	1	Yes	M	++	−	+
8	No	No	No	1	No	B	++	−	+
9	Yes	Yes	Yes	5	Yes	M	−	++	+
10	Yes	Yes	Yes	11	Yes	M	−	++	−
11	No	Yes	No	1	No	M	++	−	+
12	No	No	No	0	No	B	++	−	+
13	No	Yes	Yes	10	No	M	−	++	−

B benign, *M* malignant

appropriate treatment depends on the preoperation diagnosis.

The majority of patients were asymptomatic at presentation [4–6]. In our series, seven patients had nonspecific thoracic symptoms caused by the compression. Hypertrophic pulmonary osteoarthropathy (HPO) is the specific symptom of SFTP, which has been reported in up to 22% of patients (especially in tumors >7 cm in diameter) [7] and also occurred in case 12. However, the reason remained uncertain. Significant hypoglycemia also is related to SFTP in approximately 4% of cases [7], which was contributed to the production of insulin-like growth factors by the tumor cell [3]. However, in this study, no one presented with this symptom and all patients' blood glucose was in the normal range. Therefore, we propose that the association between hypoglycemia and SFTP needs further investigation.

Radiological examination was useful to diagnose SFTP. The manifestation of the tumor in radiology depended on

size. They varied from a sharply delineated round or lobulated mass, with or without pleural effusion, to opacification of complete hemothorax. In four patients, CT scan detected heterogeneous tumors, which contained areas of hemorrhage and necrosis microscopically. We could identify the malignancies according to the distinct CT display. In addition, MRI appearance of SFTP can reflect the relative amounts of fibrous tissue and cellular component. For example, tumors with abundant tumor cells would display high signal intensity on T2-weighted images [8], as in case 11.

SFTP can be a difficult diagnosis to establish in limited diagnostic samples, such as a needle-core tissue biopsy. However, in the present study, we identified two malignancies as if any one of the malignant morphologic features was detected by ultrasonography-guided core needle biopsy. Moreover, immunohistochemical analysis played a key role in differentiating SFTP from mesotheliomas and other similar neoplasms [9–11]. SFTP were positive for vimentin, but they lacked cytokeratin expression. In addition, most SFTP were positive for CD34, which was a reliable marker for distinguishing SFT from mesothelioma [9]. Bcl-2 also was helpful in diagnosis of SFTP [12], especially in the CD34-negative ones. Therefore, we proposed that ultrasonography-guided core needle biopsy combined with immunohistochemical analysis was a safe and rapid method to provide a confirmatory diagnosis, especially for larger lesions. The validity of this method was confirmed by others [11].

The definitive diagnosis was obtained by histopathology after resection. Identification of malignancy was established on the basis of criteria suggested by England et al, which are widely accepted and used in most recent series [13, 14]. Size bears no relation to whether the tumor is benign or malignant [15]. In our series, a giant tumor (24 cm diameter) was found in case 12; however, in pathology, it was benign. Interestingly, the tumor of case 11 was small but malignant because it showed high cellularity microscopically. Besides, we found that the expression of nestin in malignant tumors was obviously higher than in benign ones. Three tumors (cases 9, 10, and 13) with CD34-negative were strongly positive for nestin. We speculate that CD34-negative and nestin-positive might be a malignant marker for this disease. To our best knowledge, this study is the first report of the nestin in SFTP.

Nestin is an intermediate filament protein predominantly expressed in neuroectodermal stem cells, skeletal muscle progenitor cells, and tumors that originated from these cells [16]. In malignant SFTP, nestin expressed in tumor cells with CD34-negative, which suggested dedifferentiation of tumor cells. In addition, Yokoi et al [17] had postulated two mechanisms for the development of malignant SFT. The first possibility is that these malignancies occur de novo and grow rapidly. The investigator demonstrated in three cases from the pleural cavity. The other possible mechanism is transformation ("dedifferentiation") within a preexisting, benign SFT. We noted that the overtly malignant component also exhibited absence of CD34 and presence of nestin expression compared with the typical SFT architecture, which also supported the second hypothesis.

The best treatment of benign and malignant SFTP was complete surgical resection, with 1 to 2 cm margins if possible [5]. Resection can be performed through thoracotomy or VATS. In our series, VATS was performed to resect four smaller tumors with an obvious pedicle, including a malignant one. It may represent a valid option because of advantages in terms of postoperative pain, reduced respiratory impairment, and cosmetic result. Compared with thoracotomy, the patients treated by VATS also had a shorter mean hospital stay time. However, the method is only suitable for smaller, pedunculated tumors, even the malignant case (case 11) [5, 6]. Takahama et al [6] also considered VATS as a powerful and useful approach. It is necessary to perform a small thoracotomy, in addition to VATS, to remove a larger tumor. Besides, great care must be taken when removing these tumors from the chest cavity, because contact metastases have been reported [18].

Larger tumor with an invasive behavior may be difficult to be resected and enlargement of resection may be necessary. Magdeleinat et al [13] reported 11 extensive resections among 60 patients, including lung parenchyma, osteomuscular, chest wall structure, diaphragm, and pericardium.

The best prognostic factor was the completeness of resection [4, 13, 19]. In our experience, all the benign SFTP were resected completely, with no recurrence observed during the follow-up period. This result was extremely consistent with other authors [13, 20]. However, occasional recurrences of benign tumors have been reported in other studies [4, 14]. The reason is still unknown, which may be contributed to an insufficient resection. On the contrary, the malignant tumors do not have good prognosis unlike benign ones. In the series of 223 cases reported by England et al [4], 55% of the histologically malignant tumors had an aggressive behavior. Presently, there is no firm evidence in the literature that supports adjuvant radiotherapy or chemotherapy after resection of malignant tumors [5].

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