Pathology (■ 2018) ■(■), pp. 1–6

ANATOMICAL PATHOLOGY

Pleural malignant mesothelioma versus pleuropulmonary synovial sarcoma: a clinicopathological study of 22 cases with molecular analysis and survival data

Sonja Klebe[1,2], Sarita Prabhakaran[1], Ashleigh Hocking[1], Emily Pulford[1], Sarah Moore[3], Mario Nicola[3], Philip W. Allen[2], Douglas W. Henderson[1]

[1]*Department of Anatomical Pathology, Flinders University, SA, Australia;* [2]*SA Pathology Department of Surgical Pathology, Flinders Medical Centre, Bedford Park, SA, Australia;* [3]*SA Pathology Department of Molecular Pathology, Adelaide, SA, Australia*

Summary

The aim of this study was to carry out a comparative analysis by transducin-like enhancer of split 1 (TLE1) immunohistochemistry and molecular analysis of SYT-SSX, for 16 pleural predominantly sarcomatoid mesotheliomas and six cases of pleuropulmonary synovial sarcoma (five pleural in distribution only, with one case of a predominantly subpleural upper lobe synovial sarcoma), all of which were solely or predominantly monophasic. Our comparison included survival and some clinical data.

We consider that the following points emerged from this study:

- Clear discrimination between pleural sarcomatoid mesothelioma and synovial sarcoma can be impossible from H&E-stained sections and conventional immunohistochemical markers for mesothelioma, and on TLE1 immunolabelling.
- In line with current approaches to diagnosis, we defined the mesotheliomas according to their negative SYT-SSX status, versus a positive result by fluorescence *in situ* hybridisation (FISH) or by reverse transcriptase PCR (RT-PCR) for synovial sarcoma.
- In this series, predominantly sarcomatoid mesotheliomas out-numbered the synovial sarcomas in a ratio of ~3:1.
- The synovial sarcomas were diagnosed in patients significantly younger on average than the sarcomatoid mesotheliomas.
- The synovial sarcoma patients had significantly longer survivals than the predominantly sarcomatoid mesotheliomas.

Key words: Pleura; mesothelioma; sarcomatoid; biphasic; monophasic; synovial; sarcoma; TLE1; t(X;18); FISH; RT-PCR; age; survival.

Received 17 April, revised 14 June, accepted 25 June 2018
Available online: xxx

INTRODUCTION

The histological differential diagnosis between pleura-based biphasic and especially monophasic malignant neoplasms with a spindle-cell component can pose a significant conundrum. This problem especially focuses upon the distinction between malignant mesothelioma and synovial sarcoma and, occasionally, spindle-cell carcinoma of lung.[1–8] It is well known that the role of immunohistochemistry (IHC) is much more restricted for diagnosis of sarcomatoid mesotheliomas than for epithelioid mesothelioma,[9–11] so that many sarcomatoid mesotheliomas show undetectable or only limited expression of mesothelial markers, such as cytokeratin 5/6, calretinin, WT1, D2-40, mesothelin and HBME1, although they usually show expression of vimentin and low molecular weight or broad-spectrum cytokeratins.[12] In addition, there is an overlap in the patterns of immunolabelling between sarcomatoid malignant mesothelioma and synovial sarcoma.[5] Recently, IHC labelling for the transducin-like enhancer of split 1 (TLE1) has been proposed as a marker for diagnosis of synovial sarcoma.[13,14] Even so, there is a consensus that the 'gold standard' for diagnosis of synovial sarcoma arising in any anatomical site is molecular detection of the t(X:18) translocation, thought to be integral for the development of synovial sarcoma, expressed as a chimaeric gene, SYT-SSX1 or SYT-SSX2.[1,2,4,5,11,15]

The objectives of this study include evaluation of the age of occurrence and survival data for a series of consecutive pleural malignant mesotheliomas and synovial sarcomas, as delineated by a negative or positive result respectively for SYT-SSX on molecular investigation [fluorescence *in situ* hybridisation (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) or both], and IHC for TLE1.

MATERIALS AND METHODS

We reviewed 22 primary malignancies (21 pleural in location only, and one case where the tumour was located in the subpleural zone of an upper lobe[16]), encountered either 'in-house' or cases referred during the period 2005–2018 for a potential diagnosis of synovial sarcoma or where synovial sarcoma was included in the differential diagnosis, as opposed to malignant mesotheliomas with a sarcomatoid component as set forth by the laboratories whence they had originated. On the basis of molecular investigation for the t(X;18) translocation, we assessed 16 cases as predominantly sarcomatoid malignant mesothelioma, and six as synovial sarcoma.

None of the cases of synovial sarcoma was classifiable as poorly differentiated, in that none of the biopsies contained 'primitive'-appearing round-cell sarcomatoid tissue, for example as found in Ewing/primitive neuroectodermal tumour (PNET)-type tumours.[17] Only cases with molecular diagnostics for SYT-SSX and clinical follow-up, and blocks or unstained slides for further IHC studies such as immunolabelling for TLE1, were included in this retrospective study: all of our other cases of malignant mesothelioma and

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2018.06.001

synovial sarcoma were excluded. Because TLE1 labelling and molecular analysis for SYT-SSX took precedence over other IHC studies—and because of insufficiency of tissue remaining after TLE1 or SYT-SSX—additional IHC could not be carried out on some cases, so that the findings for some IHC studies relied on the result obtained by the referring laboratory.

A diagnosis of synovial sarcoma was made based on the presence of t(X;18) by either FISH and/or PCR (SYT-SSX). A diagnosis of mesothelioma was made on the basis of: (1) morphological appearances; (2) positive IHC labelling for cytokeratins (CKs) in 12/16 cases, with three CK-negative cases and one case for which there were no data (Table 1); (3) positive, albeit limited, labelling for mesothelial markers in some but not all cases (see above and Table 1); (4) a negative result for SYT-SSX; and (5) clinical-radiological undetectability of any concurrent or past mediastinal or extrathoracic biphasic or sarcomatoid tumour with the potential for pleural metastasis and histological mimicry of either sarcomatoid malignant mesothelioma or synovial sarcoma.

RESULTS

Data for both the sarcomatoid malignant mesotheliomas and the synovial sarcomas are shown in Table 1 and Fig. 1 and 2. It is evident that the synovial sarcomas occurred in patients younger on average than the sarcomatoid malignant mesotheliomas and that the synovial sarcoma patients had on average substantially better survivals. It is also plain that IHC for TLE1 was of little value for discrimination between these tumours: although all six synovial sarcomas were positive, 7/16 sarcomatoid malignant mesotheliomas were also positive (Fig. 2A and 1C, respectively). We noted the following information specific to certain cases.

For one of our earlier cases of sarcomatoid malignant mesothelioma—when neither FISH nor RT-PCR was routinely available in South Australia for sarcomatoid malignant mesothelioma or synovial sarcoma (or TLE1 IHC) for the differential diagnosis between malignant mesothelioma and synovial sarcoma—a diagnosis of pleural synovial sarcoma was favoured initially on the basis of the histological appearances and non-TLE1 IHC (focal positive labelling for cytokeratins and calretinin, with a negative result for CEA). This was reinforced by expert opinion from pathologists expert in soft tissue tumour and thoracic pathology. Despite a history of past exposure to asbestos, no pleural plaques were identified on imaging. After FISH and RT-PCR became routine, the case was re-investigated, with negative results for SYT-SSX by both FISH and RT-PCR. Tissue was then referred to Rosetta Genomics (https://rosettagx.com/) for micro-RNA analysis and the result was found to be consistent with a diagnosis of malignant mesothelioma.

For a later case, an elderly man with a history of long-past brief occupational exposure to asbestos, the histological appearances were considered to favour a diagnosis of sarcomatoid malignant mesothelioma, but FISH a little while later clearly demonstrated SYT-SSX (Fig. 2B). The findings for this patient from expert thoracic clinicians and radiologists produced opinions on imaging divided between synovial sarcoma and sarcomatoid malignant mesothelioma. This patient had a short survival in contrast to four other pleural synovial sarcomas in this case series.

The diagnosis of pleuropulmonary synovial sarcoma in one female patient,[16] with no plaques and no past history of either occupational or non-occupational asbestos exposure, was

Table 1 Features of malignant mesotheliomas with synovial sarcoma-like features and synovial sarcomas

	Mesothelioma with synovial sarcoma-like features (n = 16)	Synovial sarcoma (n = 6)
Patient demographics		
Age in years, mean (range)	72 (56–88)	44 (9–72)
Gender, M/F	13/3	2/4
Median survival, months (95%CI)	4.5 (2.96–9.42)	>48 (4 alive after 3, 5 and 21 years)
Mean overall survival, months ± SD	9.2 ± 2.1	136.2 ± 35.1
Clinical/Radiology		
Asbestos exposure		
Yes/no/no data	10/3/3	1/2/3
Pleural plaques		
Present/absent/no data	9/1/6	1/2/3
Pleural effusion		
Present/absent/no data	13/3/0	2/2/2
Pathology		
Lesion size to nearest full mm,[a]		
mean (range)	68 (7–220)	37 (20–50)
Histology		
Monophasic/biphasic	13/3	4/2
Immunohistochemistry		
Cytokeratins		
Positive/negative/no data	12/3/1	2/1/3
Calretinin		
Positive/negative/no data	9/5/2	0/2/4
Bcl-2		
Positive/negative/no data	4/1/11	2/0/4
CD99		
Positive/negative/no data	6/1/9	0/0/6
TLE-1		
Positive/negative/no data	7/9/0	6/0/0
FISH/PCR for t(x;18)		
Positive/negative	0/16	6/0

[a] Greatest diameter.

Please cite this article in press as: Klebe S, et al., Pleural malignant mesothelioma versus pleuropulmonary synovial sarcoma: a clinicopathological study of 22 cases with molecular analysis and survival data, Pathology (2018), https://doi.org/10.1016/j.pathol.2018.06.001