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Clinical and Pathologic Biomarkers of Metastases in Primary Thoracic Synovial Sarcoma

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Abstract

Limited research surrounding potential biomarkers in synovial sarcoma exists, with inconclusive results pertaining to prognostic utility of SS18/SSX fusion types. We evaluated clinical and pathologic parameters in 8 cases of metastatic primary thoracic synovial sarcoma and compared our results with published cases without metastases in an effort to identify clinical and/or pathologic biomarkers of metastatic disease. Patients were 4 males and 4 females, aged 10 to 73 years (mean, 42) with metastatic primary thoracic synovial sarcoma. Primary tumors were in lung (5), pleura (2) and mediastinum (1). Treatment was complete excision. None had adjuvant treatment. Five patients had local recurrence. Metastases were to regional lymph nodes (5), bilateral lungs (1), liver (1), and spleen (1). Histological features were those seen with usual pulmonary and soft tissue synovial sarcoma including monophasic (5) and biphasic (3) tumors with dense cellularity, interlacing fascicles, and hyalinized stroma. Five of 8 cases showed unusual histology of papillary formations (1), Verocay bodies (1), rhabdoid morphology (1), and adenomatoid foci (1). The chromosomal translocation t(x;18) was present in 6 cases with available tissue where 3 were fusion type SS18/SSX1 and 3 were fusion type SS18/SSX2. In contrast to published rates in primary thoracic synovial sarcoma cases without metastases, a higher proportion of our metastatic thoracic synovial sarcoma cases showed local recurrence of disease (63% *vs*. 28%), and histology unusual for synovial sarcoma (50% *vs*. 20%). These variables may therefore represent clinical and histologic biomarkers of metastatic disease, and may be useful in early targeting of select patients for adjuvant treatment.

Keywords: Synovial sarcoma; Pulmonary sarcoma; Metastatic sarcoma; Biomarkers

Introduction

Synovial sarcoma is a rare and aggressive neoplasm conventionally involving knee and ankle of young adults and children [1]. However, it is now known to affect older adults and involve numerous sites including soft tissue around other joints, retropharynx, oral cavity, salivary glands, abdomen, retroperitoneum, blood vessels, GI tract, kidneys, prostate, vulva and lung and mediastinum [2]. Grossly it is a well-circumscribed firm tan-pink-grey lesion with dense spindle cells microscopically. Well-formed epithelial components can be seen with biphasic tumors as can poorly differentiated tumors showing round, or rarely, rhabdoid cells. Stromal hyalinization, hemangiopericytoma-like vasculature and focal myxoid areas are also common. Tumors are typically immunoreactive with Bcl-2 and CD99 as well as at least focally with at least one epithelial marker [3]. The t(x;18) translocation and SS18/SSX fusion products are pathognomonic and present in greater than 90% of cases.

Synovial sarcomas often recur locally and metastasize to lymph nodes in 10% to 15% of cases [2], the latter being an unusual feature of other soft tissue sarcomas. Preferred treatment is surgical excision with clear margins and adjunctive high dose radiation therapy. Five-year survival is around 50%, although younger patients, and patients with distal tumour sites, smaller tumors (<5 cm) and heavily calcified lesions do better. Metastases occur in approximately 13% of primary thoracic synovial sarcomas most commonly to regional lymph nodes and bilateral lungs [4]. While this is less than the 50% to 70% metastatic prevalence in soft tissue synovial sarcoma [5], mortality from metastases in primary thoracic synovial sarcoma remains high at around 50% to 60% [4,6].

Limited research surrounding potential biomarkers in synovial sarcoma exists, with inconclusive results pertaining to prognostic utility of SS18/SSX fusion types. Several studies of soft tissue synovial sarcoma have suggested that SS18/SSX fusion type is of prognostic value [7-10], while a more recent study has found no prognostic difference between fusion types [11]. Missense mutations in ADAM17 have been found to enhance cell migration and were identified solely in

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metastatic soft tissue synovial sarcoma compared with primary tumors [5]. We evaluated clinical and pathologic parameters in 8 cases of metastatic primary thoracic synovial sarcoma and compared our results with published cases of primary thoracic synovial sarcoma without metastases [4,6] in an effort to identify clinical and/or pathologic biomarkers of metastatic disease to add to the literature of these rare tumors.

Materials and Methods

From 61 cases diagnosed as primary thoracic synovial sarcoma, from 1981 to 2020, 8 cases with metastases were retrieved from tissue archives. Hematoxylin and eosin-stained sections were reviewed. Tumors were subtyped as monophasic or biphasic according to World Health Organization criteria [3]. Grading by tumor cell differentiation, mitotic rate, and necrosis was performed following the French Federation of Cancer Centers (FNCLCC) scheme. Immunohistochemistry was performed on paraffin embedded sections. Molecular analysis was performed using RT-PCR on RNA extracted from paraffin embedded samples. Cases that failed to meet the World Health Organization histologic and/or immunohistochemical criteria for synovial sarcoma had been excluded. A chest radiograph and computed tomography study were available from one case. Follow-up data were obtained from patient records. Data was compared to published cases without metastases.

Results and Discussion

Patients were 4 males and 4 females, aged 10 to 73 years (mean, 42) with symptoms of cough, chest pain, hemoptysis and shortness of breath. Tumors ranged in size from 2 cm to 16 cm (mean, 8) and were well-circumscribed, soft, tan-white hemorrhagic necrotic masses, in lung (5), pleura (2) and mediastinum (1). Chest radiograph (1) showed a homogeneous mass with well-demarcated borders and contralateral mediastinal shift. Contrast-enhanced computed tomography (1) showed a heterogeneous cystic pulmonary mass with a thickened wall and metastatic pleural nodule (Figure 1). Treatment was complete excision. None had adjuvant treatment. Five patients had local recurrence. Metastases were to regional lymph nodes (5), bilateral lungs and pleura (1), liver (1), and spleen. (1) Follow-up was between 8 and 160 months (mean, 52) with 4 patient's dead of disease, 2 with no evidence of disease, 1 alive with disease, and 1 lost to follow-up. Histological features were those seen with usual pulmonary and soft tissue synovial sarcoma including monophasic (5) and biphasic (3) tumors with dense cellularity, interlacing fascicles, and hyalinized stroma (Figure 2). Five of 8 cases showed foci of unusual histology for synovial sarcoma, that is, papillary formations (1), Verocay bodies (1), rhabdoid morphology (1), and adenomatoid foci (1) (Figure 3). Immunohistochemical studies showed focal positive staining for at least one epithelial marker including pan-cytokeratin, epithelial membrane antigen, and cytokeratin 7 in 6/8 cases. Tumors were also focally positive for CD56. S-100, smooth muscle actin, desmin and CD34 were negative. The chromosomal translocation t(x;18) was present in 6 cases with available tissue where 3 were fusion type SS18/SSX1 and 3 were fusion type SS18/SSX2. A higher proportion of our metastatic thoracic synovial sarcoma cases showed local recurrence of disease (63% *vs.* 28%), and histology unusual in synovial sarcoma (50% *vs.* 20%) compared with rates in thoracic cases without metastases from published large case series [4,6] (Figure 4).

Research surrounding potential biomarkers in synovial sarcoma is limited. Results have been together inconclusive pertaining to the molecular biomarker SS18/SSX fusion types. Some studies of soft tissue synovial sarcoma have suggested that SS18/SSX fusion type is of prognostic value, [7-10] while a more recent study has found no prognostic difference between SS18/SSX1 and SS18/SSX2 fusion types [11]. Missense mutations in ADAM17 have been found to enhance cell migration [5], and these were identified only in metastatic soft tissue synovial sarcoma compared with primary tumors [5]. In our study, we evaluated clinical and pathologic parameters in 8 cases of metastatic primary thoracic synovial sarcoma and compared our results with published cases without metastases in an effort to identify clinical and/or pathologic biomarkers of metastatic disease in thoracic synovial sarcomas to aid in early recognition of patients who may benefit from adjuvant therapy. Although our sample of thoracic synovial sarcomas with metastases is small, it is the largest in the thoracic synovial sarcoma literature due to the rarity of this tumour. Future research will hopefully build on these findings as more cases accumulate.

Conclusion

In contrast to published rates from large case series of primary thoracic synovial sarcomas without metastases, a higher proportion of our metastatic thoracic synovial sarcoma cases showed local recurrence of disease (63% *vs.* 28%), and focal histology unusual for synovial sarcoma (50% *vs.* 20%). These variables may therefore represent clinical and histologic biomarkers of metastatic disease,

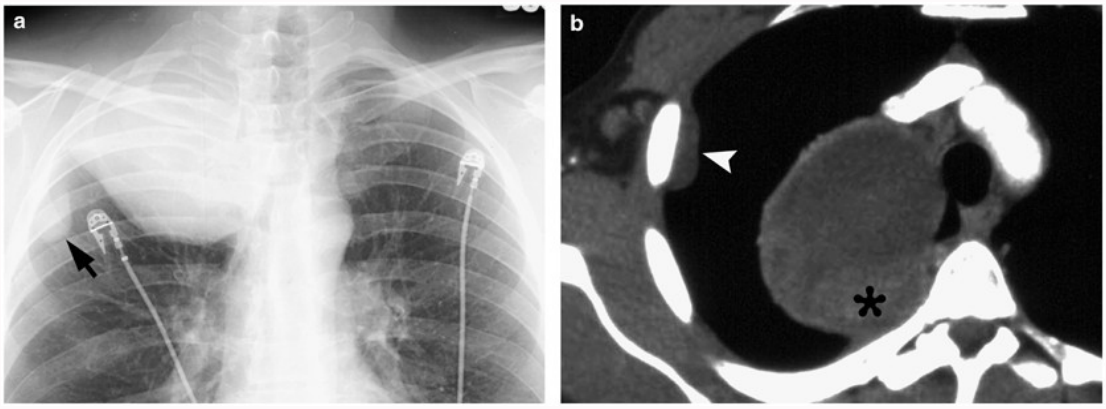

Figure 1: Synovial sarcoma in a young man with shortness of breath. Chest radiograph (**a**) demonstrates right apical mass. A pleural-based nodule (arrow) lies inferiorly. Contrast-enhanced CT scan (**b**) demonstrates a cystic pulmonary mass with thickened wall (asterisk) and a metastatic nodule (arrowhead) along lateral pleuron.

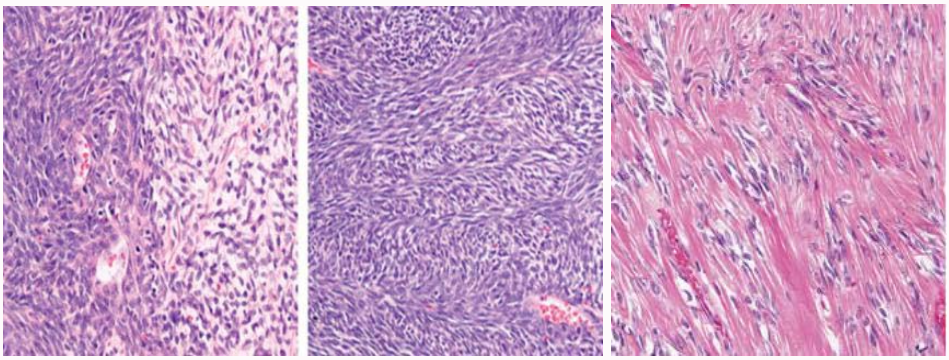

Figure 2: Histologic features of synovial sarcoma. Synovial sarcoma is one of the most cellular spindle cell neoplasms of the lung and is characteristically composed of densely cellular interlacing fascicles (center) alternating with occasional hypocellular myxoid areas (left) and shows areas of hyalinized pink stroma (right).

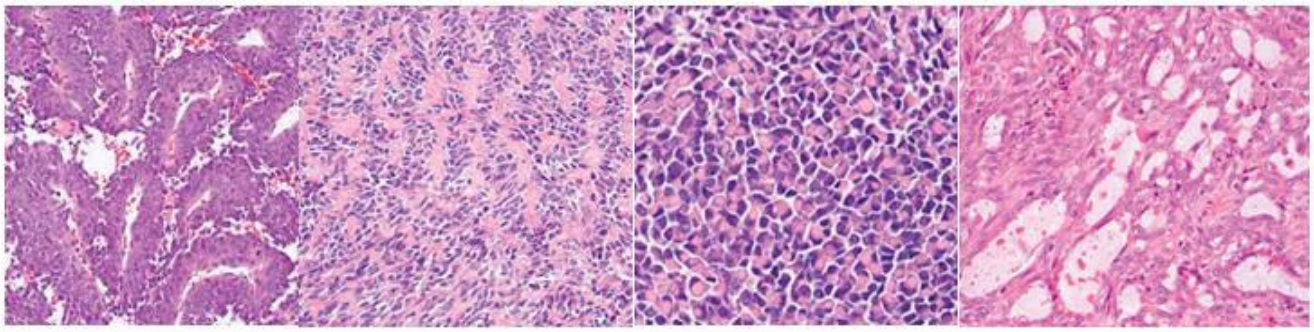

Figure 3: Unusual histology for thoracic synovial sarcoma includes (from left to right) papillary architecture, Verocay bodies, rhabdoid morphology and adenomatoid features.

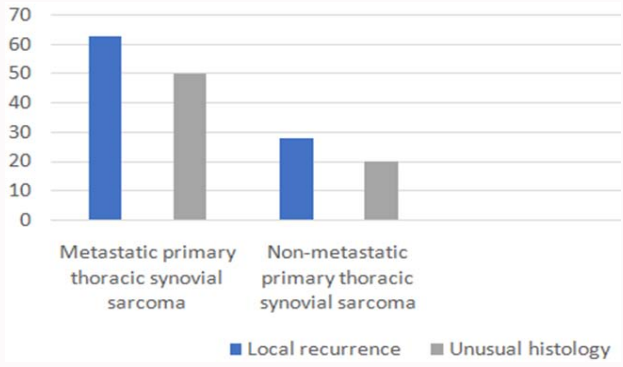

Figure 4: Local recurrence and unusual histology in metastatic *vs.* non-metastatic primary thoracic synovial sarcoma cases (%).

and may be useful in early targeting of select patients for adjuvant treatment. Close clinical follow-up to identify local recurrence and thorough histologic sampling to ensure identification of unusual histology will facilitate identification of these potentially treatment-guiding biomarkers in this rare but aggressive tumour.

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