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A retrospective study of 53 cases of primary tumors of the pleura diagnosed over a 16-year period

Mona Mlika, Aida Ayadi-Kaddour, Beya Chelly, Sadok Boudaya, Saoussen Maalej, Tarek Kilani, Faouzi El Mezni

ABSTRACT

Aims: Primary tumors of the pleura are rare, representing only 10% of the pleural tumors. These tumors are represented mainly by malignant pleural mesothelioma. Our aim is to describe the clinical, histologic and radiologic features of the most relevant primary pleural tumors. Besides, we searched to put emphasis on their challenging diagnosis and management. Methods: We describe a study of 53 cases of primary tumors of the pleura diagnosed in the Department of Pathology in the Abderrahman Mami Hospital over a 16-year period from 1995 to 2011. Results: Our study included 37 men and 16 women with a mean age of 57.5 years (range 22 to 72 years). Microscopic findings concluded to malignant pleural mesothelioma in 31 cases, solitary fibrous tumors in 19 cases, and one case each in synovial sarcoma, primary pleural thymoma, and calcifying pseudo-tumor. Inspite of the importance of the radiologic findings, the definitive diagnosis was based on histologic, immunohistochemical findings and FISH technique. The management of the patients was variable. Those with malignant and limited tumors received a multimodal therapy associating surgical resection, chemotherapy and radiation therapy. Benign tumors including benign forms of solitary fibrous tumors and calcifying pseudo-tumor were treated surgically and presented no complications. Conclusion: The primary tumors of the pleura are challenging in their diagnosis because of the multiplicity of mimickers. Besides, their management remains non consensual due to the rarity of clinical data but surgical procedures seem to play a key role not only in enabling their excision but also by providing a definitive diagnosis thanks to surgical biopsies.

Keywords: Primary pleural tumors, Malignant pleural mesothelioma, Solitary fibrous tumors

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INTRODUCTION

The pleura is frequently involved by cancers from different organs. Primary tumors of the pleura account

for only 10% of all pleural tumors. Malignant tumors are dominated by malignant pleural mesothelioma (MPM) which has a bad prognosis. On the other hand, benign tumors are dominated by benign forms of solitary fibrous tumors (SFT) [1]. The pathogenesis of these tumors is different. Some tumors including MPM, SFT or liposaroma are thought to arise from specific cells. Other tumors such as pleural thymoma are thought to arise from ectopic tissue.

MATERIALS AND METHODS

We describe a study of 53 cases of malignant primary tumors of the pleura diagnosed over a 16-year period from 1995 to 2011.

Patients and specimen

Clinical history and radiologic findings were provided from the Departments of Pneumology and Thoracic Surgery of the same hospital. The recorded clinical characteristics consisted in age, sex, eventual asbestos exposure, symptoms, physical findings, radiologic features, treatment modalities and evolution. Hematoxylin and eosin-stained slides from all patients were reviewed for morphologic assessment according to the 2004 World Health Organization classification.

Immunohistochemical methods

Immunophenotypic analysis was performed in all cases with suitable material using 4 μm thick, formalin-fixed, paraffin-embedded sections. All the slides were reviewed. We used the avidin-biotin complex method and commercially available antibodies as follows: pankeratin (monoclonal MNF-116, at a dilution of 1:50; DAKO Corporation), S100 protein (polyclonal, at a dilution of 1:600; DAKO), epithelial membrane antigen (monoclonal E29, at a dilution of 1:10; DAKO), Calretinin (DAKO, France), Vimentin (DAKO, France), HMBE 1 (DAKO, France), CD15 (DAKO, France), TTF1 (DAKO, France), ACE (DAKO, France), Bcl-2 (DAKO, France), CD34 (DAKO, France). Negative and positive control preparations were stained in parallel.

Fluorescence in situ hybridization

For the identified case of synovial sarcoma, we performed FISH analysis on interphase nuclei isolated from paraffin embedded tissue. Nuclei were extracted from paraffin-embedded 50-μm tissue sections as described by Kuchinka and colleagues [2]. For the detection of t(X;18), we used FISH probes for the chromosome X pericentromeric region and for a region within 1 megabase telomeric to the SYT locus on chromosome 18.

RESULTS

Our study contained 37 men and 16 women with a mean age of 57 years (range 22–72 years). Microscopic findings concluded to MPM in 31 cases, SFT in 19 cases, synovial sarcoma in one case, primary pleural thymoma in one case and calcifying pseudotumor in one case.

Clinical data

Clinical data are summarized briefly in Table 1.

Maligant pleural mesothelioma group: In our study, the median age of the patients was 57.5 years (range 22–72 years). A male predominance was observed with M:F ratio of 4.6:1. The mean age at presentation for women was 57.6 years versus 57.5 years for men which is relatively equal. A professional exposure to asbestos was noted in 18 cases. Past medical history was variable and was consistent for diabetes mellitus, hypertension, pneumonitis, cardiopathy, bronchopulmonary obstructive disease, thoracic trauma, inguinal hernia, cholecystectomy. Clinical symptoms were variable and non-specific with the predominance of thoracic pain reaching 86% of the cases. Nine patients were treated by a multimodal therapy associating surgical procedures and/or chemotherapy and/or radiotherapy. Surgical procedures were possible in five cases and followed first-line chemotherapy in four cases. In one case, they consisted in a palliative surgical resection followed by chemotherapy. One patient was explored for a complicated emphysematous bulla with an incidental finding of a 1.5-cm nodule and three patients were treated by extrapleural pneumonectomy. Chemotherapy was used as a first-line treatment in ten cases. First-line chemotherapy was based on the association gemcitabin (1250 mg/m^2) and cisplatin (75 mg/m^2) or the association cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2). Second-line chemotherapy was based on 5-fluorouracil and platinum. Only six patients presented no complications after a follow-up period extending 100 from 2 to 30 months.

Solitary fibrous tumors group: Nineteen cases of SFT were diagnosed over this period. Median age was 57.93 years (range 18–70 years). Five patients were asymptomatic and had benign forms, on the other side, the most frequent symptoms consisted of chest pain and cough. Surgical resection was performed in all patients. Six patients died after a follow-up period ranging from 2–90 months. Five patients presented with malignant form of SFT and one patient with a benign form died because of heart failure.

Case of synovial sarcoma: We present a case of a 49-year-old female with a past medical history of breast cancer diagnosed in 1996, who was explored for chest pain and cough. The patient died before the onset of the treatment.

Case of primary pleural thymoma: We present a case of a 36-year-old male without a significant past medical history, who was explored for respiratory symptoms. Physical examination revealed a 5 cm mass localized below the clavicle. The patient was treated by a surgical resection associated to a chemotherapy. He presented no complications after one year of follow-up.

Case of calcifying fibrous pseudotumor: We present a case of a 38-year-old woman without a significant past medical history who presented chest pain.

The patient was treated by surgical resection. She presented no complications after nine months of follow-up.

Radiologic data

Maligant pleural mesothelioma group: Chest X-ray was performed in all patients and showed pleural effusion in most cases. A chest computed tomography (CT) scan was performed in all cases which show a pleural thickening with or without a parenchymal mass in most cases (Figure 1A). It also showed an extension to the diaphragm in two cases, an aortic extension in one case, a parietal extension in four cases and a costal lysis in three cases. Many diagnoses were proposed based on the radiologic findings including pleural mesothelioma, pulmonary carcinoma, primary or secondary pleural tumor, pleural tuberculosis and pleural solitary fibrous tumor.

Solitary fibrous tumors group: Chest CT scan was performed in all patients. It showed a heterogeneous pleural mass in six patients. Three of

Table 1: Clinical data

	Sex	Age	Asbestos exposure	Symptoms	Histologic diagnosis	TT	Evolution	Follow up period
1	M	70	+	CP, cough, loss of weight	Biphasic MPM	-	LOV	1 month
2	M	50	+	CP, cough, fever	Biphasic MPM	-	Death	2 months
3	M	37	+	CP, cough, dyspnea, DGS	Epitheliod MPM	Talc+ RT+CT	DGS, CP	7 months
4	M	69	+	CP, cough, dyspnea	Epithelioid MPM	Talc+RT+CT	DGS, dyspnea	12 months
5	M	68	+	CP; cough, dyspnea	Epithelioid MPM	-	LOV	3 months
6	M	22	-	CP, cough, fever, DGS	Epithelioid MPM	Bullectomy	LOV	1 month
7	M	35	-	CP, DGS	Biphasic MPM	Palliative surgery+ CT	CP	4 months
8	M	61	+	CP, cough, DGS	Sarcomatoid MPM	CT	DGS	3 months
9	M	57	+	CP, DGS	Biphasic MPM	CT	LOV	2 months
10	M	66	+	CP, dyspnea, DGS	Epithelioid	Talc, CT, RT	LOV	4 months
11	M	58	-	CP, cough, DGS	Sarcomatoid	-	Death	3 moths
12	M	48	+	CP, DGS, cough	Epithelioid	CT	death	2 months
13	M	72	+	CP; cough, dyspnea	Epithelioid	RT	LOV	2 months
14	M	71	+	CP, DGS, cough	Biphasic	CT	LOV	4 months
15	M	40	+	CP, DGS, cough	Sracomatoid	bullectomy	good	30 months
16	F	60	-	CP, DGS, fever	Epithelioid	Talc, CT, RT	LOV	2 months
17	M	69	+	CP, weight loss	Epithelioid	-	LOV	1 month
18	F	70	-	CP, DGS	Epithelioid	-	LOV	4 months
19	M	66	+	CP, DGS	Epithelioid	RT	LOV	1 month
20	M	69	+	CP	Sarcomatoid	Talc+ CT	death	4 months
21	F	41	-	CP, dyspnea, DGS	Epitheliod	CT + EPP+ CT	good	10 months
22	M	63	+	DGS	Epitheliod MPM	EPP + CT	good	2 months
23	M	65	+	Dyspnea, cough	Epithelioid MPM	CT + EPP	good	4 months
24	F	51	-	CP, cough	Epithelioid MPM	CT + EPP	good	8 months
25	M	50	-	Dyspnea, weight loss	Epithelioid	EPP	-	-
26	F	66	-	dyspnea	Epithelioid	CT	-	-
27	M	52	-	CP	Epithelioid MPM	-	-	-
28	M	51	-	CP	Epithelioid MPM	CT	good	2 months
29	M	64	-	CP	Epithelioid MPM	CT (programmed)	-	-
30	M	71	+	CP	Biphasic MPM	-	-	-
31	M	69	-	CP	Epithelioid MPM	-	-	-
32	F	69	-	CP	Bengin SFT	Surgical resection	good	25 months

Table 1: (Continued)

33	F	70	-	Hypoglycemia	Malignant SFT	Surgery + CT+ RT	Death	90 months
34	M	52	-	Pneumonia	Benign SFT	Surgery	good	36 months
35	F	57	-	CP	Benign SFT	Surgery	good	25 months
36	M	70	-	-	Benign SFT	Surgery	Death	9 months
37	F	66	-	-	Benign SFT	Surgery	good	25 months
38	M	68	-	CP	Benign SFT	Surgery	good	46 months
39	M	27	-	CP	Malignant SFT	Surgery+ CT	Death	4 months
40	M	57	-	-	Benign SFT	Surgery	good	1 month
41	F	44	-	CP	Benign SFT	Surgery	good	24 months
42	F	18	-	CP	Malignant SFT	Surgery	death	-
43	M	68	-	CP	Malignant SFT	Surgery	Death	2 years
44	M	50	-	CP	Benign SFT	Surgery	good	20 months
45	M	64	-	CP	Malignant SFT	Surgery	Recurrence	22 months
46	F	45	-	-	Benign SFT	Surgery	good	
47	F	70	-	CP	Benign SFT	Surgery	good	1 month
48	M	63	-	CP	Benign SFT	Surgery	good	4 years
49	F	70	-	CP	Benign SFT	Surgery	good	4 years
50	M	65	-	CP	Benign SFT	Surgery	good	2 years
51	F	38	-	CP	Calcifying pseudotumor	Surgery	good	9 months
52	F	36	-	CP	Pleural thymoma	Surgery + CT	good	12 months
53	F	48	-	CP	Synovial sarcoma	-	Death	-

them had malignant forms. Extension to the adjacent organs was present in two patients with malignant forms (Figure 1B).

Case of synovial sarcoma: CT scan showed a pleural mass with extension to the adjacent organs.

Case of primary pleural thymoma: Chest CT-scan showed a pleural mass measuring 10.8x5.7 cm with a parietal extension associated with a pleural effusion. Abdominal and pelvic CT scan showed no associated abnormalities.

Case of calcifying pseudotumor: The CT scan showed a well-limited 6x5 cm mass with several calcifications.

Histologic data

Diagnosis was made by core needle biopsy in five cases and by surgical biopsies by thoracoscopy or thoracotomy in 27 cases. Surgical specimens were analyzed in 25 cases.

Maligant pleural mesothelioma group: MPM were classified as epithelioid in 21 cases, sarcomatoid in four cases and biphasic in six cases. One case of localized mesothelioma was diagnosed incidentally in an emphysematous bulla. Epithelioid mesothelioma consisted in a trabecular and tubulo-papillary malignant tumor with round cells. Their nuclei were atypical and nucleolated (Figure 2A). Sarcomatoid mesothelioma consisted of a malignant proliferation made of rounded, ovoid and fusiform atypical cells forming fascicules and nests (Figure 2B). Biphasic mesothelioma was composed of an admixture of epithelioid and sarcomatoid features. Immunohistochemical study was performed in all cases with many antibodies allowing us to make the diagnosis in 27 cases and to identify the histologic subtype. In one case, the immunohistochemical study was unhelpful because of the inadequacy of tumor tissue and the diagnosis was based upon the history of chronic asbestos exposure and the typical radiologic features. In epithelioid forms, the antibodies used were in calretinin which was positive in 89% of the cases, KL1 positive in 92%, EMA positive in 92.6%, CK 5/6 positive in 58.3%, vimentin positive in 63%, HMBE 1 positive in 75% (Figure 2C). The CD15, ACE and TTF1 antibodies were negative in all cases. In desmoplastic subtype, the immunohistochemical study allowed ruling out malignant mesenchymal tumors but the eventuality of sarcomatoid carcinoma was persistent and the diagnosis of malignant mesothelioma was retained in accordance with clinical and radiologic findings. The antibodies used with positive significance were CK5/6, calretinin, KL1, Vimentin and the antibodies with negative significance used were CD15, ACE, TTF1 which were negative in all cases (Figure 2D). Biphasic mesothelioma showed positivity with KL1, cytokeratin 5/6, EMA, vimentin and calretinin antibodies. CD15, ACE and TTF1 were not expressed in all cases. The clinical outcome of

the different subtypes is bad with the worse prognosis observed in sarcomatoid subtype.

Solitary fibrous tumors group: SFT were classified as malignant in five cases and benign in 14 cases. Benign forms were characterized by patternless spindle cell tumors. Malignant forms were characterized by increased mitotic figures and/or cellular pleomorphism (Figure 3A). Immunohistochemical analysis showed the expression of Vimentin, Bcl-2 and CD34 by tumor cells (Figure 3B).

Case of synovial sarcoma: On histopathological examination, the neoplasm consisted of a malignant spindle cell tumor, with a high mitotic figure and necrosis (Figure 3C). Immunohistochemical staining revealed positivity for cytokeratin, EMA, CD99 and Bcl-2 (Figure 3D). Cytogenetic analysis and FISH identified a translocation (X;18).

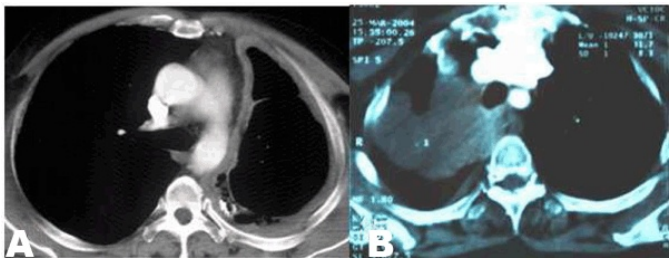

Figure 1: (A) CT scan showing a circumferential pleural thickening in a patient with malignant pleural mesothelioma, and (B) CT scan showing a pleural heterogeneous mass with extension to the adjacent organs in a patient with malignant form of solitary fibrous tumor.

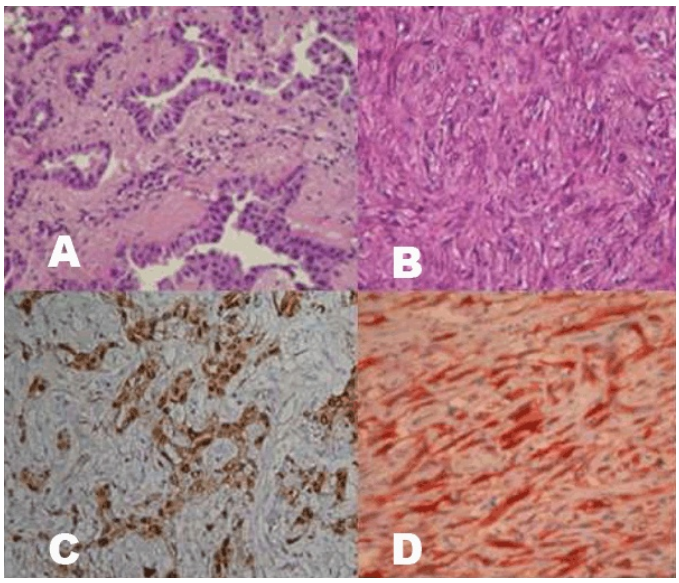

Figure 2: (A) Histologic features of epithelioid mesothelioma with a trabecular and tubulo-papillary malignant tumor with round, atypical and nucleolated cells (H&E, x400). (B) Sarcomatoid mesothelioma consisting in a malignant proliferation made of rounded, ovoid and fusiform atypical cells forming fascicules and nests (H&E, x400). (C) Nuclear expression of Calretinin antigen by epithelioid mesothelioma (H&E, x400). (D) Nuclear expression of Calretinin in sarcomatoid mesothelioma (H&E, x400).

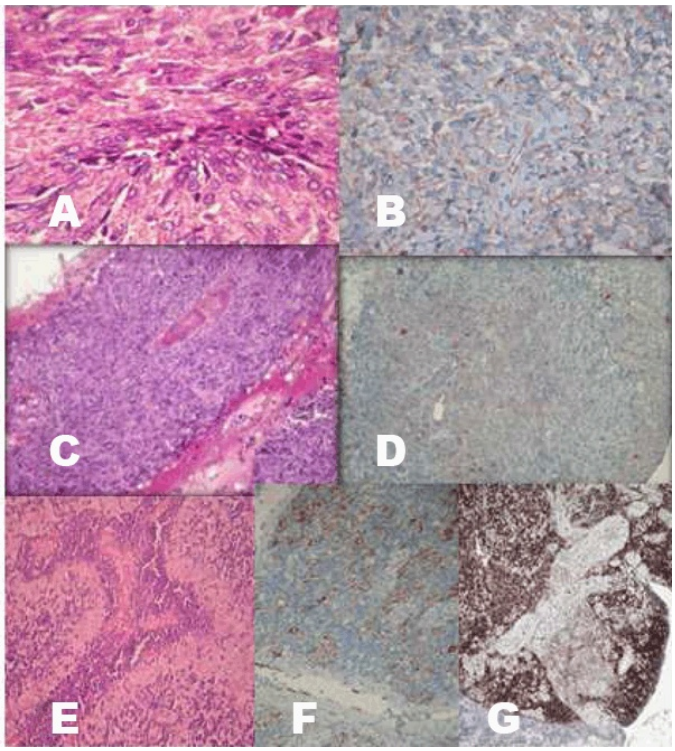

Figure 3: (A) Increased mitotic figures and cellular pleomorphism 352 in a malignant form of solitary fibrous tumor (H&E, x400). (B) Expression of CD34 by tumor cells (H&E, x400). (C) Histologic features of synovial sarcoma characterized by malignant spindle cell tumor, with a high mitotic figures and necrosis (H&E, x400). (D) Expression of Bcl2 antigen by tumor cells in the synovial sarcoma (H&E, x400). (E) Pleural thymoma characterized by lobules separated by dense fibrous bands containing small round lymphocytes admixed with variable numbers of scattered larger epithelial cells (H&E, x250). (F) Cytoplasmic expression of Cytokeratin by the epithelial cells (H&E, x250). (G) Nuclear expression of Tdt by the immature lymphocytes (H&E, x250).

Case of primary pleural thymoma: Histologic examination showed pleural tissue with lobules separated by dense fibrous bands. The lobules contain small round lymphocytes admixed with variable number of scattered larger epithelial cells (Figure 3E). The epithelial cells were highlighted on immunohistochemical stains for cytokeratin (Figure 3F). Background lymphocytes were positive for terminal deoxynucleotidyl transferase (Tdt) and CD99 (Figure 3G).

Case of calcifying fibrous pseudotumor: The lesion was mostly composed of dense hyalinized collagenous tissue containing calcifications. The lesion was interspersed with sparse spindle cells and with scattered lymphoid and plasma cells. No atypical features of spindled cells were noted. Most spindle cells were positive for cytokeratin, vimentin and S100 protein.

DISCUSSION

Primary malignant pleural tumors are rare accounting for 10% of pleural neoplasms. Specific cell

types are MPM, which arise from the mesothelial cells, solitary fibrous tumors, arising from submesothelial cells and liposarcoma. Primary pleural thymoma is thought to arise from ectopic thymic tissue. Other rare tumors are represented by angiosarcoma or hemangioendothelioma [3, 4]. On the other hand, secondary tumors account for 90% of pleural neoplasms [1]. Therefore, the diagnosis of primary malignant tumor remains a diagnosis of exclusion necessitating to rule out a secondary localization. MPM is the most common primary neoplasm that typically affects patients usually exposed to asbestos. In our study, this diagnosis was the most frequent representing 56.5% of the cases [1]. The clinical symptoms are non specific, mainly chest pain and dyspnea. These symptoms were most frequently observed in our study. Paraneoplastic signs such as hypertrophic osteoarthropathy syndrome and refractory hypoglycemia have been reported to be more frequently associated to SFT [5]. In fact, one patient with SFT presented with a refractory hypoglycemia. The chest CT scan allows quite an accurate study of the tumor, as it indicates its boundaries and its relationship to adjacent organs. Generally, the CT scan shows well limited tumors in benign cases and extension to the adjacent organs in malignant cases. This was observed in our study. Thoracic MRI can be of great help in case of imprecise data on the CT scan [6]. Some authors describe the PET scan as a useful tool in the diagnosis of these tumors. In fact, they describe an FDG-uptake in malignant tumors which is generally absent in benign tumors [7]. Means of diagnosis are represented by pleural fluid cytology, percutaneous needle biopsy, transparietal puncture and surgical biopsy. Transparietal puncture and needle biopsy or cyology are often inconclusive with a risk of dissemination on the route of the needle [6]. Pleural fluid cytology may yield a definitive diagnosis of MPM in 20–33% of patients. Surgical biopsy seems necessary, especially in MPM, in order to make an accurate diagnosis [1]. This procedure enables to obtain significant specimen. The final diagnosis is based on histologic examination. The WHO classification divides pleural tumors into mesothelial tumors, other tumors of mesothelial origin, lymphoproliferative disorders and mesenchymal tumors [8]. MPM are generally divided into three histologic categories, epithelioid, sarcomatoid and biphasic. Epithelioid mesothelioma constitutes approximately 55–65% of malignant mesotheliomas. It may be difficult to differentiate from pulmonary adenocarcinoma or a secondary adenocarcinoma. The sarcomatoid variant constitutes approximately 10–15% and must be differentiated from a true sarcoma. The remaining mesotheliomas (20–35%) fall into the biphasic category [1]. Immunohistochemical techniques are helpful in assessing the diagnosis. In epithelioid forms, it is recommended to use two antibodies of positive value, such as anti-calretinin or anti-wt1, in association with two markers of negative value such as Ber-EP4 or TTF1 [9, 10]. In our study, immunohistochemical findings enabled us to make the diagnosis in 30 cases. In the last case, the material was unsufficient to perform special staining. SFT are divided into benign and malignant forms. Microscopically, about 60% are benign and 40% are malignant. In our study, malignant forms represented approximately 20%. The distinction between these two forms may be based on microscopic criteria including nuclear crowding, pleomorphism, necrosis and increased mitotic count, but this is not always possible and the presence of a pedicle is the best evidence of benignity [1]. Among the 14 benign forms described in our study, a pedicle was present in 12 of them. SS is a very rare and challenging diagnosis which most relevant differential diagnosis is represented by MPM and surgeons must be aware of this entity. Histologically, they are either monophasic (composed entirely of spindle cells) or biphasic. The biphasic tumors are more distinctive and thus are easily distinguished from other pleural sarcomas. Immuno-histochemical features distinguish SS from pleural sarcomas by showing the staining of tumor cells for cytokeratin and epithelial membrane antigen. The chromosomal translocation t(X;18) (p11.2;q11,2) has been found in more than 90% of SS, regardless of histologic subtype [11, 12, 13]. Molecular techniques are useful in revealing the fusion protein product by RT-PCR, FISH or conventional cytogenetics [14]. In our study, one patient presented with a synovial sarcoma and FISH method allowed to highlight the specific translocation. Inspite of its high sensitivity, the FISH method is not compulsory for the diagnosis and it is indicated in only in confusing cases [15]. Primary pleural thymoma is a very rare entity reported by some authors to be secondary to a transformation of an ectopic thymic tissue. Histologic findings are similar to those observed in the thymus. The management of these tumors remains non-consensual but surgical procedures play a key role by providing a definitive diagnosis in some cases and by enabling the excision of the tumors in others [6]. In malignant tumors including MPM, malignant forms of SFT and SS, a multi-modal therapy including surgical resection and/or chemotherapy and/or radiation therapy is recommended because of the worse prognosis of these tumors. Other therapeutic procedures including radiofrequency thermal ablation, hyperthemia therapy have been also reported [16, 17]. Benign tumors are generally treated by surgical resection.

CONCLUSION

Primary pleural tumors are characterized by their rarity and their difficult diagnosis. They necessitate an accurate assessment because of their medical and legal implications. Histologic, immunohistochemical and molecular findings are mandatory to make a diagnosis. The rarity of these tumors justifies the necessity of creating diagnostic groups such as the Group Mesopath in France.

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Author Contributions

Mona Mlika – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Aida Ayadi-Kaddour – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published
Beya Chelly – Substantial contributions to conception and design, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published
Sadok Boudaya – Contribution to interpretation of data, Drafting the article, Final approval of the revised version
Saoussen Maalej – Interpretation of data, Drafting the article, Final approval of the final version
Tarek Kilani – Interpretation of data, Drafting the article, Final approval of article
Faouzi Mezni – Interpretation of data, Drafting manuscript, Final approval of the definite version

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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