**Case Report**

**A second primary synovial sarcoma of pleural developed nine-years after the first synovial sarcoma of plantar pedis: a case report and review of literature**

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Received February 13, 2019; Accepted March 26, 2019; Epub July 1, 2019; Published July 15, 2019

**Abstract:** Synovial sarcoma is a rare cancer which occurs primarily in the extremities of young adults. Among them, synovial sarcoma of pleura is a very rare type. Only less than 50 cases have been reported in the literature. Here we report a unique case of synovial sarcoma of pleural. The patient was a 53-year-old man complained of cough, hemoptysis and shortness of breath for 5 month. Chest CT scan revealed a large mass lesion in the left lung, and several metastatic legions in both lungs. No other organs were involved at the time of examination. The patient had synovial sarcoma at right plantar nine years ago. The tumor was surgically removed and followed with radiotherapy for half a month. The patient did regularly follow-up examinations for 5 years, and no metastasis and recurrence were found. He was in remission for 9 years. The patient was admitted in hospital, and the fine needle biopsy and histology studies supported the diagnosis of primary synovial sarcoma of pleural. Cytogenetic fluorescence in situ hybridization (FISH) confirmed the tumor had t(X;18) chromosomal translocation. He received 2 cycles of chemotherapy, and unfortunately tumor didn’t response to the treatment. The patient was discharged without further treatment. This is the first case report that patient developed a second primary synovial sarcoma of pleural after nine years remission of the first primary synovial sarcoma in plantar.

**Keywords:** Synovial sarcoma, pleural, synovial sarcoma, chemotherapy, lung malignancy

**Case report**

The patient was a 53-year-old man complained of increasingly expectoration, cough and hemoptysis for 5 months. Physical examination was unremarkable. His medical history was significant as he was diagnosed with synovial sarcoma of plantar pedis 9 years ago. The tumor was surgically removed and the patient was followed with half-month radiotherapy. He received regularly follow-up examinations for 5 years, and no tumor recurrence and metastasis were found. He was in remission for nine years until he developed pulmonary symptoms recently. PET/CT scan revealed a mass legion (8.5×6.2×8.9 cm³) in the left lower lung, and standardized uptake value (SUV) max was 5.5. There were several smaller mass legions in both lungs (Figure 1). According to PET/CT, lung metastasis of left lung cancer was considered. The CT-guided lung mass fine-needle biopsy was performed. The patient was diagnosed with poorly-differentiated synovial sarcoma based on pathological presentation (Figure 2). Further immunohistochemistry staining showed the tumor was CD99+ EMA+ Vimentin+, and there were a few CD56+ cells (Figure 3), and 20% Ki67+ cells. Fluorescence in situ hybridization (FISH) analysis disclosed a signal constellation indicative of t(X;18) chromosomal translocation (Figure 4A). Therefore the patient was diagnosed with synovial sarcoma of pleural.

In August 2008, the patient went to see a doctor because of right plantar tumor accompanied with pain for 1 year and it began to grow bigger in recent 2 months. He was diagnosed with synovial sarcoma, and the lesion was removed completely by surgery. Pathologically the tumor was mainly composed of spindle cells with abundant nuclear division, and tumor interstitial vascular hyperplasia was observed.
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Figure 1. Computed tomography scan showed a large lump mass in left lung, and several metastasis in both sides. A. Lung window. B. Meditational window.

Figure 2. Hematoxylin-eosin staining of specimens. (A) Synovial sarcoma of plantar. Biphasic glandular structures were formed amid a spindle cell background (H&E ×100), (B) poorly-differentiated sarcoma of pleural. The tumor was mainly composed of spindle cells with abundant nuclear division, and tumor interstitial vascular hyperplasia can be seen easily (H&E 100×).

Moreover immunohistochemical staining indicated that tumor was CK EMA S100 Vimentin bcl-2 CD99 CD34 SMA SA. He was treated with radiotherapy for half a month after surgery. He did follow-up with comprehensive examinations every 3 months for 2 years, and then twice a year in the following 3 years. No tumor recurrence or metastasis was found. The patient remained in cancer-free condition until recent complains of cough and hemoptysis.

The patient was diagnosed with synovial sarcoma of pleural based on biopsy results. The second synovial sarcoma developed 9 years after the first primary sarcoma of the foot was clinically cured. And we further did FISH re-

analysis of previous sarcoma tissues from planar, and found out there was no rearrangement of the gene SYT (Figure 4B), while the recent lung sarcoma had positive SYT translocation (Figure 4A). In addition, the two sarcomas were pathologically different. The first sarcoma was biphasic sarcoma, which was composed predominantly of spindle cells. On the other hand, the second sarcoma was poorly differentiated sarcoma. Taken together, we concluded that the second synovial tumor of pleural was a primary tumor, but unlikely a metastasis tumor from previous synovial sarcoma.

This is the first case report of patient developed second primary synovial sarcoma after he was in remission for 9 years of his first sarcoma. It is hypothesized that the patient may have a unique genetic risk factor that may contribute to both incidences. However, since we didn’t do whole genome sequencing, we couldn’t provide any further explanation why this patient developed two sarcomas in ten years.

After the diagnosis was confirmed, the patient was treated with 2 cycles of 21-day systemic chemotherapy. The regimen included statin (30
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mg at D1-2), Docetaxel (160 mg at Day 2), and carboplatin (700 mg at Day 2). The patient’s overall condition and tumor response to chemotherapy was closely monitored. Unfortunately, after 2-cycle of chemotherapy, the tumor didn’t shrink. The patient was very weak and he refused further chemotherapy and targeted immunotherapy. He requested Chinese herbal medicine for three months and he was discharged. He was alive as of last follow-up in May 2018.

Discussion

Among thoracic malignancies, soft tissue sarcomas (STS) are estimated to be as low as 0.5% [1]. Synovial sarcomas are a rare variety of STS possessing features of both sarcoma and carcinoma. It is usually observed to occur in the extremities of young adults [2]. Synovial sarcoma of pleural is extremely rare, and only less than 50 cases have been reported previously [3-6]. Because of its rarity, pleural synovial sarcoma is often mistakenly diagnosed as mesothelioma, the most common type of the pleural malignancy [7, 8]. The diagnosis requires clinical, radiological, pathological, and immunohistochemical investigations to exclude alternative primary tumors and metastatic sarcoma [9]. Synovial sarcoma is highly aggressive and overall 5-year survival rate is 50%. The risk factors associated with poor prognostics include ages over 20 years-old, female, incomplete resection, tumor size >5 cm, extensive tumor necrosis, high number of mitoses (10 per 10 high-power fields), SYT-SSX1 variants, and neurovascular invasion [10-15].

According to cellular morphology there are three subtypes: (1) monophasic, which contains predominantly spindle cells; (2) biphasic, which contains spindle and epithelial-like cells, with areas recapitulating gland formation; and (3) poorly differentiated, which can be characterized by necrosis, bizarre mitoses, high cellularity, and nuclear atypia, but perhaps more often is seen as a proliferation of small, round cells. Synovial sarcomas are usually positive for vimentin, EMA, bcl-2, CD99 (60%-90%) and S100 (30%) [16]. The majority of synovial sarcomas (90%) carry the pathognomonic t(X; 18) translocation, resulting in fusion of the SS18 (formerly SYT) gene on chromosome 18 with an SSX gene on chromosome X (SSX1, SSX2, or rarely SSX4) [17].

In this case, the patient had two incidences of primary sarcoma, one was in right planar, and the other one was in pleural membrane of lung. Pathologically, the first sarcoma presented as

Figure 3. Immunohistochemistry staining of tumor biomarkers. (A) CD99, (B) EMA, (C) CD56, and (D) Ki67 (100×).

Figure 4. FISH analysis using a SS18 break-apart probe. (A) synovial sarcoma of pleural disclosed a rearrangement of the gene, (B) synovial sarcoma of right planar showed no rearrangement (1000×).
biphasic synovial sarcoma, the tumor was mainly composed of spindle cells with abundant nuclear division, and tumor interstitial vascular hyperplasia was observed (Figure 2A). The tumor stained CK EMA S100 Vimentin bcl-2 CD99 CD34 SMA SA. FISH analysis showed no (X; 18) translocation. The second pleural synovial sarcoma was poorly differentiated synovial sarcoma pathologically. The tumor stained positive for CD99 EMA and Vimentin, and 20% cells were Ki67+, and a few cells were CD56+. FISH analysis confirmed t(X; 18) translocation. Therefore, the two incidences of sarcoma were genetically and pathologically different, supporting the diagnosis that the recent tumor in lung was a primary pleural synovial sarcoma, instead of the metastasis of previous synovial sarcoma in plantar.

Surgery removal is the first choice to treat synovial sarcoma, if it is possible. The adjuvant chemotherapy or radiotherapy after surgical resection may increase disease-free survival. As in this case, the patient had synovial sarcoma on his planar nine years ago. That tumor was surgically removed and followed by radiotherapy for half a month. He was in remission for almost nine years. For un-resectable advanced disease, systemic chemotherapy is widely applied. However, there is no standard chemotherapy regime for this rare tumor. Single-agent anthracycline (mainly doxorubicin) or an anthracycline-based combination with others such as ifosfamide and dacarbazine had been used to treat synovial sarcoma [16]. In this case, at the time patient was diagnosed, the tumor was already metastasized to both lungs. He was treated with systemic chemotherapy with statin, docetaxel, and carboplatin. However, after 2 rounds of chemotherapy, the tumor was not responsive to this treatment.

Immunotherapy is new era for cancer treatment. So far there are many exciting and encouraging progress have been made in cancer treatment, especially after the discovery of antibodies targeting PD-1/PD-1L in cancer treatment [18]. There is a report that multiple receptor tyrosine kinase (RTK) networks are proved to be active in synovial sarcoma [19]. Their co-inhibition may be expected to get synergistic antitumor effects [20-22]. There are a few ongoing clinical trials that try to find the optimum treatment for synovial sarcoma. Recent phase II and III studies suggested that pazopanib, a potent and selective multi-targeted RTK inhibitor, has activity in metastatic and refractory synovial sarcoma. In EORTC study 62043 the 3-month progression-free survival rate was 49% (18/37 patients), partial responses were noted in five patients, and the median overall survival duration was 310 days [23]. In another ongoing phase II trial, a VEGFA antibody plus radiation were used to treat large primary or recurrent synovial sarcoma [20]. However, in a previous phase 2 study (NCT-00831844), the IGF-1R antibody cixutumumab was found to have no benefit in 11 patients with recurrent refractory synovial sarcoma [20, 24]. Taken together, there are still no very effective treatment for synovial sarcoma, and more basic research and clinical trials will be needed to understand the pathological mechanism of synovial sarcoma and find an effective treatment regime for patients.

Conclusion

Synovial sarcoma is a malignant disease that mostly occurs in the extremities of young adults. Primary pulmonary synovial sarcoma presenting with intrapulmonary metastasis is extremely rare, which may have been a bad factor in the poor prognosis. In this situation, the raised awareness of diagnosis and knowledge concerning the clinical presentation of primary pulmonary synovial sarcoma are key factors in ensuring an immediate diagnosis and adequate intervention. Current multidisciplinary treatments include surgical resection, radiation, chemotherapy and targeted therapy. Whereas the overall prognosis is still poor, understanding the molecular mechanisms of the disease will possibly help in finding newer and more effective therapies prolonging survival time for patients with advanced and relapsed synovial sarcoma.

Disclosure of conflict of interest

None.

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