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Primary Synovial Sarcoma of the Lung

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We describe a case of primary pulmonary synovial sarcoma. A 19-year-old man presented with low-grade fever, dyspnea, chest pain and left arm numbness. Chest radiographs revealed a large, well-circumscribed left perihilar mass and a small ipsilateral pleural effusion. Chest computed tomography (CT) revealed a large well-defined, heterogeneous lung mass. Magnetic resonance imaging (MRI) demonstrated a mass of heterogeneous signal intensity on T1-weighted and proton density images, and high signal intensity on short tau inversion recovery (STIR) images. Whole-body bone scintigraphy showed no evidence of skeletal involvement. Abdominal and pelvic CT showed no intra-abominal or pelvic metastases. A CT-guided biopsy provided the diagnosis of monophasic synovial sarcoma. Following four cycles of chemotherapy, integrated F-18 fluorodeoxyglucose positron emission tomography-computed tomography (18F FDG PET/CT) was performed, which demonstrated interval decrease in the size of the lesion and no significant metabolic activity. Surgical resection was then undertaken. Microscopically, the lesion was a high-grade spindle cell sarcoma consistent with monophasic synovial sarcoma. A variant X;18 translocation was identified by cytogenetic analysis and confirmed with metaphase in situ hybridization. The imaging and pathological features of this rare lesion are reviewed.

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Abbreviations: CT, computed tomography

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Introduction

Synovial sarcomas typically occur as primary neoplasms of the periarticular soft tissues, but have also been reported to arise from a variety of other locations [1]. The lung and pleura have recently been identified as sites of primary synovial sarcoma [2, 3]. Primary pulmonary sarcomas of all varieties total less than 0.5% of all lung malignancies, of which synovial sarcoma is being reported with increasing frequency [4]. Pulmonary metastases from extrapulmonary synovial sarcoma are far more common than primary pulmonary synovial sarcomas. Affected patients undergo a thorough analysis of clinical history, physical examination, and imaging findings to exclude a primary malignancy

elsewhere. Although reports of primary pulmonary synovial sarcoma have increasingly appeared in the pathology literature, few reports of the imaging features of this unusual neoplasms have been published [5]. We present a case of primary synovial sarcoma of the lung in a 19-year-old man with particular emphasis on the radiologic and pathologic findings of this rare lesion.

Case Report

A 19-year-old man was referred to our institution for evaluation of a lung mass detected on chest radiography performed for assessment of dyspnea and low-grade fever. The patient described a six-week period of intermittent dull chest pain alternating with brief periods of palpitations, severe chest pain, and numbness and tingling radiating down his left arm. His past medical history was notable only for a week-long episode of cough productive of dark green sputum 6 months previously, for which no evaluation or intervention was sought. The patient was a nonsmoker with no history of radiation or chemical exposures. His vital signs and physical examination were unremarkable. Electrocardiography and pulmonary function tests were within normal limits. Sputum and blood cultures grew Neisseria meningitidis, which was treated with ciprofloxacin. All other laboratory data were within normal limits.

Chest radiography revealed a large, left lung mass with well-defined margins and a small left pleural effusion (Fig. 1). Contrast-enhanced chest CT (Fig. 2) demonstrated a well-defined, heterogeneous ovoid lung mass in the left lung that measured 8.9 by 9.5 cm. The lesion involved the left upper and lower lobes, abutted the left major fissure,

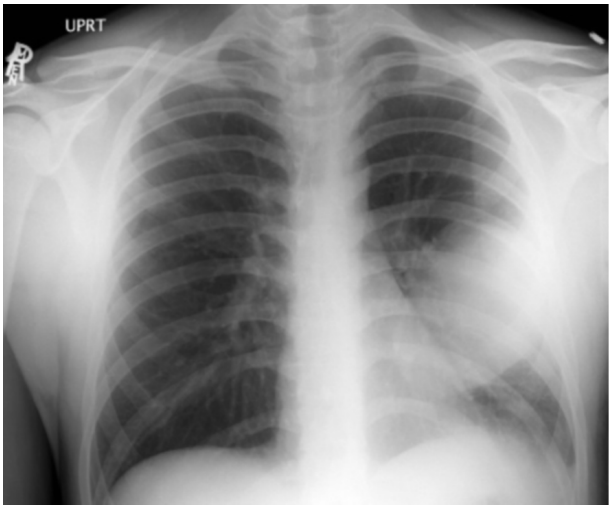

Figure 1. 19-year-old man with primary synovial sarcoma of the lung. AP chest radiograph shows a large well circumscribed mass in the left mid lung and a small left pleural effusion.

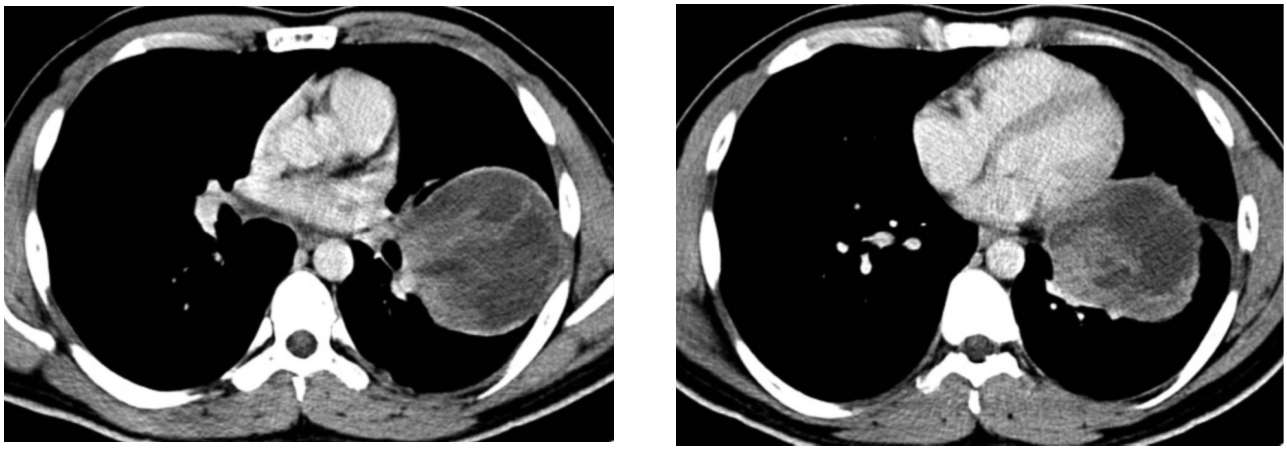

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Figure 2. A, B, Contrast-enhanced chest CT (mediastinal window) shows a well circumscribed heterogeneous left lung mass abutting the left hilum and pericardium. The lesion exhibited soft tissue and low attenuation components, the latter with fluid-fluid levels consistent with cystic change.

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left hilum, and posterior aspect of the pericardium and produced mass effect on the central tracheobronchial tree. Irregular, enhancing tissue elements were appreciated within the lesion as well as low attenuation areas and fluid-fluid levels (Fig. 2A). No intratumoral calcifications were detected. Surrounding ground glass opacity was noted in the lung adjacent to the lesion, likely related to relaxation atelectasis. Trace left pleural effusion was also present. No other abnormalities of the mediastinum, thoracic lymph nodes, or contralateral lung were identified. The diagnoses of primary pulmonary sarcoma and primary lung cancer were considered. Pleuropulmonary blastoma and intrapulmonary germ cell neoplasm were also suggested in view of the internal cystic and heterogeneous appearance of the lesion. On subsequent thoracic magnetic resonance imaging (MRI) the mass showed heterogeneous signal intensity on T1-weighted and proton density pulse sequences (Figs. 3A, B). Short tau inversion recovery (STIR) images revealed areas of relatively high signal intensity within the mass. Contrast-enhanced fast gradient echo sequences demonstrated heterogeneous enhancement of the lesion with peripheral polylobular enhancement and enhancing tissue septa surrounding low signal intensity areas that likely corresponded to necrosis (Figs. 3C, D). Whole body bone scintigraphy using intravenous technetium-99m labeled methylene diphosphonate (MDP) showed minimal radiopharmaceutical uptake within the lesion itself and no convincing evidence of osseous metastatic disease. Contrast-enhanced CT of the abdomen and pelvis showed no evidence of intra-abdominal or pelvic metastatic disease or other primary malignancy.

An endoluminal lesion was not detected on bronchoscopy. Bronchial aspirate cytology and endobronchial frozen section biopsies were negative for malignancy. A CT-guided biopsy showed malignant spindle cell sarcoma consistent with monophasic synovial sarcoma. Medical and surgical oncologists agreed to treat the tumor with four cycles of neoadjuvant ifosfamide and adriamycin chemotherapy prior to resection with the goal of reducing the size of the mass. A preoperative restaging whole-body fluorine-18 fluorodeoxyglucose integrated PET-CT study was performed (Fig. 4) after completion of chemotherapy, which demonstrated reduction in the size of the lesion from 8.9 by 9.5 cm to 7.8 by 4.7 cm. This pre-operative study showed no significant metabolic activity within the lesion, with a peak standardized uptake value (SUV) of 1.3. A left pneumonectomy and lymph node dissection were performed. The tumor was noted to be located centrally within the left upper lobe, crossed the major fissure, and was densely adherent to the adjacent pulmonary artery and inferior pulmonary vein.

The tumor specimen was described as a 7.6 x 7.0 x 6.4 cm well circumscribed tan and fleshy to rubbery mass with focal areas of softening and hemorrhage. The cut surface was multicystic in appearance, and the mass abutted the left lower lobe. All five resected lymph nodes were negative for malignancy, and the surgical resection margin was free of tumor. Microscopically (Fig. 5), the tumor showed a dense, monotonous and atypical spindle cell proliferation consistent with high-grade monophasic synovial sarcoma. The tumor exhibited extensive areas of hemorrhage, stromal hyalinization, and focal areas of necrosis - the latter were presumed to be the result of preoperative chemotherapy. Immunohistochemical stains showed focal positivity for cytokeratins (Fig. 6A) AE1/AE3, epithelial membrane antigen (EMA), cluster of differentiation (CD) 99, and strong positivity for bcl-2 (Fig. 6B) and calponin. Stains for smooth muscle actin (SMA), S-100 protein and CD34 were negative. Ultrastructurally, the tumor showed oval to spindle cells displaying closely apposed cell membranes with frequent desmosome-type intercellular junctions. The cell nuclei were elongated and irregular with frequent indentations of the nuclear envelopes and peripheral margination of chromatin. Prominent eccentric nucleoli were also present. The cytoplasm of the cells contained numerous organelles, including scattered ribosomes, intermediate filaments, mitochondria, Golgi apparatti, and prominent rough endoplasmic reticulum. Cytogenetic analysis confirmed the diagnosis of synovial sarcoma by demonstrating a variant X;18 translocation. This complex rearrangement resulted in an abnormal chromosome 1, which was the result of an insertion of most of the chromosome arm 18q with the proximal part of Xp inserted into the q-arm of the chromosome 1. This finding was confirmed by metaphase fluorescence in situ hybridization (FISH), yielding a final diagnosis of primary monophasic synovial sarcoma.

The patient's postoperative course was complicated by pulmonary thromboembolic disease detected at CT pulmonary angiography on post-operative day number two and treated with anticoagulation. Following surgical resection of the tumor, two more cycles of adjuvant chemotherapy were administered.

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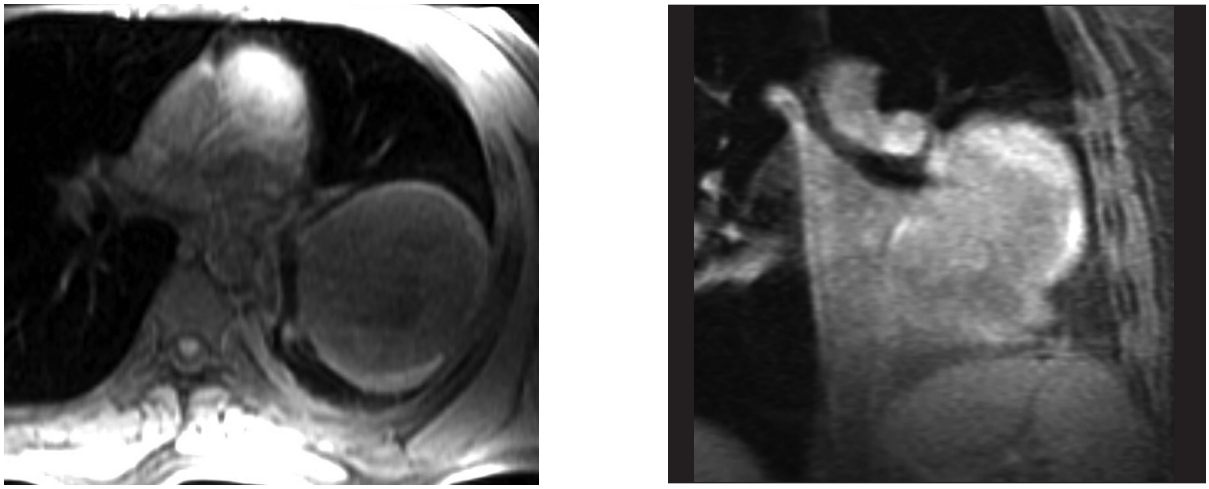

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Figure 3. A, Axial, and B, coronal, double inversion recovery magnetic resonance images through the lesion demonstrate a heterogeneous mass in the left mid lung that abuts the ipsilateral hilum and displaces the hilar structures.

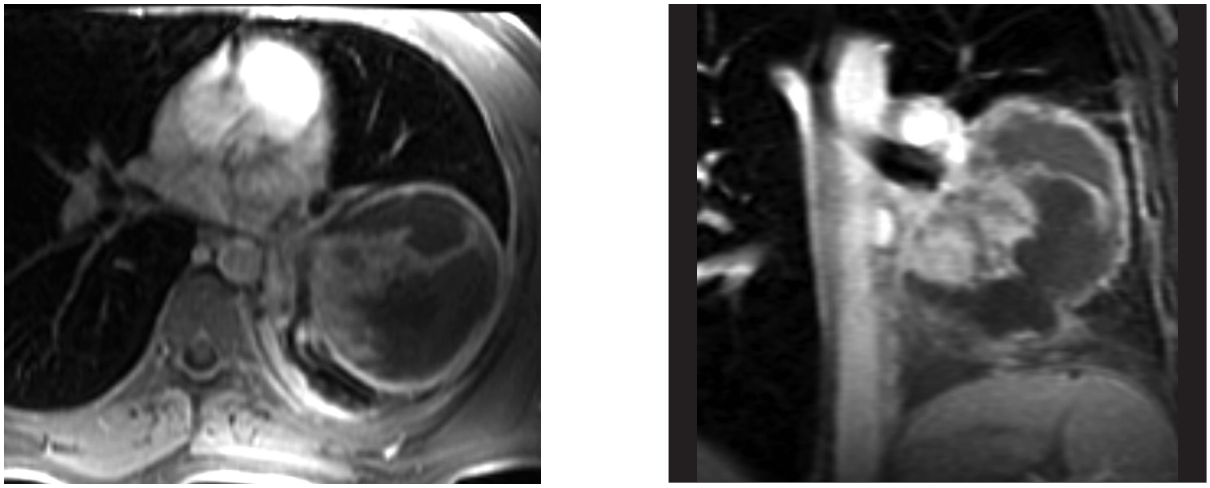

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Figure 3. C, Axial, and D, coronal, contrast-enhanced fast gradient echo sequences through the lesion demonstrate heterogeneous signal with medially located nodular enhancement and enhancing tissue septa and areas of low signal intensity that correlated with the cystic changes observed on CT.

Discussion

Synovial sarcoma is a malignant mesenchymal neoplasm that represents 10% of all primary malignant soft tissue tumors. It primarily affects the periarticular soft tissues of the extremities [6]. Despite initial thoughts that these tumors originated from synovial cells due to their common association with joints [6], recent literature suggests that synovial sarcoma is instead derived from pluripotential mesenchymal cells capable of aberrant epithelial differentiation [2, 7, 8]. Among the observations that support this theory are reports of synovial sarcomas arising from a variety of locations, including the head and neck, mediastinum, heart, esophagus, and vulva [9]. Recently, the lung

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and pleura have been identified as sites of primary synovial sarcoma [2, 3]. Although synovial sarcoma only rarely involves the lung primarily, reports of primary intrathoracic tumors have recently begun to accumulate likely due to an increasing ability to diagnose the tumors with immunohistochemical and cytogenetic techniques [4, 10]. Primary pulmonary sarcomas are responsible for less than 0.5% of all lung malignancies. The most commonly described histologic types include leiomyosarcoma, malignant fibrous histiocytoma, fibrosarcoma, and now, increasingly, synovial sarcoma [11]. The term "pleuropulmonary" was first recommended by Essary and colleagues to describe the anatomic subset of primary synovial sarcomas originating from either the lung or pleura due to inherent difficulties in assigning a precise anatomic origin in most cases [9]. A small but growing number of cases of primary pulmonary synovial sarcoma (PPSS) have been reported in the literature over the past decade, but very few of these reports focus on the imaging findings of this rare lesion [5, 11-15].

The radiologic features of PPSS have been enumerated in a recent series by Frazier et al, and are briefly summarized here. Radiographically, PPSS is most commonly described as a pulmonary mass with either sharp or ill-defined borders, a pleural-based mass, or nearly total opacification of the affected hemithorax. Ipsilateral pleural effusion is common, and the contralateral lung is characteristically not involved. Intratumoral calcifications have been reported once [3]. At CT, PPSS commonly manifests as a well-defined, heterogeneously enhancing mass with intrinsic areas of fluid attenuation, often with ipsilateral pleural effusion. Differentiation between lung and pleural-based lesions at CT is often difficult, particularly with large lesions [3, 12, 16-18]. Associated lypmhadenopathy has rarely been reported [12, 19]. A peripheral rim of ground-glass opacity surrounding the mass has been reported in one case [20]. In the few published MRI descriptions of the lesion, the appearance has varied from internally heterogeneous with intermediate signal intensity on T1-weighted images with nodular areas of intermediate signal intensity on T2-weighted images to homogeneous hypointensity on both T1- and T2-weighted images [5, 11].

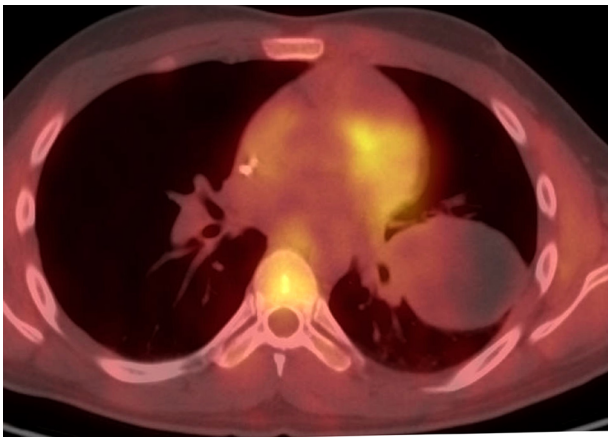

Figure 4. F-18 FDG PET/CT fused image following chemotherapy shows interval decrease in the size of the mass, decreasing mass effect on the adjacent hilum and very little metabolic activity (SUV of 1.3).

Patients with primary pulmonary synovial sarcoma most often present with chest pain, dyspnea, and cough. Up to 24% of patients are asymptomatic and are diagnosed because of an abnormality found incidentally on chest radiography [9]. In the largest series of 25 patients with synovial sarcoma, Zeren et al. reported that affected patients ranged in age from 16 to 77 years at diagnosis (mean age; 38.5 years) [2]. Our patient was young and presented with an atypical cluster of symptoms, including low-grade fever and left arm numbness. Synovial sarcoma metastatic to the lung is far more common than primary pulmonary synovial sarcoma. The diagnosis of primary synovial sarcoma in the lung is supported by a thorough analysis of clinical history, physical examination, and imaging findings that fails to detect a primary cancer elsewhere [21]. Our patient had no evidence of present or past soft tissue neoplasms and no localizing symptoms or physical examination findings suggestive of extra-pulmonary malignancy. Additionally, bone scintigraphy and CT examinations of the abdomen and pelvis showed no evidence of metastatic disease or other primary neoplasm. The treatment and clinical outcome of patients with PPSS have primarily been addressed anecdotally in the literature [11]. Synovial sarcomas of the lung are thought to behave in a more locally aggressive fashion than their soft tissue counterparts, perhaps due to inherent difficulties in obtaining adequate surgical margins combined with the tendency for affected patients to present late with minimal symptoms [9, 10]. The small number of published cases report treatment with surgical resection, combined with preoperative radiation or postoperative adjuvant chemotherapy.

Although the radiologic features of synovial sarcoma of the extremities are well-characterized [22-26], the imaging features of pleuropulmonary synovial sarcoma have not been well documented in the literature. Most reports have focused on radiographic and CT descriptions. Far fewer MRI or PET/CT descriptions have been published [5, 11, 14, 15]. Frazier et al. reported the largest series (n = 12)

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of cases that categorized the imaging findings of primary PPSS. At chest radiography, seven lesions (N = 9) had sharply marginated borders with round, ovoid, or lobulated contours. The most common CT findings were those of a heterogeneously enhancing mass with well-defined margins containing nodular soft-tissue components mixed with areas of low attenuation. Calcification and lymphadenopathy were not present, but ipsilateral pleural effusion was present in seven of eleven patients [11]. At MR imaging, Frazier et al found that the most common appearance was that of a well-circumscribed mass with no evidence of spiculation or satellite nodules in three of three patients. An internally heterogeneous appearance on T1 was present in two of three patients combined with nodular areas of intermediate signal intensity and punctate or cystic areas of high signal intensity. At PET/CT, one case (N = 1) demonstrated focal increased uptake of FDG with maximum standardized uptake value (SUV) of 7.0. This finding differs significantly from our case, in which the PET/CT was performed after 4 cycles of neoadjuvant ifosfamide and adriamycin chemotherapy. The lesion at that time showed no hypermetabolic activity, with a peak SUV of 1.3. This finding could have implications in regards to re-staging of tumors and detection of distant metastases after treatment with chemotherapeutic agents. To our knowledge, this is the first report of a synovial sarcoma manifesting low metabolic activity on PET/CT after neoadjuvant chemotherapy. It should be noted that pre-treatment PET/CT was not performed.

The radiologic differential diagnosis of primary pulmonary synovial sarcoma includes other primary and metastatic lung neoplasms, localized fibrous tumors of the lung and pleura, pleuropulmonary blastoma, and other rare primary parenchymal sarcomas [11, 12]. A number of clinical and radiologic features can help narrow the differential diagnosis. The presence of significant lymphadenopathy would favor the diagnosis of lung cancer over PPSS. Metastatic disease rarely manifests as a large solitary pulmonary lesion, although thorough clinical and imaging evaluation must be undertaken to exclude this possibility. A number of other rare primary parenchymal sarcomas (fibrosarcoma, leiomyosarcoma, hemangiopericytoma, malignant nerve sheath tumor, sarcomatous carcinoma) cannot be reliably distinguished from synovial sarcoma based upon clinical and radiologic features alone.

In our case, the diagnosis of PPSS was established based on tissue obtained via CT-guided needle biopsy. A review of eight cases of primary pulmonary synovial sarcoma in the published literature in which preoperative biopsies were performed shows that the preoperative diagnosis of this lesion may be difficult to obtain. A diagnosis of probable PPSS was made on only one CT-guided fine needle aspiration biopsy [27]. One CT guided biopsy showed a malignant non-epithelial tumor [5]. An ultrasound-guided needle biopsy showed a spindle cell tumor with a differential diagnosis of synovial sarcoma or mesothelioma [28]. An unspecified fine needle aspiration biopsy showed atypical spindle cells and two unspecified needle biopsies showed malignant small round cells arranged in a hemangiopericytomatous pattern [20] and non diagnostic findings [29] respectively. Two bronchoscopic biopsies showed findings suggestive of mesenchymal tumor [15] and a spindle cell tumor not otherwise specified [30].

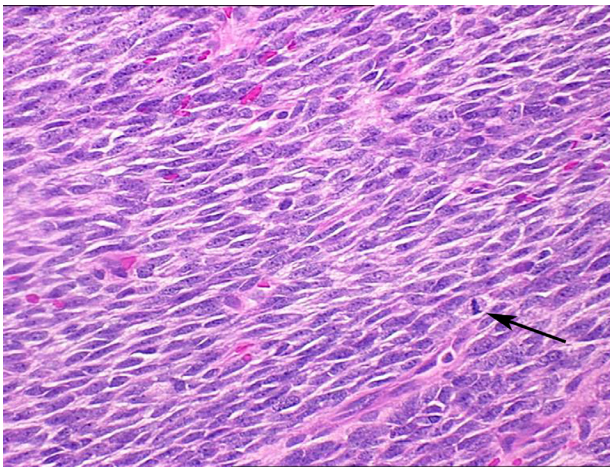

Figure 5. Photomicrograph (Hematoxylin and Eosin stain; original magnification 200 power) demonstrates a tumor composed of fascicles of monotonous atypical spindle cells with scattered mitoses (arrow).

The pathologic features of pulmonary synovial sarcomas have been well described [9, 31, 32]. Histologically, synovial sarcoma is primarily divided into biphasic and monophasic subtypes. The monophasic variant is more common in the lung, and is composed entirely of spindle cells. The biphasic subtype consists of a combination of epithelial and spindle cells. In our case, the dense, monotonous and atypical spindle cells without a glandular component were consistent with monophasic synovial sarcoma. The characteristic chromosomal translocation t(X;18)(SYT-SSX) is present in 80%-90% of these tumors and is considered specific for the diagnosis [10, 33, 34]. Detection of this translocation through cytogenetics and reverse transcriptase-polymerase chain reaction (RT-

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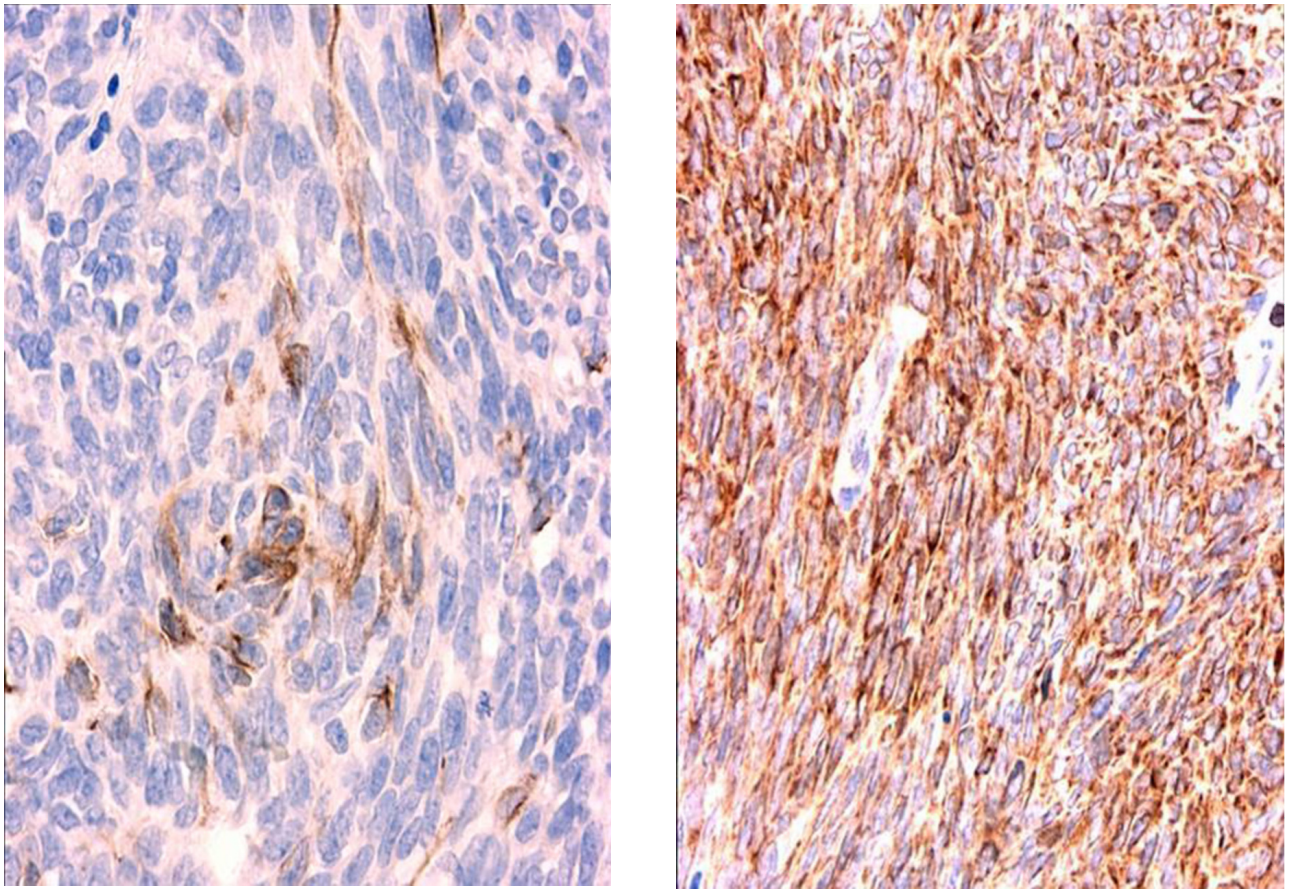

Figure 6. A, Immunoperoxidase stain for cytokeratin shows focal positivity in the tumor cells (KER, X200). B, Immunoperoxidase stain for bcl-2 protooncogene shows strong cytoplasmic positivity in the majority of the tumor cells (BCL-2, X200).

PCR)-based techniques has greatly increased the sensitivity and specificity of the diagnosis of synovial sarcoma [10]. Immunohistochemically, most synovial sarcomas are positive for cytokeratins and or EMA. Vimentin is usually expressed in the spindle cell portions of the neoplasm, and S-100 reactivity can be identified in up to 30% of tumors. BCL-2 and CD99 are frequently positive, and CD34 is usually negative [31]. Our case showed typical immunohistochemical findings of synovial sarcoma. The t(X;18) translocation was detected with metaphase FISH analysis, confirming the diagnosis of synovial sarcoma.

The most important pathological differential diagnosis is metastatic disease. Additionally, other epithelial and mesenchymal tumors need to be differentiated from synovial sarcoma, including fibrosarcoma, leiomyosarcoma, hemangiopericytoma, peripheral nerve sheath tumors, sarcomatous carcinoma, and intrapulmonary solitary fibrous tumors [2].

In summary, we have presented a case of primary pulmonary synovial sarcoma in a young man who presented with symptoms referable to the chest and upper extremity. The diagnosis was established via a transthoracic CT guided needle biopsy. The patient underwent neoadjuvant chemotherapy prior to excision and post therapy integrated PET-CT demonstrated low metabolic activity in the tumor which also decreased in size. Pneumonectomy and lymph node dissection achieved tumor free margins.

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