CASE REPORT

Clinicopathological Features of Solitary Fibrous Tumors of the Pleura: a Case Series and Literature Review

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We assessed the clinicopathological features of solitary fibrous tumors of the pleura in a case series comprising 30 patients (20 women, 66.6%) with a mean age of 58.39 years. Forty-five percent of the cases were asymptomatic. In 70% of the cases the tumors arose in the visceral pleura. Twenty percent presented multiple tumors, a finding that was associated with intrapulmonary localization and malignant behavior (*P*<.0001) Histology revealed low cell density in 15% of the cases, moderate density in 50%, and high density in 35%; further findings showed atypia in 45% of the cases, necrosis in 25%, and hemorrhage in 15%. More than 4 mitoses per 10 high-power fields were noted in 30% of the cases. Immunohistochemistry results were positive for vimentin in all cases; cells were CD34$^+$ in 85% of the cases, BCL2$^+$ in 65%, and CD99$^+$ in 40%. Findings for keratin and protein S100 were negative in all cases. Malignant biological behavior (local recurrence and metastasis) was observed in 4 cases, 2 of which were CD34$^-$.

Solitary fibrous tumors of the pleura are uncommon neoplasms with unpredictable biological behavior; follow-up should therefore be based on early detection of recurrence or metastasis.

Key words: *Solitary fibrous tumor. Pleura. Biological behavior.*

Tumor fibroso solitario pleural: características clinicopatológicas de una serie de casos y revisión de la bibliografía

Hemos evaluado las características clinicopatológicas del tumor fibroso solitario pleural en una serie de 30 casos. El 70% de los pacientes eran mujeres. El promedio de edad fue de 58,39 años. El 45% de los casos fueron asintomáticos. La localización más frecuente fue la pleura visceral (70%). En el 20% de los casos se observaron tumoraciones múltiples y se asociaron a localización intrapulmonar (p < 0,0001). Histológicamente mostraron densidad celular escasa en el 15% de los casos, moderada en el 50% e intensa en el 35%; atipia en el 45%; necrosis en el 25%; hemorragia en el 15%, y mitosis mayor de 4 por 10 campos en el 30%. La inmuhistoquímica mostró positividad para vimentina (100%), CD34 (85%), BCL2 (65%) y CD99 (40%), y negatividad en el 100% de los casos para queratinas y la proteína S100. Cuatro pacientes presentaron un comportamiento biológico maligno (recurrencia local y metástasis); en 2 de ellos el CD34 había sido negativo.

El tumor fibroso solitario pleural es una neoplasia poco común de comportamiento biológico impredecible, por lo que el seguimiento debe centrarse en la detección precoz de la recurrencia o de metástasis.

Palabras clave: *Tumor fibroso solitario. Pleura. Comportamiento biológico.*

Introduction

A solitary fibrous tumor (SFT) is a rare neoplasm that accounts for 8% of benign chest neoplasms and 10% of pleural tumors.[1] Although the clinical course of most SFTs is biologically benign, malignant behavior has been reported in cases with prolonged follow-up.[2] Such behavior has been related to certain histological features of these tumors.[3] The objective of this study was to evaluate the clinicopathological features of the SFTs in a series of consecutive cases in our hospital.

Case Description

The study included 30 cases of patients who were diagnosed with SFTs of the pleura and surgically treated between 1994 and 2004 in the Hospital General Universitario Gregorio Marañón. We gathered data on patient characteristics, clinical features, and variables related to course of disease over time. The cases were classified according to the criteria of malignancy established by England et al.[4] Specimens for immunohistochemical studies were obtained from all patients, and clinical follow-up was

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TABLE 1
Antibodies Used in the Immunohistochemical Techniques

Antibody	Manufacturer	Dilution
Vimentin	DAKO	1:1.500
CD34	Biogenex	Prediluted
BCL2	Novocastra	1:80
CD99	Novocastra	1:50
Muscle specific actin	DAKO	Prediluted
Estrogen receptors	DAKO	1:6
Progesterone receptors	DAKO	1:3
S100	DAKO	1:1.500
Pancytokeratin	Novocastra	1:100
Androgen receptors	Biogenex	1:40
Calretinin	Zymed	1:50
MioD1	Novocastra	1:40
Mif3	Novocastra	1:40
Mif4	Novovastra	1:30
Ki67	DAKO	1:200

TABLE 2
Immunohistochemical Profile of Solitary Fibrous Tumors of the Pleura

Antibody	Positivity, Grade	Positivity, %
Vimentin	+ + +	100% (20/20)
CD34	+ + +	85% (17/20)
BCL2	+ +	65% (13/20)
CD99	+ +	40% (8/20)
Muscle specific actin	+	20% (4/20)
Estrogen receptors	+	10% (2/20)
Progesterone receptors	+	5% (1/20)
S100	–	0
Pancytokeratin	–	0
Androgen receptors	–	0
Calretinin	–	0
MioD3	–	0
Myf4	–	0

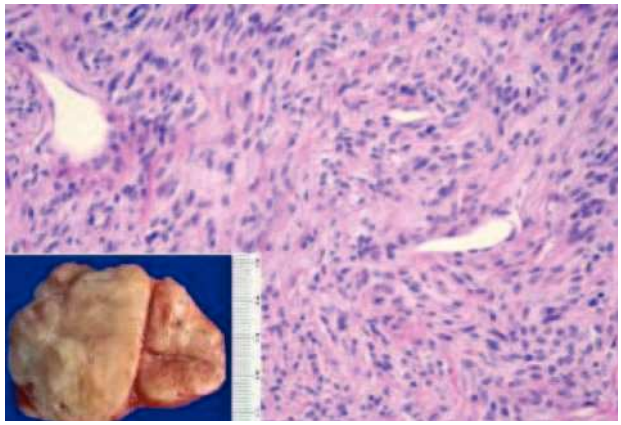

Figure 1. Macroscopic image of a nodular tumor with a smooth external surface. The tumor weighed 282 g and measured 10 9 5 cm. The cut surface is whitish, fascicular, and homogeneous. The microscopic image shows a highly vascularized spindle cell neoplasm with alternating areas of high cellular and low cellular density.

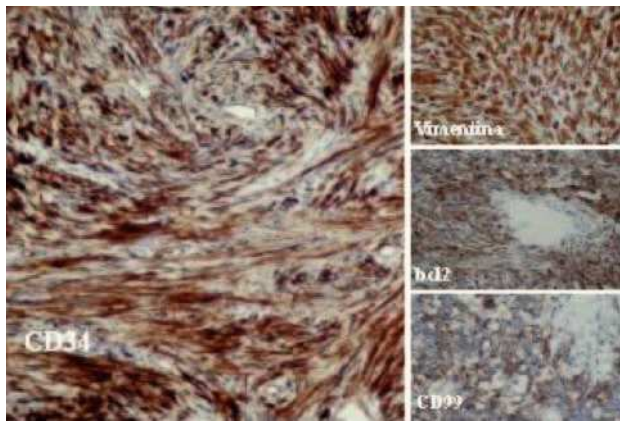

Figure 2. Results by immunohistochemical techniques, positive for CD34, BCL2, CD99, and vimentin.

carried out in the last 20 cases. A monoclonal antibody panel (Table 1) was used for immunohistochemical staining. Four grades of immunoreactivity were established according to the percentage of stained cells (+++: greater than 60% of the cells; ++: 10% to 60%; +: less than 10%; –: absence of positivity). Patients had follow-up visits at monthly intervals immediately after surgery and then later at yearly intervals. Information was gathered from medical records.

The patients' mean age was 58.39 years (range, 18 to 73), and 66.6% (20/30) were women. In 46.6% of the cases the diagnosis was based on incidental findings. Cough was present in 10% of cases, dyspnea in 20%, and chest pain in 20%. No associated extrathoracic signs or symptoms were noted.

Tumors arose in the visceral pleura in 70% of cases (21/31), in the lungs in 10% (3/30), and in the parietal pleura in 16.6% (5/30). Nodules were detected in both the visceral pleura and the lung in 1 case (3.3%). Single tumors were found in 80% of the patients (Figure 1) and multiple tumors in 20%. Fifty-five nodules were observed in 1 case. The mean tumor size was 7.35 cm (range, 2 to 21 cm).

Histology revealed low cell density in 15% of the cases, moderate density in 50%, and high density in 35%; no atypia was noted in 55% of the cases while mild atypia was present in 30% and moderate atypia in 15%; necrosis was observed in 25% of cases, hemorrhage in 15%, and more than 4 mitoses per 10 high-power fields in 30%. Immunohistochemistry results were positive for vimentin in all cases, for CD34 in 85% of the cases, for BCL2 in 65%, and for CD99 in 40%. All cases were negative for keratin and protein S100 (Table 1 and Figure 2).

The mean time of follow-up was 66.32 months. During this time malignant biological behavior was observed in 4 cases (local recurrence and metastasis). Histological signs indicating malignancy in these cases were high cell density, mild or moderate atypia, and a mitotic index greater than 4 mitoses per 10 high-power fields, corresponding to a level of Ki67 staining greater than 10%. Of all the potential histological predictors of malignancy, only the mitotic index was associated with malignant behavior (P=.008). It is important to mention that 2 (50%) of the cases with malignant tumors were $CD34^-$, in the primary as well as in recurrent tumors. Very aggressive development, ending in death, was observed in 1 case. Cytogenic analysis was carried out in this patient to detect SSX/SYT fusion and therefore rule out monophasic synovial sarcoma, but the results were negative.

Discussion

A wide variety of names have been used to describe SFTs of the pleura. We have found the following terms in the literature: localized mesothelioma, benign fibrous mesothelioma, localized benign fibroma, submesothelial fibroma, and subserous fibroma.[5] Although the majority of SFTs are located in the visceral or parietal pleura, they are currently known to arise in other sites such as the peritoneum,[6] pericardium,[6] mediastinum,[7] meninges,[8] lung,[4] thyroid,[9] parotid,[10] orbit,[11] and nose and nasal sinuses.[12] Such a variety of locations indicates that a SFT may start from a common stem cell present in several organs and tissues and that it is probably myofibroblastic in origin.[2] Our series only included cases with tumors located in the chest cavity. Four of these cases had multiple intrapulmonary lesions that were associated with malignant behavior—an association that could suggest a worse prognostic factor.

Clinically, a SFT is asymptomatic, and its diagnosis is usually based on an incidental finding in a chest x-ray. Localized symptoms reported in the literature are cough, dyspnea, chest pain, and pleural effusion, while systemic manifestations include arthralgias, clubbed fingers, and hypoglycemia.[2-4] In our series, the SFTs were incidental findings in 46.6% of cases, and no associated systemic manifestations were noted in any of the cases.

According to Alvarez and Escalona,[13] the histogenesis of SFTs has been debated, and the technique applied to study the tumor has played a direct role in discussions. In 1940, Stout and Murray[14] cultivated a fibrosarcomatous tumor of the pleura in short-term cultures, observing 2 types of cell growth: spindle cells and epithelioid polygonal cells. The cells were arranged in fascicles, arranged radially around the explant. Maximow[15] observed similar growth in cultures of normal as well as inflamed canine pleura, while Murray et al[16] observed the pattern in a biphasic synovial sarcoma. No other study of cultures was reported until that of Sano et al,[17] who observed this same type of cell growth in a similar case. This led Stout and Murray[18] to suggest that the fibrous tumor was a less aggressive one among the malignant forms, so that it also could be classified as a mesothelioma, thus justifying the term benign fibrous mesothelioma. Later, Alvarez and Escalona say that the differential growth of the fibrosarcomatous mesothelioma was described as characteristically occurring inside and outside the lung. Its fibroblastic appearance was easily distinguishable from that of synovial sarcoma, justifying the separation of these 2 entities initially on the basis of description. Immunohistochemical techniques have since emerged to corroborate the distinction that was originally grounded exclusively in microscopic methods and tissue culture studies.

The malignancy potential of a SFT warrants particular attention. The criteria for grading malignancy established by England et al[4] include high cellularity, atypia and nuclear pleomorphism, more than 4 mitotic figures per 10 high-power fields, large areas of hemorrhage and necrosis, pleural effusion, atypical location, and invasion of adjacent structures. The mitotic index was the only histologic criterion associated with worse biological behavior in our study.

The immunohistochemical phenotype should be established by the combination of positive markers (such as vimentin, CD34, BCL2, and CD99) and negative ones (pancytokeratin and S100).

The differential diagnosis of a SFT includes pleural mesothelioma, neurogenic sarcoma, synovial sarcoma, hemangiopericytoma, fibrosarcoma, and malignant fibrous histiocytoma. Sarcomatoid mesotheliomas express high levels of cytokeratin, which is negative in cases of SFT. Neural tumors are positive for S100, which is negative in SFTs. The majority of the monophasic synovial sarcomas are positive for cytokeratin, and they also show the genetic translocation resulting in SSX/SYT fusion.[19] We tested for SSX/SYT fusion in the patient whose development progressed rapidly until her death, and the results were negative. For distinguishing SFTs from hemangiopericytomas, the latter diagnosis is considered to apply only to tumors with pericytic differentiation (glomic cells/smooth muscles), while SFTs are pathologically distinct and have not been associated with a pericytic origin.[20]

Of particular interest in our series were the 3 cases that were negative for CD34; 2 tumors were malignant, and 1 patient died due to tumor progression. Therefore, in SFT cases, CD34 negativity seems to be associated with more aggressive biological behavior, an association that has been reported in previous studies and that could have clinical use in predicting tumor behavior.[21]

Local recurrence has been observed in 9% to19% of cases in spite of complete surgical excision; distant metastasis occurs in 0% to19%, and tumor-related death in 0% to 27%.[4,7] In our series 20% of the cases showed tumor progression despite surgical excision, and 1 of these patients (5%) died.

In summary, pleural SFTs are uncommon neoplasms that are usually asymptomatic and diagnosed by incidental findings on a chest x-ray. The treatment of choice is complete surgical excision. Moreover, in the follow-up of these cases the focus should be on the early detection of local recurrence or of metastasis because the biological behavior is unpredictable.

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