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Case Report

Large primary pulmonary synovial sarcoma successfully treated with pazopanib: a rare case report and literature review

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Abstract: Primary pulmonary synovial sarcoma (PPSS) is a rare spindle cell tumor derived from pulmonary mesenchymal tissue, accounting for 0.5% of all primary lung malignancies. Diagnosis is established after metastatic sarcoma or other primary lung malignancies have been excluded. This present study reports a rare case of a 19-year-old woman that presented with a large soft tissue mass filling the entire right thoracic cavity. Histopathological and immunohistochemical analysis confirmed this mass as pulmonary synovial sarcoma. The patient received pazopanib targeted therapy and is currently being followed up. Large PPSS tumors are rare with very few case reports in the literature. To the best of our knowledge, this present study is the first to report the successful treatment of PPSS with pazopanib.

Keywords: Primary pulmonary synovial sarcoma, exclusive diagnosis, pazopanib

Introduction

Synovial sarcoma (SS), also known as malignant synovioma, accounts for 5-10% of all soft tissue malignancies [1]. Currently, it is believed that synovial sarcoma does not originate from synovium or differentiate into synovium but rather originates from primitive mesenchymal cells and can differentiate into epithelial and mesenchymal tissues [2]. The most common site of SS is the large joint of limbs. PPSS is rare, accounting for 0.5% of all primary lung malignancies, with poor prognosis [3]. Lack of specificity and the complicated histological structure of PPSS may contribute to its delayed diagnosis or misdiagnosis. Diagnosis of PPSS is established after metastatic sarcoma or other primary lung malignancies have been excluded and should be combined with histopathology, immunohistochemistry, and cytogenetic detection [4]. At present, there are no uniting diagnostic standards or practicable systematic treatment programs for PPSS. Surgery remains the preferred treatment [5]. This present study reports a case of large primary pulmonary synovial sarcoma treated with pazopanib. Additionally, clinical and imaging features, pathological diagnosis, molecular genetic mechanisms, treatment, and prognosis of PPSS were reviewed.

Case report

A 19-year-old female was admitted to the Department of Respiratory Medicine of Shengli Oilfield Central Hospital on 15/09/2017, due to violent coughing for half a year, asthma and chest pain for three months, and fever for four days. General health was good and blood analysis revealed the following results: white blood cell count, 17.3×10^9/L (normal range, 3.5-9.0×10^9/L), 76.7% neutrophils (normal range, 55-75%); hemoglobin, 114 g/L (normal range, 100-150 g/L); platelet count, 353×10^9/L (normal range, 100-300×10^9/L); blood biochemical showed: albumin 30.8 g/L (normal range, 35-51 g/L), lactate dehydrogenase, 400 IU/L (normal range, 120-330 IU/L); erythrocyte sedimentation rate: 27 mm/h (normal range, 0-20 mm/h); C-reaction protein: 87.8 mg/L (normal range, <9 mg/L); D-dimer: 9.17 mg/L (normal range, <0.2 mg/L); and tumor markers: NSE 21.04 ng/mL (normal range, <2.5 ng/mL). Routine urine, coagulation function, PCT, tuberculosis

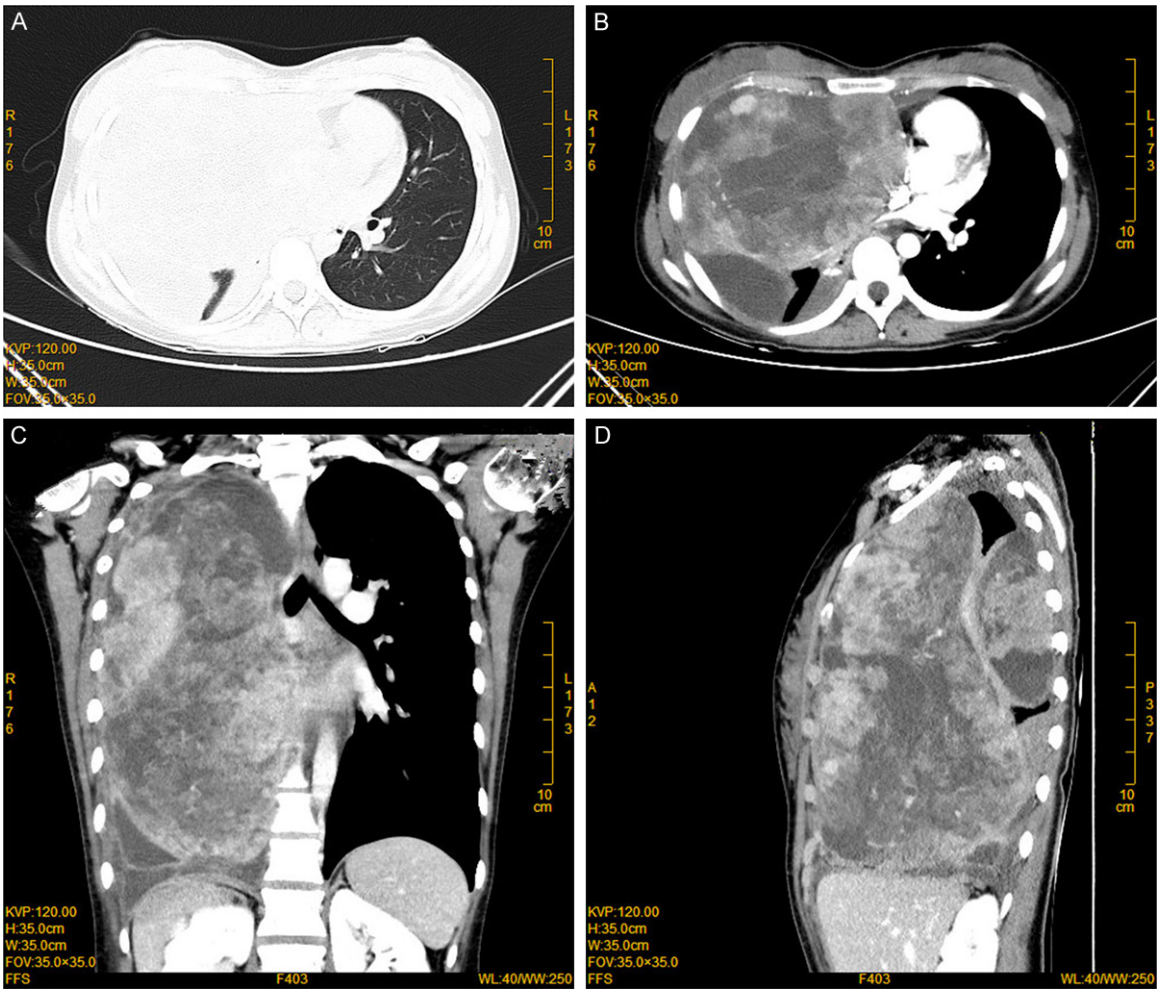

Figure 1. Computed tomography (CT) scan revealed there were two irregular mixed density masses filling the entire right thoracic cavity, which showed patchy low density. Enhanced scan showed inhomogeneous enhancement, the right lung tissue was not clear, and no enlarged lymph nodes in the mediastinum. A. Lung window; B. Mediastinum window; C. Coronal CT; D. Sagittal CT.

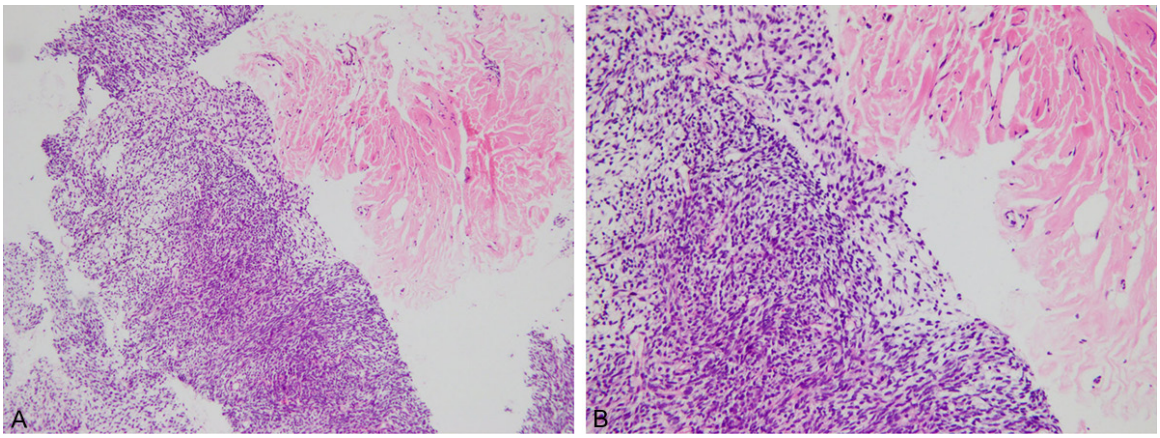

Figure 2. Histopathological analysis of the tumor specimen. A. HE stain, magnification, ×200; B. HE stain, magnification, ×400.

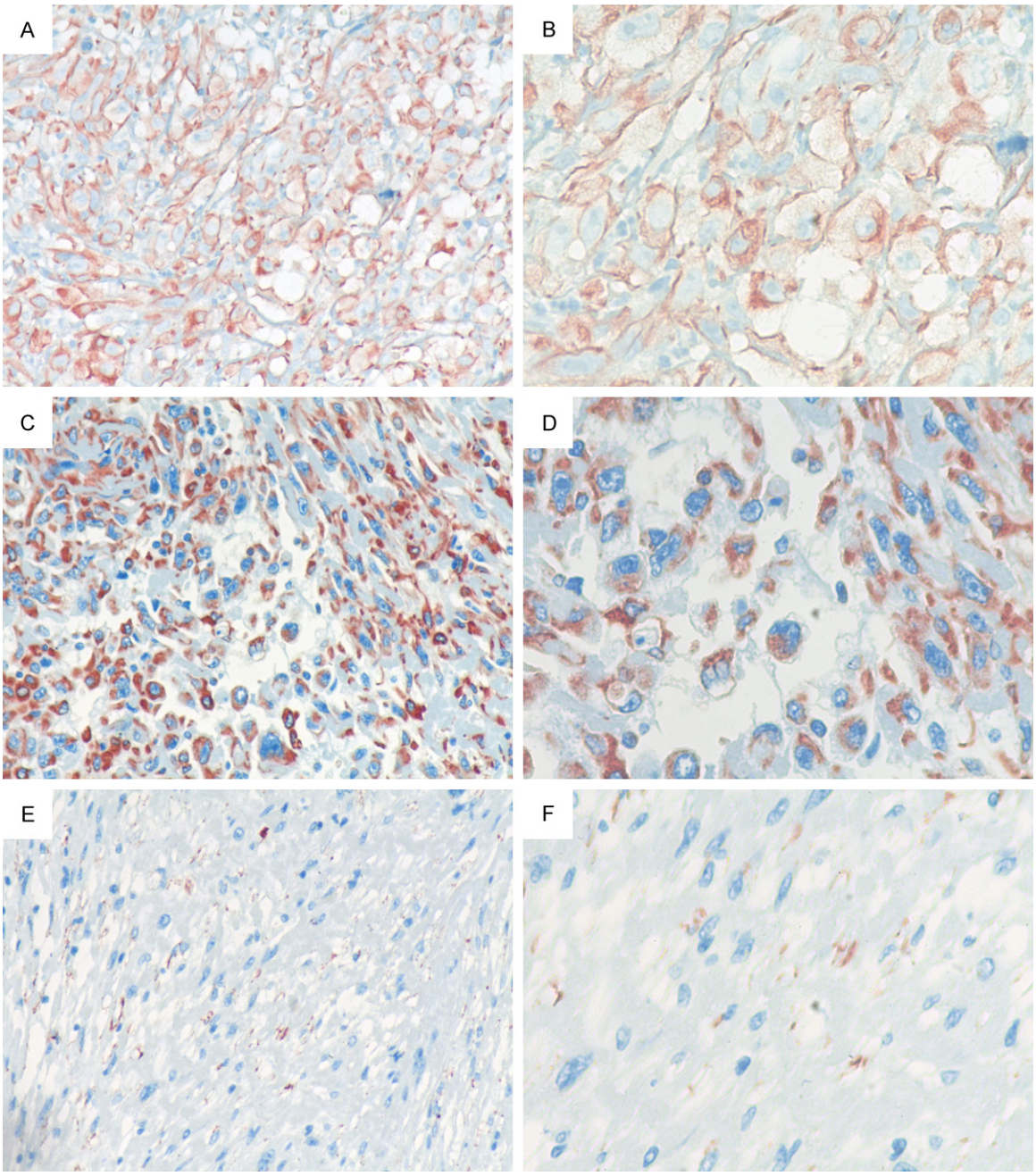

Figure 3. Immunohistochemical staining of the tumor specimen. A. CK (++) (HE stain, magnification, ×200); B. CK (++) (HE stain, magnification, ×400); C. Bcl-2 (+++) (HE stain, magnification, ×200); D. Bcl-2 (+++) (HE stain, magnification, ×400); E. EMA (+) (HE stain, magnification, ×200); F. EMA (+) (HE stain, magnification, ×400).

antibody, T-SPOT, fungal D-glucan, respiratory tract pathogen IgM antibody, sputum culture, and sputum seeking mycobacterium tuberculosis were all in the normal range. Computed tomography (CT) scan revealed that there were two irregular mixed density masses filling the entire right thoracic cavity, showing patchy low density. Enhanced scanning showed inhomogeneous enhancement and unclear right lung tissue, with no enlarged lymph nodes in the mediastinum (**Figure 1**). Right pulmonary needle biopsy, combined with immunohistochemistry, revealed that the right lung spindle cell tumor was considered a single-phase fibrous type of primary pulmonary synovial sarcoma (**Figure 2**). Immunohistochemically, the tumor cells were

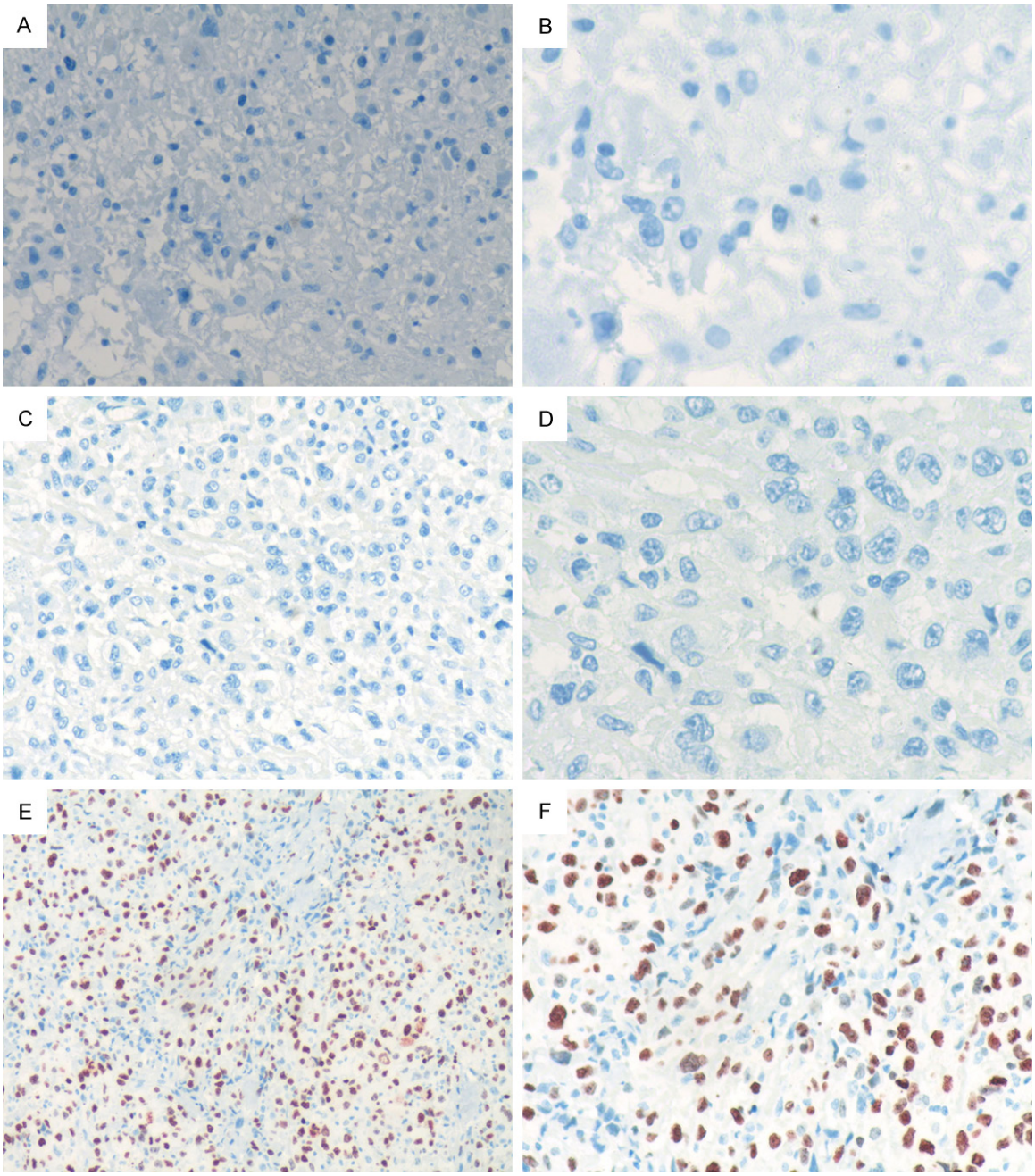

Figure 4. Immunohistochemical staining of the tumor specimen. A. Vim (++) (HE stain, magnification, ×200); B. Vim (++) (HE stain, magnification, ×400); C. CD99 (+++) (HE stain, magnification, ×200); D. CD99 (+++) (HE stain, magnification, ×400); E. Ki-67 (42%-45%+) (HE stain, magnification, ×200); F. Ki-67 (42%-45%+) (HE stain, magnification, ×400).

positive for expression of creatine kinase (CK) (+++; **Figure 3A** and **3B**), B-cell lymphoma-2 (bcl-2) (+++; **Figure 3C** and **3D**), and epithelial membrane antigen (EMA) (+; **Figure 3E** and **3F**). Cells were also positive for expression of vimentin (vim) (++; **Figure 4A** and **4B**), CD99 (++; **Figure 4C** and **4D**), and Ki-67 (42%-45%+; **Figure 4E** and **4F**), but they did not express desmin, smooth muscle actin (SMA), CD117, Dog-1, myoglobin, NSE, calretinin, and S-100. The patient had no surgical indications. Once daily administration of 80 mg of Pazopanib was initiated on 23/09/2017. She is presently in stable condition with cough and chest pain symptoms

Table 1. Comparative analysis of immunohistochemistry

Immunohistochemistry	CK	EMA	Vim	S-100	Bcl-2	Calretinin	CD99	Desmin	SMA
PPSS	+	+	+	+/-	+/-	-	+	-	+/-
Mesothelioma	+	+	+	-	-	+	+		
Leiomyosarcoma	-	-	+		+			+	
Fibroma sarcomatosum	-	+/-	+		-				
Angiosarcoma	-	-	+	+	-				
Rhabdomyoma Sarcomatosum	-	-	+		-				+

markedly improved. The patient is currently being followed up.

Discussion

Synovial sarcoma (SS) is a rare mesenchymal tumor, accounting for 5-10% of all soft tissue malignancies. SS often occurs in juveniles and young adults. Incidence of male SS is slightly higher than that of females [6]. Primary pulmonary synovial sarcoma (PPSS) is very rare with insidious onset and without gender difference. The main symptoms are cough and sputum, shortness of breath, fever, and thoracic pain. Typical CT manifestations of PPSS are heterogeneous solid masses with clear margins and liquefied areas, suggesting bleeding or necrosis. Lesions can cause pleural effusion and, to a lesser extent, mediastinal lymph node metastasis. Magnetic Resonance Imaging (MRI) has revealed that PPSS shows equal signal or high signal, with uneven signaling suggesting bleeding or necrosis. There are no specific clinical and imaging differences between PPSS and other pulmonary malignancies, often leading to delayed diagnosis or misdiagnosis [7].

The histogenesis of PPSS remains controversial. Most scholars believe that synovial sarcoma originates from mesenchymal stem cells and has the ability to differentiate into epithelial and/or mesenchymal cells. PPSS tissues are generally void of intact pseudocapsules. The section is often yellow and canous and cystic degeneration is common [8]. According to World Health Organization (WHO) classification, PPSS can be divided into four subtypes consisting of single fiber type, bipolar type, single phase epithelial type, and low differentiated type. Microscopically, epithelial and sarcomatoid cells are visible in the biphasic type and only epithelial or sarcomatoid cells are found in the single fiber type. Single fiber type is the most common. Immunohistochemistry has shown that most of biphasic PPSS expressed (cytokeratin, CK) and (epithelial, membrane, antigen, EMA), but EMA was more common and extensive and epithelial cells had stronger staining than spindle cells [9]. CK7 and CK19 can be expressed in epithelial cells and vimentin is expressed in spindle cells of single types. Spindle cells usually express vimentin, tumor nuclei and cytoplasm express S-100 over 30% and some can express calretinin and SMA, in part. More than 30% of tumor cells expressed S-100 in cytoplasm and the nucleus, along with partial expression of calretinin and SMA. Bcl-2 protein has been expressed diffusely in almost all synovial sarcomas, especially spindle cells. Also, 62% of synovial sarcomas were positive for CD99 expression [10] and 86% were negative for desmin expression [11]. Immunohistochemical comparison of PPSS with other primary malignancies has significant value in differential diagnosis (**Table 1**).

The ultrastructure of epithelial components of PPSS is similar to adenocarcinoma. Cell masses are surrounded by an outer plate containing intermediate filaments (including tonofilaments). Cells are connected by a junctional complex and the surface of cells has an abundance of microvilli. Single type PPSS cells have shown no characteristic features and occasionally have contained many rough endoplasmic reticulum, suggesting fibroblasts. Gaps between tumor cells are very rare. Occasionally, there have been short outer plate fragments around a single cell. There was no migration between spindle cells and epithelial cells. Calcified tumors have mitochondrial needle-like calcification. T (X; 18) (P11; Q11) is the major cytogenetic marker of PPSS. This translocation usually results in fusion of the SYT gene on chromosome 18 with SSX1 or SSX2 genes on the X chromosome. This fusion protein influences cell growth and cell proliferation. Further-

more, this signal leads to chromatin remodeling mediated by TP53 pathways, contributing to the carcinogenesis of PPSS.

Recent studies have shown that more than 90% of synovial sarcoma have SYT-SSX fusion genes, which is specific for synovial sarcoma diagnosis. When diagnosis is difficult, cytogenetic detection of T (X; 18), SYT-SSX fusion gene, and its expression products detected by FISH or RT-PCR is helpful for differential diagnosis [11].

Currently, there is not a united diagnostic standard or practicable systematic treatment program for PPSS. Surgery remains the preferred treatment. According to clinical stage, preoperative and postoperative chemoradiotherapy can be used. An effective dose of radiotherapy should not be less than 40 Gy. Chemotherapy often uses anthracycline monotherapy or a combination with cyclophosphamide. At present, molecular targeted therapy has become the focus of research in the field of SS therapy [12]. In April 2012, the FDA approved pazopanib for treatment of patients with advanced soft tissue sarcoma. Pazopanib is an oral small molecule multitargeted receptor tyrosine kinase inhibitor for VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, FGFR-1, alpha beta, FGFR-3, and cell factor receptor (Kit) [13]. In phase III clinical trials of PALETTE, 30 patients with SS were enrolled and results showed that, compared with control group, pazopanib treatment patients prolonged progression-free survival (PFS) (4.6 mo vs. 1.6 mo, $P<0.0001$) and overall survival (OS) (12.5 mo vs. 10.7 mo, $P<0.0001$). Bevacizumab, in combination with chemotherapy and PD-1 immunotherapy, is also an effective treatment. However, further clinical studies are necessary. In this present study, the patient was treated with pazopanib. One month later, she was evaluated for SD and the symptoms had improved. PPSS is a rare tumor with a high degree of malignity and high incidence of recurrence and metastasis. The malignant degree of PPSS is very high, the onset is occult, and rate of recurrence and metastasis is also high. Overall prognosis of PPSS is poor, with a five-year survival rate of 40-50% and median survival time of less than four years. Female, age (>20 years), tumor >5 cm, necrosis area >50%, low differentiation type, SYT-SSXI type, mitotic rate >10/10 HPF, and neurovascular invasion are poor prognosis factors in patients with PPSS.

In conclusion, larger PPSS is an extremely rare malignancy with poor prognosis. Clinical and imaging findings are generally nonspecific. Diagnosis should be combined with pathology, immunohistochemistry, and cytogenetic detection. There are no uniting diagnostic standards or practicable systematic treatment programs for PPSS, at present. Surgery remains the preferred treatment. In the future, targeted therapy will be a new effective way of treating PPSS. To the best of our knowledge, this study is the first to report the successful treatment of larger PPSS with pazopanib.

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Disclosure of conflict of interest

None.

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