Molecular Detection of SYT-SSX Fusion Gene Transcripts Currently Represents the Most Specific and Sensitive Tool for Diagnosing Intrathoracic Synovial Sarcoma

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Synovial sarcoma develops as a primary neoplasm of soft tissues, particularly of the extremities, but it has been also reported in a large variety of sites. This tumor is not derived from “synovium”, but from immature mesenchymal elements. Synovial sarcoma accounts for approximately 8-14% of soft tissue sarcomas (1, 2). Although metastases to the lung and/or pleural cavity are common events in the clinical course of neoplastic diseases, primary pulmonary sarcomas are very uncommon in comparison with metastatic sarcomas and sarcomatoid carcinomas. Primary intrathoracic synovial sarcoma, arising from lungs, pleural cavity, mediastinum, and heart, was believed to be a rare disease in the past. However, the recent report provides evidence that malignant fibrous histiocytomas and synovial sarcomas might be the most frequent primary sarcomas of the lung (3). Furthermore, in the series of intrathoracic synovial sarcoma, the lung was most frequently involved, followed by the pleural cavity and mediastinum (2). In previously reported cases of primary synovial sarcomas of the lung, patients presented with cough, dyspnea, chest pain, and hemoptysis. Hemothorax, hemopleuresia, pneumothorax, and/or pleural effusions were mostly related to pleural involvement. In general, synovial sarcoma presents in adolescents and young adults, but patients with primary synovial sarcomas of the lung were significantly older than those with their soft tissue counterparts (2). Almost all the patients had large pleural-based intrathoracic masses at presentation. Intrathoracic synovial sarcomas must be differentiated from other primary thoracic neoplasms, such as malignant fibrous histiocytomas, malignant mesotheliomas, adenocarcinomas, and carcinosarcomas. According to the histologic pattern based on the predominance of either epithelioid or spindle cell types, synovial sarcomas are divided into four different histologic types: biphasic, monophasic fibrous, monophasic epithelial, and poorly differentiated. Immunohistochemistry is a useful tool for detecting some signs of epithelial differentiation in the spindle cell component. Pelmus et al recently showed that the immunoreactivity of the tumor cells for EMA and cytokeratins (clone AE1/AE3), in combination with negative reactivity for CD34, were the most reliable markers for the diagnosis of synovial sarcoma (4). However, this immunophenotype is not completely specific for synovial sarcoma. Begueret et al indicated a frequent positivity for bcl-2 and CD99 in intrathoracic synovial sarcoma as well as occasional expression of S-100 protein, alpha smooth muscle actin, c-Kit, and CD34, and calretinin (2). There seems to be some potential pitfalls of immunohistochemical evaluation in the diagnosis of synovial sarcoma. Coindre et al reported a prospective study of 204 cases of possible synovial sarcoma to investigate the utility of molecular testing (5). They concluded that molecular testing proved to be very helpful or necessary when the diagnosis of synovial sarcoma was possible or the monophasic spindle cell type of synovial sarcoma was recognized in uncommon or unexpected sites, such as the lungs, pleural cavity, mediastinum and retroperitoneum. Molecular diagnosis has been successfully performed by reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, using RNA extracted from frozen materials or archival paraffin-embedded specimens. This molecular-based examination has increased the sensitivity and specificity of the diagnosis of synovial sarcoma by detecting the specific translocation t (X;18) (SYT-SSX). The t (X;18) (p11.2;q11.2) translocation found in synovial sarcoma results in the fusion of the SYT gene on chromosome 18 to either of two homologous genes, SSX1 or SSX2 on chromosome X. Although the SYT-SSX fusion proteins may trigger the development of synovial sarcoma, the biological function of SYT-SSX genes remains to be elucidated; the SYT protein is thought to function as a transcriptional activator, whereas the SSX protein as a transcriptional co-
repressor.

In No. 10 issue of Internal Medicine, Zamarron et al reported a case of primary synovial sarcoma of the lung, with SYT-SSX2 gene transcripts demonstrated in the tumor tissues using RT-PCR analysis (6). In order to make a definite diagnosis as intrathoracic synovial sarcoma, molecular-based examination is considered to be an essential adjunct to conventional histology and immunohistochemistry. Most biphasic tumors have been found to have an SYT-SSX1 fusion transcript, and most monophasic tumors have an SYT-SSX2 transcript. Several studies on soft tissue synovial sarcomas have demonstrated a tendency for SYT-SSX1 variant to behave more aggressively than SSX2 variants (7), while the opposite results were obtained in a recent study (8). Therefore, the relationship between fusion gene types and the prognosis is thought to be still controversial. Intrathoracic synovial sarcomas are much more aggressive than their soft tissue counterparts and the prognosis for patients with primary synovial sarcoma of the lung is poor, with an overall 5-year survival rate of approximately 50% (1). Factors predicting a worse prognosis for patients with synovial sarcomas include large tumor size, male gender, older age (>20 years), extensive tumor necrosis, large number of mitotic figures, neurovascular invasion, and poorly differentiated type in histology. There is no standardized treatment; most patients are treated with surgery or with surgery plus adjuvant radiotherapy. Synovial sarcomas are chemosensitive to ifosfamide and doxorubicin, with an overall response rate of approximately 24% (9). In spite of the rarity of this tumor, randomized phase III studies will be required to clarify the superiority of postoperative adjuvant chemotherapy, as compared with surgery alone.

References


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