Original Article Clinicopathologic features and prognostic factors of extrapleural solitary fibrous tumor

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Abstract: Extrapleural solitary fibrous tumor (ESFT) is a rare tumor and its prognosis features are not clear. In this study, the clinical manifestations, imaging characteristics, and pathology features of ESFT were analyzed. Long-term survival (LTS) was analyzed in detail. The histological characteristics and immunohistochemistry expression profiles were compared between, before, and after relapse. Of 29 ESFT, six patients (20.7%) developed recurrence and metastasis to other organ. Cohort median follow-up was 75 months, and the median disease free survival was 111 months. Both the primary and metastatic tumor had similar imaging features especially a single focal metastatic cases. ESFT was found to be well circumscribed and most primary tumors were separated from the peripheral tissue by tumor capsule. Compared with the primary tumor, metastatic SFT was not well circumscribed. The high cell density and atypia; perivascular growth pattern of cells; increased karyokinesis can be found in the tumors. Immunohistochemical staining indicated that the metastatic tumor revealed abnormal expression of P53 and high-er Ki67 index. There was no significant difference between the primary ESFT and metastatic tumor both in clinical and radiological manifestation. We found that tumor size larger than 10 cm, incomplete tumor capsule, more than 2 mitosis figures per high power field, Ki67 index larger than 3% and overexpression of P53 were important pathologic risk factors of recurrence and/or metastasis of ESFT. Metastasis of ESFT may present itself over a decade following the surgery. Clinical follow-up is imperative for early detection of tumor relapse and metastasis.

Keywords: Extrapleural solitary fibrous tumor, recurrence and metastasis, prognosis

Introduction

Solitary fibrous tumor (SFT) is a rare spindle cell mesenchymal tumor that occurs mostly in the visceral pleura. In 1931, Klemperer and Rabin reported the first case of SFT, which was initially thought to arise from mesothelial/submesothelial mesenchymal cells [1]. With the development of immunohistochemistry and electron microscopy, SFT was identified from the CD34positive dendritic mesenchymal cells that diffusely distributed in human connective tissues. Most of the solitary fibrous tumors localized in the thoracic cavity. But it may also involve a wide variety of the extrapleural sites. Extrapleural SFTs are now known to occur in multiple sites with diverse morphology and manifestations. They generally behave in a benign manner with a relatively favorable prognosis; however, most of the clinical doctors wonder the

clinical course of SFT because about 15%-20% cases may present relapse, metastasis, and invasiveness. Meanwhile, some of the metastatic cases had similar clinical and imaging manifestations. The staging of SFT of pulmonary pleura was well recognized by Perrot [2, 3]. The World Health Organization (WHO) Classification for Pathology and Genetics of Tumors of the soft tissue was also adopted to access the risk-stratification. However, there is no a definite criteria to predict the clinical course of extrapleural SFT. Several studies revealed that complete resection with tumor-free margins represent the best predictor of good prognosis of pleural-pulmonary SFT [4]. Herein, we retrospectively reviewed 29 cases of extrapleural SFT, analyzed the clinicopathologic features, imaging characteristics, immunophenotypes as well as the biological behavior.

		Metastatic SFT	Non-metastatic SFT	P value	χ²
Tumor size (mean, cm)	≤ 10	2	20	0.006	7.472
	> 10	4	3		
Integrity of the tumor capsule	Complete capsule	1	23	0.000	23.162
	Incomplete capsule	5	0		
Cell dysplasia	Without cell atypia	4	21	0.119	2.249
	Mild to moderate	2	2		
Necrosis	Without necrosis	5	22	0.289	1.125
	With necrosis	1	1		
Mitotic figure per HPF	< 2	1	22	0.000	18.091
	≥2	5	1		
Ki67 index	< 3%	1	23	0.000	23.16
	≥3%	5	0		
P53 expression	Negative or weakly expressed	4	23	0.004	8.235
	Diffused expression	2	0		
TNM stage	IA	1	7	0.319	3.243
	IB	4	16		
	IIA	1	0		

Table 1. The pathology features of primary SFT and metastasis SFT

Materials and methods

A total of 29 surgically-removed specimens of extrapleural SFT were obtained from the Department of Pathology in Shanghai East Hospital between October 2007 and December 2014, were analyzed in the present study. The clinical information including age, gender, clinical symptoms and tumor location, the image and pathology data was collected.

All the completely resected specimens were fixed with 4% neutral buffered-formalin, routinely dehydrated, and embedded with paraffin. 2-µm thick sections were then obtained and stained with hematoxylin and eosin. All of the slides were reviewed by two pathologists (Y Han and J Wang). The clinicopathologic parameters analyzed in the study were the following: the patients' age and gender, symptoms at diagnosis, tumor size, and location, radiology, gross appearance, cell density, cell dysplasia, mitosis figures (per HPF) and necrosis (present or absent). All of the parameters listed above were recorded in both primary tumor and the metastatic tumor.

Immunohistochemical analysis was performed using Dako EnVision Systems and the primary antibodies-CD34, CD99, bcl-2, desmin, vimentin, smooth muscle actin (SMA), S-100, epithelial membrane antigen (EMA), panCk, and ki67 (both, the system and antibodies were purchased from DAKO Corporation, Carpinteria, CA, USA). The validation of the immunohistochemical analysis was performed through positive and two series of negative controls. A tumor was quoted as highly expressing P53 when at least 5% of tumor cells reacted with an intensity staining of at least 2+.

All of the patients were followed up and the survival data were documented. The correlation between clinicopathologic parameters and immunohistochemical variables was calculated using Pearson Chi square test (SPSS version 13.0, Chicago Inc). A difference with probability (*P*) values < 0.05 was considered as significant.

Results

Clinical features

17 males and 12 females were collected for this study. The mean age was 59 years (range from 25-84) at the time of surgery, and the peak age was 60-80 years. The primary sites of investigation included the liver (n=2), kidney (n=1), vulva (n=1), broad ligament (n=1), pelvis (n=1), retroperitoneum (n=3), cerebellum (n=1), and soft tissues-head and neck, chest wall,



Figure 1. The imaging of primary ESFT and metastatic ESFT. A. Primary hepatic ESFT showed clear borderline, heterogeneous density, and rich of blood supply on CT scan. B. Hepatic metastatic SFT presented a unifocal solitary lesion and obscured division with peripheral structures. C. MRI showed that the primary retroperitoneum tumor was well circumscribed with focal/diffuse low signal intensity on T2 weighted images, and enhancements in euangiotic areas. D. MRI image of recurrent SFT were characterized by intensified lobulated mass with clear borderline.

thigh, and groin (n=20). With respect to the clinical symptoms, fourteen percent (4/29) of patients were asymptomatic and diagnosed incidentally. Most patients with soft tissue tumor presented with painless, but gradually enlarging mass; the patients with hepatic, retroperitoneal, or pelvic tumor often experienced abdominal pain and swelling; and the patients with renal tumor presented with lower back pain and hydronephrosis. Nevertheless, other symptoms, such as hypotension and hypoglycemia were not observed in any of the patients. All patients were surgically treated with curative intent. All of the tumors did not showed positive lymph nodes and metastasis at the time of surgery. Of the 29cases, 27.6% (8/29) were in stage IA, 69% (20/29) in stage IB and 3.4% (1/29) in stage IIA.

The postoperative follow-up revealed 20.7% (6/29) of the cohort present with recurrence and metastasis over a span of 4 to 11 years after the surgery (**Table 1**); the list included four patients with liver metastasis, one patient with lung metastasis, and one with neck metastasis. The subsequent follow-up after second sur-



Figure 2. Gross features of hepatic primary SFT and metastatic SFT. A. Hepatic primary SFT was well circumstanced with solitary fleshy cutting sections (Fresh specimen). B. The hepatic metastatic SFT was not well circumscribed with irregular appearance and without necrosis and cystic degeneration (Formalin fixed specimen).

gery revealed one patient with soft tissue (neck and back) metastasis, one with vertebral, pulmonary, and multiple intrahepatic metastases, while two patients died of unrelated causes. Cohort median follow-up was 75 months (range, 32-180 months), and median disease free survival was 111 months.

Imaging characteristics

CT scan showed that all primary tumors were solitary with unequal size, clear borderline, heterogeneous density, and rich of blood supply; additionally, the solid components were enhanced to different degrees (Figure 1A). However, four of the six cases with liver metastasis presented unifocal solitary lesions and obscured division with peripheral structures (Figure 1B). Likewise, MRI showed that the primary tumors were well circumscribed with focal/diffuse low signal intensity on T2 weighted images, and enhancements in euangiotic areas (Figure 1C). The images of recurrent SFT were characterized by intensified lobulated mass (Figure 1D).

Pathological findings

The primary tumor size ranged from 5-14 cm in maximum dimension and the mean tumor size was 9.4 cm. Macroscopic examination revealed that the tumors were well circumscribed, and most tumors had a complete capsule with nodular, off-white, solid, and tenacious cutting

section. Two cases of malignant SFT, however, were not well circumscribed and showed necrosis and cystic degeneration; while metastatic tumors were also not well circumscribed, but were softer (**Figure 2**).

On microscopic evaluation, the tumors were found to be well circumscribed and composed of different proportions of hypocellular and hypercellular regions. Collagen bands, thinwalled branching, hemangiopericytoma (HPC)like vessels, as well as perivascular hyalinization were observed. In hypocellular regions, the tumor cells were spindle-shaped and thin, and were associated with anisometric collagenous fascicles and edema-like matrices (Figure 3A). Some tumors were lobular, while others were hypercellular and arranged in a number of ways, including fascicular, palisading, storiform, woven, bud-like, and micro-capsular growth patterns. Nearly half of the cases in this study presented different degrees of interstitial myxoid degeneration (Figure 3B). Spindle or ovoid tumor cells displayed scant cytoplasm, uniform chromatin, unremarkable atypia and karyokinesis, and even bud-like nested tumor cells (Figure 3C) and mature adipose cells (Figure 3D) (as was presented in one case) were observed. The mitosis figures were seldom seen. Histologically, malignant SFT presented high-grade spindle cell sarcoma-like morphology, obscured tumor boundary, invasive growth, moderate-to-severe cell atypia,



Figure 3. The histology and immunohistochemistry of ESFT. A. The tumor cells were spindle-shaped and thin in the hypocellular region, and were associated with anisometric collagenous fascicles and edema-like matrices (HE × 100). B. In the hypercellular region of ESFT, the tumor cells arranged as fascicular pattern with focal interstitial myxoid degeneration (HE × 100). C. In the collagenous background, the spindle or ovoid tumor cells displayed bud-like nests (HE × 100). D. In some cases, adipose formation was observed (HE × 100). E. Metastatic SFT in liver had an infiltrative growth pattern and the hepatic sinusoid cell growth patterns were observed in some areas (HE × 200). F. In the metastatic cases, the tumor cells showed perivascular growth pattern with epithelioid morphology (HE × 200). G. The tumor cells had moderate-to-severe atypia, medium cytoplasm, marked pathologic karyokinesis (HE × 200). H. Immonohistochemical staining indicated that Ki67 index was higher in the metastatic cases than primary ESFT (EnVision × 200). I. In some case of ESFT, P53^{mutant} was highly expressed in both primary and metastatic ESFT (EnVision × 200).

and marked karyokinesis (> 4/10 HPF). Metastatic SFT had an infiltrative growth pattern and showed collagen bands, local necrosis, homogeneous spindle cells, narrow staghornbranching vascular patterns, and (in some areas) hepatic sinusoid cell patterns (**Figure 3E**). Moreover, the tumor cells had moderateto-severe atypia, medium cytoplasm, marked pathologic karyokinesis, and epithelioid morphology (**Figure 3E**). In the metastatic cases, the tumor cells showed perivascular growth pattern (**Figure 3F**). The mitosis figure per 10 HPF was also higher in metastatic tumor (median 11, range 4-25) than primary (median 2, range 0-4) tumors (P < 0.01) except for primary malignant tumor (**Figure 3G**).

All the cases subjected to immunohistochemical analysis expressed Vim and CD34. Among them 90% of (26/29) expressed CD99 and 79% (23/29) expressed bcl-2. S-100, SMA, neuron specific enolase (NSE), and EMA expressions were focally positive, and the budlike cells were negative for CD68. In addition, the expressions of panCK, desmin, CD117, glial fibrillary acidic protein, and calretinin were found to be negative. Ki67 index was used to assess the tumor proliferation. P53^{mutant} was

	Sex	Age (years)	Primary site	Tumor size (cm)	Metastatic site	Histological characteristics of metastatic tumor	Time interval (years)	Treatment
1	Μ	26	Lung	12 × 10	Liver, chest wall	Increased atypia and karyokine- sis with pathological karyo- kinesis. Perivascular growth patterns, without necrosis.	4	Surgical resection
2	Μ	64	Thigh	22 × 14 × 8	Lung	Malignant, with necrotic and euangiotic areas.	4	Surgical resection
3	F	56	Cerebellum	4.5 × 4	Liver, thoracic vertebra	Atypical hyperplasia with increased Ki67 index but no necrosis.	11	Surgical resection
4	F	59	Thigh	8 × 6	Liver	Increased atypia and karyokine- sis with epithelioid cells.	9	Surgical resection
5	F	68	Mediastinum	10 × 8	Neck	Malignant with adipogenesis.	10	Surgical resection
6	F	49	Pelvis	21 × 15 × 9.5	Liver	Malignant with increased atypia and karyokinesis > 4/10 HPF without necrosis.	5	Surgical resection

Table 2. Clinicopathologic features of metastatic SFT

also assessed in all tumors. Among them, Ki67 index was increased in the metastatic cases and three cases positively expressed P53^{mutant} and two of them showed metastasis (**Figure 3H** and **3I**).

Compared with the morphology of primary surgical specimens, metastatic tumors had (1) increased cell density and atypia; (2) perivascular growth pattern of cells; and (3) increased karyokinesis, Ki67 proliferative index, and pathological mitosis.

We analyzed multiple factors related to recurrence and metastasis. Clinically, 14% patients presented tumor-related symptoms. Tumor size (larger than 10 cm), integrity of the tumor capsule, mitosis figures (> 2/HPF), Ki67 index and P53^{mutant} expression pattern were statistically significant between the metastatic SFT group and the non metastatic SFT group by Chi's square analysis. But the cell atypia, the presence of necrosis and TNM stage were not statistically significant (Table 2). In this study, tumor size lager than 10 cm, incomplete capsule of the tumor, more than 2 mitosis figures per high power field, mean MIB index greater than 2% were the predicting factors of indicating expleural SFT metastasis.

Discussion

SFT, a relatively infrequent mesenchymal spindle cell tumor characterized by fibroblast differentiation. SFT usually occurs in the pleura, but may occur in nearly all human anatomic sites, predominantly in head, neck, and soft tissues, while the parenchymatous organs are rarely affected. Majority of the patients with ESFT demonstrate a benign clinical course after a complete surgical resection, whereas some of the tumors showed malignant behavior resulting in recurrence or metastasis. So far there are still no definite factors predicting the prognosis of ESFT. Herein, we studied 29 cases of ESFT, analyzed the imaging, morphology and immunophenotypic changes in the corresponding recurrence or metastatic cases and assessed the prognostic factors to predict recurrence and survival.

Clinically, it is difficult to differentiate between benign and malignant SFTs based on the imaging data and puncture biopsy. Our analysis showed that primary ESFT and the metastatic tumor, especially a single focal one, had similar imaging features though the enhancements may be observed in the latter. It remains a challenging clinical topic of radiologic diagnosis. The pathological examination is essential for the ultimate diagnosis.

We also confirmed that ESFTs are clinically and histologically similar to their pleural SFT, such as well circumscribed with off-white and solid cutting sections, and various growth patterns. In addition, there was a characteristic lobulated growth pattern, along with alternate hypercellular and hypocellular regions. The spindle or ovoid tumor cells can arrange in fascicular, storiform, woven, and HPC-like growth patterns. Based on the major morphological characteristics, we classified ESFTs into fibrous, hypercellular, lipomatous, and giant cell-rich subtypes. The biological behavior of these subtypes remained uncertain. Furthermore, one case originated in broad ligament showed prominent cystic structures of unequal sizes with intracystic serous liquid lacking cyst-lining epithelial cells and with pericystic immature ropy spindle cells that mimic ovarian mesenchymal cells. It was reported that a number of ESFT presented with cysts of unequal sizes. Immunohistochemical analysis revealed a few cyst-lining epithelial cells expressing CD31 and factor VIII, and spindle cells expressing CD34, CD99, bcl-2, focal ER, and PR [5, 6].

Compared with the primary tumor, there were some histology and immunophenotypic differences in the recurrence or metastasis cases. Metastatic ESFT has increased cell density and atypia, local epithelioid morphology, higher karyoplasmic ratio, visible nucleoli and increased karyokinesis with perivascular growth pattern, and even pathological mitosis. Several studies have reported epithelioid features in tumor cells [7, 8]. The epithelioid cells focally expressed EMA [8]. But in our series the epitheliod cells do not expressed epithelial biomarkers, such as EMA and keratin.

The immunophenotypes of ESFT include the classical CD34, CD99, and bcl-2. These markers were important for differential diagnosis. But they could not define the benign and malignant tumor, and predict biological behavior. P53 was focally or weakly expressed in two cases and the expression intensity increased in the metastasis tumors. Nowadays, STAT6 is a popular marker in SFT. STAT6 expressed in both benign and malignant SFT. It's useful in the differential diagnosis including SFT, synovial sarcoma and heamoangiopericytoma [9]. NAB2-STAT6 fusion gene can also be detected in some SFT, but it showed low predictive value on the biological evaluation because of lacking large-scale prospective studies [10, 11]. Besides, Masuda et al [12] and Kurisaki-Arakawa et al [13]. independently reported a malignant SFT case with dedifferentiated components, and apart from the classical histological characteristics of SFT, both of them observed osteosarcoma and chondrosarcoma components carrying NAB2-STAT6 fusion gene [13] and P53 mutation 158 CGC > CAC (A158H). We revealed that Ki67 proliferative index was higher and the expression of mutant p53 was expressed in the recurred or metastatic ESFTs. This is consistent with previous studies [14, 15].

The results indicate that the tumor size larger than 10 cm, incomplete tumor capsule, more than 2 mitosis figures per high power field, Ki67 index larger than 3% and overexpression of P53 were important pathologic risk factors of expleural SFT recurrence and/or metastasis. Neither presence of necrosis nor hemorrhage showed a predictive value in present study. Interestingly, this founding was partly inconsistent with the data regarding the prognosis factor of pleura SFT reported by Schmid et al [16]. Brunnemann et al reviewed 24 cases of explerual SFT and concluded that the histological findings such as mitotic counts, necrosis, cellularity, and marginal status were not associated with outcome [17]. Besides, Cox et al [18] retrospectively analyzed 153 cases with head and neck SFT to identify positive surgical margin as the principal factor for tumor prognosis. They documented that 4 out of 9 cases with positive surgical margin relapsed, and only 1 out of 10 cases with atypical and/or malignant SFT relapsed. These conclusions partly related with short length of clinical follow-up.

Our results suggest that the pathologist should report the mitosis figures that may predict ESFT malignant behavior. Those patients need close following-up. We recommend that the patients can be divided as low risk group and high risk group according to the mitosis figures and ki67 index. However, only six cases showed metastasis in our group. Therefore, larger cohorts or multi-center studies may further clarify whether MIB is a prognostic factor in patients with ESFT.

The biological behavior of ESFT has no differences in various organs [19, 20]. It seems that SFT originated in CNS (Central Nervous System) is more invasive than that in other organs. However, there was no statistical significance due to the limited cases. In our study, we identified one case of primary cerebral SFT presenting liver metastasis 10 years after the first surgery, and three years later after the second surgery the patient presented with vertebra and lung metastases. A review of pathological sections of primary tumor further demonstrated the presence of spindle tumor cells and mild atypia, in contrast to increased atypia and karyokinesis as well as pathological karyokinesis in metastatic sites. Kyle M et al [21] reviewed 187 reported cases with CNS SFT and drew a similar conclusion. Most CNS SFTs occurred intracranially and a few appeared in vertebra. In addition, around 16% of intracranial SFT occurred in tentorium cerebella, 9 of 143 cases were malignant SFT, and around 8% cases showed atypia that manifested as skull invasion, cranial nerve invasion, high tumor cell density, marked polymorphism, mesenchymal infiltration, and increased Ki67 proliferative index (> 5%). Eight cases died during the follow-up.

Clinically, there is no sole staging system for ESFT. The classification suggested by De Perrot et al [2] is not applicable for ESFT. Although TNM staging system for soft tissue sarcoma was adopted in this study, there's no statistic significance among them. The tumor size 5 cm may not be suitable for ESFT. We found that tumor size larger than 10 cm was a prognostic factor. In this study, we focused on the morphology and immunophenotypic change for predicting the disease prognosis. In the era of precision medicine the genetic evaluation may improve the prediction of the ESFT outcome [22]. A limitation of this retrospective study is the low incidence of recurrences examined during our follow-up. Survival data need to be interpreted with caution due to limited number of events, though the observation period was quite long. Furthermore, it has to be mentioned that the presented risk stratification models were initially constructed for prediction of recurrence only. As there were only three recurrence cases in this study, we chose to apply the different models to predict disease-free survival.

ESFT is a rare mesenchymal tumor, which typically follow an indolent clinical course. In this study, we observed that some tumors showed the abilities of relapse and metastasis. There was no obvious difference between the primary ESFT and metastatic tumor both in clinical and radiological manifestation. Tumor size larger than 10 cm, incomplete tumor capsule, more than 2 mitosis figures per high power field, Ki67 index larger than 3% and overexpression of P53 were important pathologic features to indicating expleural SFT recurrence and/or metastasis. It can, therefore, be concluded that the surgical resection is the major therapy for ESFT, and postoperative long-term follow-up is a basic requirement for the timely detection of tumor recurrence and metastasis.

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Disclosure of conflict of interest

None.

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