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Case Report

A Case of Giant Primary Pleuropulmonary Synovial Sarcoma

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ABSTRACT

Synovial sarcomas represent an extremely rare subtype of an already rare group of malignancies, soft tissue sarcomas. Among these, primary pulmonary synovial sarcomas comprise an even smaller number, though they have become more frequently reported in the literature. This case report details a case of giant primary pulmonary synovial sarcoma in a 44-year-old male patient who presented with left-sided chest pain and shortness of breath and was found to have a large left-sided pleural effusion. No malignant cells were demonstrated on cytology of pleural fluid after thoracentesis; however, CT-guided needle biopsy of pleural nodules seen on imaging demonstrated pathologic features consistent with monophasic type synovial sarcoma. He was treated with neoadjuvant chemotherapy with minimal response; thus, he was referred for surgical management. A left extrapleural pneumonectomy with resection of the left hemi-diaphragm and Gore-Tex prosthetic reconstruction was performed. Imaging at six-month follow-up demonstrated a new nodule in the contralateral lung, suggestive of metastasis at that time and the patient later developed ascites at nine months, consistent with further intra-abdominal metastasis. Perhaps early diagnosis and aggressive multimodality therapy may have a place in the treatment of this aggressive disease.

Introduction

Soft tissue sarcomas are relatively rare, heterogeneous tumors, representing less than 1% of all solid tumors and, of these, only 5% are synovial sarcomas [1, 2]. These tumors typically occur in the soft tissues of the extremities, near joints and tendon sheaths, with a predominance for males and individuals younger than age 50 [1]. Increasingly these tumors are being reported as primary lung tumors, often with local invasion into the ribs, diaphragm and pericardium; and with no correlation to synovium. Radiographically, findings typically include evidence of local bony destruction and a heterogeneous mass, often with associated calcifications. The majority of these tumors demonstrate a balanced reciprocal translocation t(X;18) (p11.2; q11.2), forming the fusion gene *SYT-SSX* chimeric RNA, which is detectable by fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) and which has become a key indicator of synovial sarcoma [3]. Key antibodies and immunohistochemistry that support a diagnosis of synovial sarcoma include keratins, bcl-2, epithelial membrane antigen (EMA) and TLE1 [3].

Case Report

A 44-year-old male with a history of type 2 diabetes mellitus and a 30-pack-year smoking history presented to our Thoracic Surgery clinic after he was found to have a left pulmonary synovial sarcoma. The patient initially presented with left-sided chest pain and later developed shortness of breath. Workup revealed a very large left pleural effusion. On computed tomography (Figure 1) of the chest, he was noted to have multiple pleural-based lung nodules, of which the largest measured 6 x 5 cm. He underwent two thoracenteses, draining 2 liters and 1.5 liters, respectively. Pleural fluid was sent for cytological testing and

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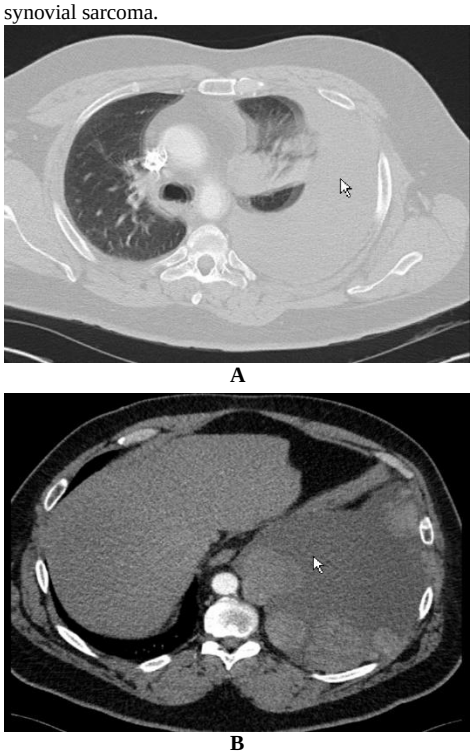
demonstrated reactive-appearing mesothelial cells in a background of inflammation and mesothelial cells, overall negative for malignancy. The patient then underwent CT-guided needle biopsy of one of the posterior pleural nodules. Microscopically, pathologic sections demonstrated a sarcomatoid neoplasm consisting of plump spindle cells with scant cytoplasm, oval-to-round nuclei with fine chromatin and small nucleoli. Immunostains performed included chromogranin, synaptophysin, TTF 1, calretinin, S100, BCL2 and pankeratin, for which both bcl-2 and pankeratin were strongly positive. The remaining stains were negative. FISH study performed detected SS18 (SYT) gene rearrangement. These findings were consistent with monophasic type synovial sarcoma.



A

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Figure 1: CT scan of the chest showing tumor mass in **A)** the lung and **B)** affecting pleura.

PET/CT was later performed, demonstrating multiple hypermetabolic left pulmonary and pleural-based masses. The reference mass in the medial left lower hemithorax demonstrated an SUV max of 10.6 with additional areas of uptake in the left upper lung laterally (SUV max 1.4) and left lower lung anteriorly (SUV max 7.0). Hypermetabolic activity was noted in the mediastinal, hilar and axillary lymph nodes as well, with SUV max ranging from 4.1 in the AP window and subcarinal periesophageal lymph nodes to 9.6 in the left hilar lymph node conglomerate (Figure 2). The patient was discussed in the Thoracic Oncology multidisciplinary tumor board, during which neoadjuvant chemotherapy was recommended. He underwent two cycles of mesna (850 mg/m^2/dose daily), ifosfamide (6300 mg daily), and doxorubicin (25 mg/m^2/dose). Upon completion of this chemotherapy regimen, repeat CT chest performed demonstrated growth of the largest lesion to 7.2 x 4.7 cm. In light of the further growth of the tumor, the patient was referred for surgical management. He underwent a left extrapleural pneumonectomy, resection of the left hemi-diaphragm with Gore-Tex prosthetic reconstruction, mediastinal lymphadenectomy and intercostal pedicle muscle intrathoracic transposition to the bronchial stump. He was discharged home on the fourth post-operative day.

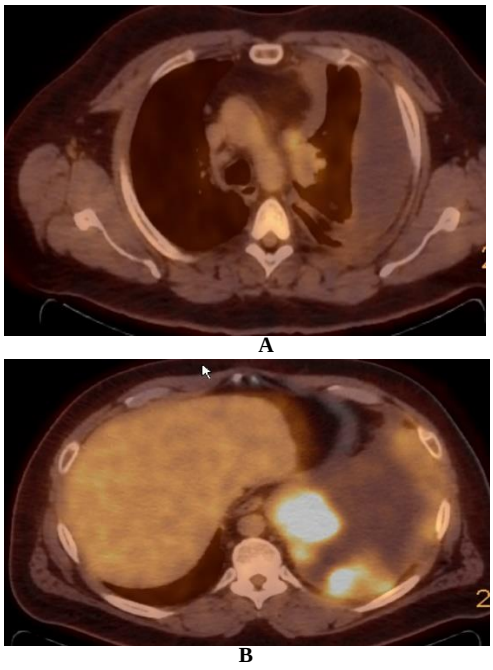

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Figure 2: PET scan, images showing the multiple lesions in **A)** the pleura and lung and **B)** the hilar lymphadenopathy.

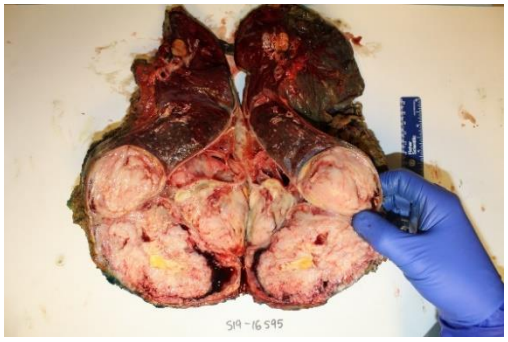
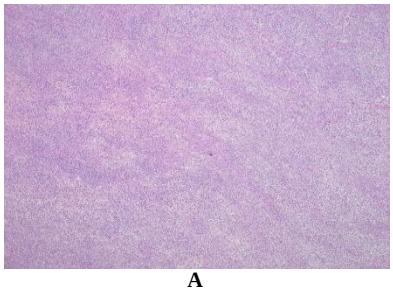


Figure 3: The specimen is bi-valved through the hilum. The cut surface shows a tan-pink, friable mass (mass #1) that is lobulated occupying the entirety of the inferior portion of the specimen. The lobules are divided by fibrous septae. There are areas of haemorrhage. The mass measures 16.9 x 16.3 x 12.4 cm. Additionally, there is a small, encapsulated, yellow mass (mass #2) in the upper lobe that measures 2.4 x 2.0 x 1.5 cm. A third mass (mass #3) is identified in the apex of the lung measuring 4.5 x 4.0 x 3.0 cm. It is biphasic with a pink-tan fleshy area and a tan-white solid component.

Surgical pathology from intraoperative specimens was again remarkable for multifocal, monophasic synovial sarcoma involving the pleural surfaces over the upper and lower lobes and the diaphragm. The cut surface shows a tan-pink, friable mass (mass #1) that is lobulated occupying the entirety of the inferior portion of the specimen. The lobules are divided by fibrous septae. There are areas of haemorrhage. The mass measures 16.9 x 16.3 x 12.4 cm. Additionally, there is a small, encapsulated, yellow mass (mass #2) in the upper lobe that measures 2.4 x 2.0 x 1.5 cm. A third mass (mass #3) is identified in the apex of the lung measuring 4.5 x 4.0 x 3.0 cm. It is biphasic with a pink-tan fleshy

area and a tan-white solid component (Figure 3). Microscopic examination confirmed the tumor was a synovial sarcoma, spindle cell, histologic grade (FNCLCC) 3. The microscopic margins were clear. Mitotic Rate: >20 mitoses per 10 high power fields (HPF), the extent of necrosis was 25%. Immunohistochemistry showed that the tumor cells were positive for Bcl-2, CD99 and showed patchy positivity with cytokeratins AE1/AE3 and 8/18 (Figure 4). The tumor cells are negative for WT-1.



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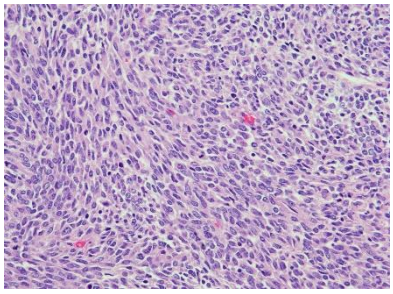

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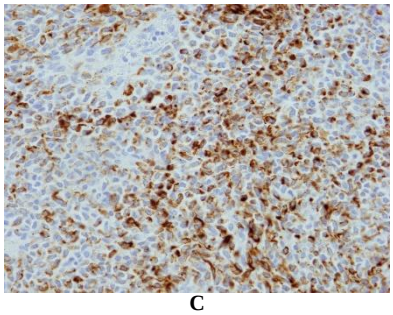

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Figure 4: A) Sections show a spindle cell neoplasm comprising of intersecting fascicles of monotonous, spindle cells (4x). Higher magnification shows proliferation of monotonous, ovoid to spindle hyperchromatic cells interspersed with capillary-sized vascular channels. **B)** Tumor cells possess scant eosinophilic cytoplasm, ovoid to spindly nuclei with finely dispersed nuclear chromatin. Mitotic figures are appreciable. Areas of necrosis are also identified. **C)** Keratin AE1 AE3 immunostaining demonstrates patchy but robust reactivity within the tumor cells. **D)** Tumor cells are positive for CD99.

In total, twenty-four lymph nodes were examined with metastatic sarcoma demonstrated in two of seven inter- and intra-lobar nodes sampled. Based on these findings, final staging for this patient was pT2aN1. Imaging at six-month follow-up demonstrated a novel nodule, consistent with metastasis to the contralateral lung. Considering the disease recurrence, he was treated with SDV200 (gemcitabine) 1,627 mg in NaCl 0.9% 250 mL IVPB and taxotere (docetaxel) 241 mg in NaCl 0.9% 250 mL IVPB (6 cycles planned) with palliative intent. One month after initiation of treatment, lab studies revealed elevated alkaline phosphatase (218), ALT (44), and total bilirubin (5.4), most likely attributable to the gemcitabine. The patient was then transitioned to votrient (pazopanib). Ten months after his initial presentation, he was referred for comfort care.

Discussion

Synovial sarcoma is a mesenchymal spindle cell tumor that accounts for 5-10% of all soft tissue sarcomas and has a predominance for young males [2]. Historically, the average age of synovial sarcoma was documented as 25 years, though more recent case reports suggest a later age of incidence of primary pulmonary synovial sarcoma in the fourth decade of life. It most commonly occurs in the soft tissues of the extremities, near tendon sheaths or joints, with the head and neck region the second most frequent site (~5%), although recent case reports have described more frequent occurrences of primary synovial sarcomas in the lung. Pleuropulmonary synovial sarcoma may initially present as a pneumothorax, but also commonly presents as dyspnea, cough and hemoptysis and chest pain and with symptoms related to the local invasion of the surrounding structures, such as ribs, pericardium, diaphragm and local neuro vasculature [2, 4]. Constitutional symptoms, such as weight loss and decreased appetite, usually accompany this more specific symptomatology as well. Due to the rarity of primary pulmonary synovial sarcoma, the differential diagnosis, which involves broad and extensive workup, including imaging and genetic analysis, should be completed to exclude other primary conditions and metastatic sarcoma.

I Imaging

Plain radiographs of the chest are relatively non-specific for primary pulmonary synovial sarcoma. They may demonstrate a range of presentations, including a ‘benign’ pneumothorax or a cystic mass [2]. They may also demonstrate a sharply marginated mass with uniform opacity, often, but not always, accompanied by an ipsilateral pleural effusion. These masses may be based in either the lung or the pleura [5]. Findings on computed tomography typically include local bony destruction and a well-defined, heterogeneous or multicystic mass [1, 2, 6]. Differentiation from other tumors, especially pleural solitary fibrous tumors, may present a challenge, as both pleuropulmonary synovial sarcomas and these tumors demonstrate well-defined lobulated isodensity with patchy low density on unenhanced CT, as well as a heterogeneous enhancement on contrast enhanced CT [6]. Pleural solitary fibrous tumors, however, may also demonstrate prolonged, delayed enhancement on a multiphase scan, which aids in differentiation on CT. Pleuropulmonary synovial sarcomas also may demonstrate either focal or dispersed calcifications, helping to distinguish synovial sarcomas from other types of sarcomas [3].

Magnetic resonance imaging often demonstrates a well-defined mass with lobulations and internal multilocular fluid components, as well as peripheral rim enhancement after gadolinium-based contrast administration, corresponding to lobules of viable tumor [1, 2, 5, 7]. Multicystic synovial sarcomas often are characterized by internal haemorrhage, which may also be demonstrated by a high signal intensity on T2-weighted MRI images [1]. The role of 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) has not been well defined; however, as in other pleuropulmonary malignancies, it is useful for the evaluation of local and distant disease.

II Pathology

Histologically, synovial sarcoma may be differentiated into monophasic, biphasic, or poorly differentiated subtypes. Monophasic synovial sarcoma consists of only a spindle cell component, whereas biphasic synovial sarcoma has both a spindle cell and an epithelial component. The spindle cell nuclei are generally uniform, ovoid, pale-staining and overlapping, with scant cytoplasm. The epithelial cells of the biphasic type, however, have round to oval vesicular nuclei, contain abundant cytoplasm and have distinct cellular borders, classically forming mucinous glands or spindle cell-containing papillary structures. Poorly differentiated synovial sarcoma demonstrates high cellularity, comprised of sheets of dark-stained round-to-ovoid cells, numerous mitoses and often necrosis.

III Genetic Analysis

An essential component of the diagnosis of synovial sarcoma is the demonstration of the balanced reciprocal translocation t(X;18)(p11.2;q11.2), resulting in *SSX18-SSX1*, *SSX18-SSX2* (more common in female patients) and *SSX18-SSX4* gene fusions. Immunohistochemistry is often positive for the expression of keratins, bcl-2 protein and epithelial membrane antigen (EMA) as well. Both biphasic and monophasic synovial sarcoma share immunoreactivity to bcl-2, as well as to vimentin and CK, however, positive CD99 stains suggest biphasic synovial sarcoma, which may represent an important distinguishing factor between subtypes [8-10].

IV Prognosis

Prognostically, pleuropulmonary synovial sarcoma portends a poorer outcome than soft tissue synovial sarcoma due to its increased aggressiveness, often demonstrating local recurrence after treatment, along with distant metastases, truncal primary synovial sarcomas such as pleuropulmonary synovial sarcoma demonstrate up to 2.5 fold higher sarcoma-specific mortality and all-cause mortality than those of other primary sites [6]. Compared to other synovial sarcomas, however, there is no difference in disease-free survival [9].

Conclusion

Primary pulmonary synovial sarcomas are rare synovial sarcomas, even more scarce among all soft tissue sarcomas, but they are being reported increasingly more frequently in the literature worldwide. Diagnosis may be made with relative confidence in the presence of the reciprocal translocation t(X;18) (p11.2; q11.2), in the setting of multiple histochemical markers (e.g., bcl-2, EMA, and keratins) and certain clinical and radiographic findings. Insufficient evidence exists on whether the increase in reporting directly relates to an increase in incidence or rather an increase in awareness. As it stands, no guidelines exist on the management of this particular disease. Wide surgical resection with/without neoadjuvant chemoradiation has been advocated in selected patients. Its apparent male predominance, implications of subtype and association with gene mutation, smoking status and other pulmonary comorbidities are considerations for future investigation. Detailed, long-term follow-up of patients will allow for more targeted treatment approaches to improve the overall survival and quality of life in this very aggressive disease.

Conflicts of Interest

None.

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