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Differentiation between Pleural Mesothelioma versus Pseudo-Mesothelioma Demonstrated in Eight Autopsy Cases

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ABSTRACT

The pleural lobes are the origin of different pathologies, including malignant tumors, e.g., pleural mesothelioma. In some cases, clinical and macroscopic presentation point strongly to the diagnosis but often enough the patient has another underlying disease; malignant neoplasms of the lung as well as other organs (skin, pancreas, prostate or kidney) can mimic pleural mesothelioma and if so, are defined as 'pseudo-mesothelioma'. We present eight cases that are clinically and macroscopically highly suspicious for pleural mesothelioma. All patients were autopsied due to medico-legal issues and work-related diseases. Six out of eight patients underwent autopsy to exclude possibility of asbestos-related malignancy and two out of eight due to exclusion of silicosis. From the eight cases, only three were real pleural mesotheliomas. Another three were adenocarcinomas of the lung mimicking pleural mesotheliomas. One had squamous cell carcinoma of the lung. Lastly, one patient had an extraordinary case of papillary renal cell carcinoma metastasizing universally in both pleura lobes. Due to striking morphological similarities, the exact final diagnosis was only possible after extended immunohistochemical analysis of the tissues. In summary, not only is it difficult to distinguish between real or pseudo pleural mesothelioma in patients having had contact with asbestos. Even patients with no evidence of asbestos contact can have clinical and pathological events strongly suggesting asbestosis and mesothelioma, without having it.

Introduction

Chronic asbestos exposure, particularly to amphibole fiber types, may lead to the development of malignant pleural mesothelioma [1]. Characteristic features of MPMs are a long latency of development after initial asbestos exposure (up to 40 years) and poor prognosis with a median survival range of 8 to 14 months. Clinically, patients present unspecific symptoms of dyspnea, chest pain and pleural effusion. Macroscopically, tumorous pleural thickening and ensheathing of the lungs, as well as pleural plaques are characteristic for chronic asbestos exposure and MPMs. In histology, MPMs can have a plethora of different appearances, the most frequent being epithelioid, sarcomatoid and mixed (biphasic) [2].

Differential diagnosis of malignant pleural diseases and other malignant neoplasms of the pleura are oftentimes not easy and straightforward. Various non-mesotheliomatous neoplasms may mimic MPMs clinically and pathologically, making it difficult to put a definite diagnosis prior to extensive immunochemical analysis. These non-mesotheliomatous neoplasms are grouped and titled as 'pseudo-mesotheliomas'. In Germany, asbestos was banned in 1993 [3]. Considering the relatively long latency time, asbestos-related mesothelioma should have reached its peak in 2010-2020. Due to that, differentiation between pleural mesothelioma and pseudo-mesothelioma becomes more and more important, since it is expected, that asbestos-induced pleural mesothelioma will relatively decline in favour of pseudo-mesotheliomatous neoplasms. A big proportion of pseudo-mesotheliomas consist of peripheral malignant carcinomas of the lung, mostly adenocarcinoma [4]. Additionally, other malignant diseases and corresponding metastases have been reported to mimic pleural mesothelioma, including carcinoma of the bladder, prostate, parotic gland, pancreas, skin and kidney [5, 6].

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Immunohistochemistry plays an important role in distinguishing between real and pseudo-mesothelioma. Pleural mesothelioma typically shows positive staining reactions for CK 5/6, WT-1 and Calretinin. In contrast, adenocarcinoma of the lung is oftentimes positive for CK7 and TTF-1 [7, 8]. Furthermore, genetic markers are discussed to specifically differentiate actual pleural mesothelioma from inflammatory reactions. Among those, homozygous deletion of CDK2NA/INK4a is the most common [2].

Attanoos *et al.* published a case series in 2003 presenting 53 cases of pseudo-mesothelioma and the importance of immunohistochemical analysis to solidify the diagnosis [5]. Almost two decades have passed since then. In this study, we present eight patients who underwent autopsy in our department over a 3-year period (2017-2019). Almost half of them (3/8) had an epithelioid variant of pleural mesothelioma, whereas the rest (5/8) had variants of pseudo-mesothelioma. Among the latter three patients had peripheral adenocarcinoma of the lung, one patient had squamous cell carcinoma of the lung and one patient presented an extraordinary case of papillary renal cell carcinoma metastasizing widely and diffusely in the pleural lobes of both sides. Therefore, after almost twenty years, correct differentiation of pleural and pseudo-mesothelioma remains a diagnostic challenge and we still heavily rely on the importance of thorough immunohistochemical analysis and the insufficiency of clinical, macroscopic and histological analysis alone. Lastly, we discuss the patient with renal cell carcinoma more in detail since it presents a very rare and special case of pseudo-mesothelioma [9-11].

Materials and Methods

I Autopsies, Pathological Data and Clinical Data

All patients in this study were exposed professionally to dusts (silicic for case #1-#2 and asbestos for case #3-#8) and clinically suspected to suffer from the consequence of silicosis/asbestosis. Autopsies were performed by MM Saleh, MD and specialized autopsy assistants in the Department of Pathology, University Hospital Cologne, under the supervision of JWU Fries, MD, head of autopsy department. The discussed results are based on a full body autopsy and subsequent histopathological and molecular analysis for which prior consent was obtained in writing by the respective spouses as part of an insurance investigation regarding an occupational related lung disease. Specialized analysis of asbestos bodies and fibers containment of the lung samples was performed by Professor Tannapfel, Department of Pathology, University of Bochum.

II Histology and Immunocytochemistry

Inner organs (thyroid glands, heart, lymph nodes, liver, spleen, pancreas, kidneys, adrenal glands, small and large intestine, genital organs) were routinely inspected histologically and analysed using routine hematoxylin & eosin (H&E) staining. Besides pleura, special stains were employed for kidney (periodic acid Schiff (PAS), elastic van Gieson stain (EvG)), and for liver (PAS, EvG, Gomorri, iron staining (Fe) with Berlin Blue reaction. The lungs were fixed by extension via tracheal perfusion with 4% buffered formalin for two days, and coronally sectioned in one-centimeter-thick slices. At least one para-hilar and peripheral tissue sample was analysed from each lung lobe using H&E and EvG staining. Diagnoses and grading of tumors were made in accordance with the current WHO classification. Immunohistochemical analyses and used antibodies are summarized in (Table 1). Analysis was performed on Leica Bond Max (Leica Biosystems, Nussloch). To differentiate pleural mesothelioma from diffuse metastases, the following immune histologic evaluations were performed on each tumor.

Table 1: Antibodies.

Marker	Company	Clone
Calretinin	ZYMED	Polyclonal
Wt-1	Leica	WT1
Ttf1	Dako	8G7G3/1
Ck5/6	CellMarque	D5&16B4
Ck7	Dako	OV-TL12/30
Pan-ck	Dako	MNF116
berEP4	Dako	Ber-EP4
Napsin	CellMarque	polyclonal
D2-40	Covance	D2-40
Pax-8	CellMarque	MRQ-50
AMACR	Dako	13H4
Hbme-1	Dako	HBME-1
MelanA	Dako	A103
Ki-67	ThermoFisher	SP6
p40	BioCare Medical	Polyclonal
CD56	ThermoFisher	123C3
S-100	Dako	Polyclonal
PSA	Dako	ER-PR8
Synaptophysin	Thermofisher	SP11
Oct4	CellMarque	MRQ-10
Sall4	CellMarque	6E3
Sox-10	BioCare	SOX10(M)
Ck20	CellMarque	Ks20.8

III Next Generation Sequencing

Samples were analysed with a validated gene panel of 14 lung-cancer related genes [12]. We performed NGS with the QIAseq human lung cancer panel (NGHS-005X-96) (Qiagen, Hilden, Germany) with the version 2 chemistry.

Results

We performed full-body autopsy on patients by decision of the patient's relatives in regards to legal issues of medical insurance companies and in search of work-related pathologies, e.g. silicosis and/or asbestosis. All of our eight patients were male and around the age of 65-88. Table 2 summarizes the most important data. From the eight patients, two (#1 and #2) were suspected for silicosis ("S-group"), whereas the other six (#3-#8) were suspected for asbestosis/mesothelioma ("A-group"). Secondly, we divided our patients into five cases of pseudo-mesothelioma (#1-#5) ("pseudo-group") and three cases of pleural mesothelioma (#6-#8) ("pleura-group").

Table 2: Summary of clinical, macroscopic and histologic features.

Case #	Age, gender	Suspected for	Contact with asbestos, fiber-year count	Macroscopic features	Histology	Asbestos bodies/ asbestos fibers [*per gram lung tissue*]	Final diagnosis
1	76, M	Silicosis	No	See (Figure 1)	See (Figure 1)	N.D.	Papillary renal carcinoma
2	71, M	Silicosis	No	Pleural adhesions with mediastinum, diaphragm, and chest wall; small white nodule within lung tissue	Disseminated tumor cells in the lower lobe. Lymphangiosis. Hemangiosis. lymph node metastases	N.D.	Adeno-carcinoma right lung, Neuroendocrine tumor left lung
3	65, M	Asbestosis Mesothelioma	Yes, 14.5	Pleura plaques left side, pleural thickening + adhesions to chest wall and right sided mediastinum	Alveolar carcinoma. Lymphangiosis. Hemangiosis. LN metastases: carina, paratracheal. Right sided pleural infiltration	N.D.	Adeno-carcinoma right lung
4	85, M	Asbestosis/ Mesothelioma	Yes	Pleural thickening	Non-differentiated adenocarcinoma of the lung with large-cell neuroendocrine differentiation; diffuse pleural metastasis	30/10	Adeno-carcinoma
5	67, M	Asbestosis/ Mesothelioma	(Yes)	Pleura plaques, pleural thickening	Non-differentiated keratinizing squamous cell carcinoma	1240/200	Squamous lung carcinoma
6	77, M	Asbestosis/ Mesothelioma	Yes	Universal thickening of the pleura including interlobular septa	Cuboid epithelial cells; hyperchromatic nuclei. Lymphangiosis. Tumor extends in right lung hilar and tracheal bifurcation.	880/40	Pleural mesothelioma
7	81, M	Asbestosis/ Mesothelioma	Yes	pleural thickening left side	solid growing malignant tumor with pleomorphic nuclei, fine-granulated chromatin, prominent nucleoli. Multiple mitotic figures	110/100	Pleural mesothelioma
8	88, M	Asbestosis/ Mesothelioma	Yes	Pleural plaques, pleural thickening on the right side, infiltrating in the lung, thorax wall, diaphragm	Tumor of the right pleura, infiltrating all lung lobes, and the diaphragm. Lymphangiosis of the right pleura	4400/	Pleural mesothelioma

All of the patients of the pleura-group reported a history of asbestos-contact, but only one of them (#3) had a fiber-year measurement of 14.5 fiber-years. Looking at the macroscopy, most of our patients had thickening of the pleura and adhesions with surrounding compartments like chest wall, pericard and diaphragm. Pleura plaques, which are considered to be caused by asbestos exposure were reported for #3, #5 and #8 (two of pseudo-group and one of pleura-group, no of S-group) [13]. Involvement of thickening of the interlobular septa, which is reported to be common in pleural mesothelioma is seen for #1 and #6 (both pseudo-group, one of S-group and one of A-group) [14].

Asbestos bodies or asbestos fibers were detectable in both, the pseudo and pleura group patients (pseudo group: #4: 30/10, #5:1240/200 and pleura group; #6:880/40, #7:110/100, #8:4400/?; first number indicates

asbestos bodies, second asbestos fibers). Therefore, neither the appearance nor the amounts of asbestos particles were suitable to predict development of MPM.

In summary, by looking at macroscopic features and qualitative/quantitative assessment of asbestos bodies and fibers we can distinguish neither between S and A group, nor between pseudo and pleura group. Pleura plaques appear to be specific for asbestos exposure, since no patient of S-group presented them. Next, we performed immunohistochemical staining of the tumors. Detailed expression patterns can be found in (Table 3). In summary, we found that all patients of the pleura group expressed Calretinin and Ck5/6. Further, all were negative for TTF-1 and Ck20. Case 1 was specifically negative for berEP4, Napsin, Pax-8 and AMACR. Two probes expressed Ck7, although #8 only micro-focally. Pseudo-mesotheliomatous adenocarcinomas of the lung were positive for TTF-1 and Ck7 and two out of three expressed Ck5/6. Further, they were negative for Calretinin, Wt-1, Ck20, Napsin, D2-40, Pax-8 and AMACR. Therefore, positive expression of TTF-1 in pseudo-mesothelioma and Calretinin in MPM delivered the most reliable results for distinction. Our case #5 (pseudo-mesothelioma; squamous carcinoma of the lung) displayed positive expression for Ck5/6 and pan-CK, with all other markers being negative.

Table 3: Immunohistochemical results.

	Pseudo group					Pleura group		
	'S'-group		'A'-group					
	1	2	3	4	5	6	7	8
Calretinin	-	-	-	-	-	+	+	+
Wt-1	-	-	-	-	-	(+)	-	+
Ttf1	-	+	+	+	-	-	-	-
Ck5/6	-	+	+	-	+	+	+	+
Ck7	-	+	+	+	-	+	-	(+)
Ck20	-	-	-	-	-	-	-	-
Pan-ck	+	+	+	+	+	+	+	+
berEP4	-	+	-	+	-	-	-	-
Napsin	-	-	-	-	-	-	-	-
D2-40	-	-	-	-	-	(+)	-	+
Pax-8	+	-	-	-	-	-	-	-
AMACR	+	-	-	-	-	-	-	-
Cxcr4	-	-	-	-	-	-	-	-

To test whether pleura and pseudo-mesothelioma show any molecular differences, we performed next generation sequencing on our probes using an established in-house "lung-panel" testing for 14 common oncogenic driver mutations in lung cancer (including EGFR, KRAS, MET and more). Neither the cases with pleural mesothelioma nor the pseudo-mesotheliomatous tumors had any mutations in the tested genes (data not shown). Further illustrating the difficulty of diagnosing or predicting real pleural mesothelioma, we like to discuss case #1 due to its extraordinary and rare character more in detail. The patient M.H. belongs to the S and pseudo-group, so neither did he have contact with asbestos, nor does he have actual MPM. Nonetheless, he presents clinical, macroscopic and microscopic features highly suggestive for MPM. M.H. was a 76-aged white man. Unfortunately, we received no further information about his clinical history. It is known that he was suspected to suffer from work-related silicosis.

Autopsy revealed unusual white thickening (up to 2cm) of almost the whole pleura on both sides of the chest. Thickening included the interlobular septa (Figure 1A). Furthermore, it involved the thoracic wall and partly the mediastinum. Surprisingly, our autopsy also revealed big tumor masses in both kidney hili. Predominantly on the left side, we saw a big tumor mass circulating and invading the renal vessels. In addition to that, the right and left renal tissues had smaller, greyish nodules on the surface (up to 0,5cm). Moreover, para-aortal lymph nodes were enlarged.

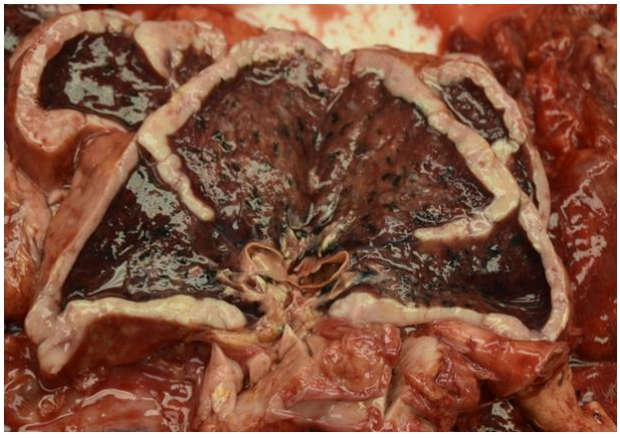

Figure 1A: Macroscopic aspects of lung lobe with a thick, mantle like pleura preventing normal lung expansion (bar equals 1000µm).

Besides that, autopsy revealed hypertrophic heart disease as well as left-dominated heart failure with dilatation. The lungs were emphysematous. Of note, the patient showed sigma diverticulitis and benign prostate hyperplasia. Microscopy of the pleura showed a very cell-rich tumor with non-cohesive cells. There was no adenoid transformation. Nuclei of tumor cells were partly lymphoid cells but with uneven surface. Nuclei-plasma relation was shifted. No obvious mitotic figures. PAS staining showed no nuclear or cytoplasmic inclusions. Finally, there was invasion of small lymphatic vessels (Figure 1B).

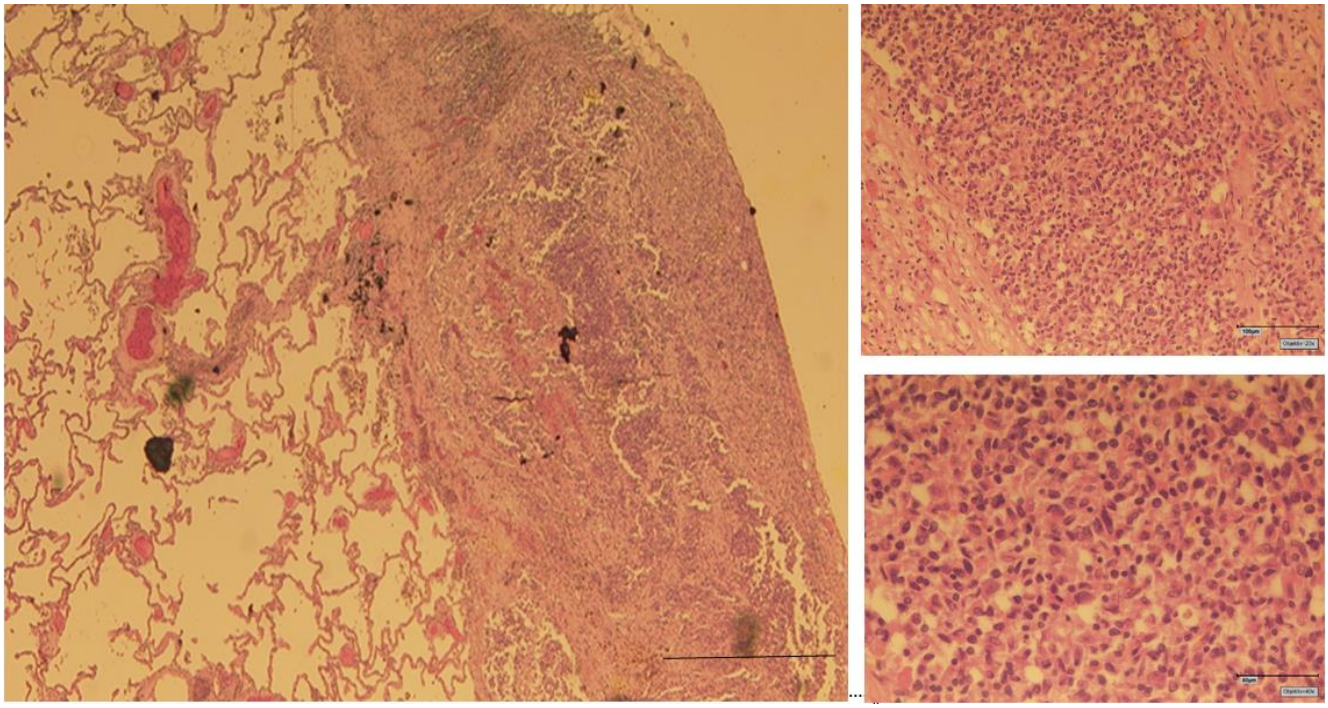

Figure 1B: Histologic aspects of hematoxylin staining. At the left, overview of lung parenchyma with thickened pleura, in which areas with tumor cells can be seen. To the right, two different magnifications of the pleural tumor from the left picture, showing dishesive epithleioid tumor cells with remanant of a papillary growth pattern.

Surprisingly, although highly indicative for pleural mesothelioma, immunocytochemistry revealed negative expression for Calretinin, D2-40, Ck5/6 and Wt-1. Moreover, expression was negative for: Hbme-1, TTF-1, CD56, Synaptophysin, Oct4, Sall4, MelanA, Sox-10, S-100; PSA, p40, Ck5/6 and Ck20. Interestingly, we had a positive expression for panCk, Pax-8 and AMACR and also a low Ki-67 count, thus indicating renal cell carcinoma (Table 2 and data not shown). Tumor cells in the kidney were also positive for Pax-8 and AMACR and displayed papillary formation, so that the final diagnosis was papillary renal cell carcinoma with pleural metastases.

Discussion

In this study, we have shown that differentiating between pleural mesothelioma and pseudo-mesotheliomatous neoplasms is still a diagnostic challenge and requires extensive knowledge about differential diagnoses and immunohistochemical markers. We have presented eight cases, which all had comparable clinical, macroscopic and histological features but differed in diagnoses. For example, three of our patients with reported asbestos-exposure presented pleural plaques, a macroscopic feature, which is considered reliable for the detection of asbestos exposure. Our two patients with no asbestos exposure had no detectable pleural plaques, further supporting existing evidence of a good sensitivity for detection of pleural plaques and previous asbestos exposure. Nonetheless, distinction between pleural mesothelioma and pseudo-mesothelioma was not possible. Pleural plaques alone are neither sufficient to predict whether or not malignant transformation occurs, nor whether it occurs in the lung or in the pleura [15, 16].

Our study adds up well to previous investigations by Attanoos *et al.*, who analysed 53 patients with pseudo-mesothelioma [5]. They have found that macroscopic and histological presentation can be very similar and that IHC can be helpful in diagnosis. Particularly positive expression of Calretinin is proposed to be a reliable marker for pleural mesothelioma, which supports our findings in our case series. However, almost two decades have passed since then.

What has changed? Until now, IHC remains the most widespread and used method for diagnosing malignant pleural mesothelioma. In general, positive expression of Calretinin, CK 5/6 and Wt-1 are characteristic for pleural mesothelioma. Further, Kerger *et al.* proposes that negative expression of CEA, CD15, berEP4, MOC-31, TTF-1 and B72.3 should be tested [8]. However, due to cellular variety and histological heterogeneity, IHC can still deliver difficult-to-interpret results. Our data shows, in agreement with previous published data, that positive expression for Calretinin seems to be the most reliable marker, as well as negative expression for TTF-1, Ck20, berEP4 and Napsin.

Interestingly, our study also shows that in some instances, positive expression of IHC markers were only focally present and thus can easily be missed by targeted small-sample biopsies (#6 and #8). This fact underlines that IHC analysis requires quite a broad histologic sample size to sufficiently interpret the results. Taken into account that primary neoplasms of the pleura will decrease, and secondary neoplasms will increase due to abandonment of asbestos-containing materials in affected working fields, a clear distinction with a more sensitive and specific approach will be of great need. Further, it is to be discussed, why some pleural neoplasms only have focal expressions of specific markers and whether or not that could have therapeutic consequences. Little is

known about the biological effects, or these expressed markers in pleural mesothelioma. For better diagnostic tools, extensive research has been performed using highly sophisticated genetic methods like gene sequencing, methylation analysis and micro-RNA expression analysis [8]. Unfortunately, no clear genetic marker could be found which was specific for pleural mesothelioma [17-19]. If at all, loss of chromosome 22 seems to be the single most consistent karyotypic alteration in pleural mesothelioma [8].

Further, it has not been introduced into clinical practice. For our cases, we performed next generations sequencing and screened for genes, which are typically mutated in lung carcinoma (so called driver-mutations). We have found no mutations in our tested genes neither in our pseudo nor in our pleural mesotheliomas (data not shown). Previous studies suggest that EGFR mutated lung adenocarcinomas have a higher probability for metastasizing in the pleural cavity and causing malignant pleural effusions [20, 21]. That observation could not be supported by our data. One important limitation of our study is the small sample size, so more patients are needed to solidify our data. However, based on our existing data, pseudo-mesotheliomatous carcinoma of the lung as well as MPM show no difference in mutations of "lung-cancer related genes", so that seems to be a non-optimal differentiation tool.

Our last discussed patient with metastatic papillary renal cell carcinoma deserves special interest due to its rarity and the magnitude of pleural metastases that macroscopically seemed indistinguishable from pleural mesothelioma. In 1981 Saitoh found pleural metastases in 12% of all RCC autopsy cases in a large case series of 1451 cases [9, 11]. Furthermore, Ordonez analysed 28 cases of metastatic RCCs, from which only eight were of papillary formation (29%), although we have no information whether metastases were found in pleura or lung [7]. In summary, not only are pleural metastases rare in RCC, they are even more uncommon in papillary RCC. Existing data shows that CXCR4 overexpressing tumor cells of NSCLC are prone to metastasize in distant organs and to invade local tissues [22, 23]. We stained our samples for CXCR4 and saw no difference in expression patterns between pseudo and pleural mesothelioma, indicating a subordinate role of CXCR4 in pleura carcinogenesis. One of our theories was that the pleura might be more susceptible for metastases due to prior silica dust exposure of the patient. However, literature research did not reveal any association between silica dust exposure and change of pleural micro and macro environment. It is to be suggested that exposure of prior silica dust changes expression patterns of certain chemokine receptors or integrins thus making the pleura susceptible for metastases.

In summary, our data shows that differentiation between pseudo-mesothelioma and pleural mesothelioma remains a diagnostic challenge, still relying on extensive IHC analysis. Research on genetic and molecular markers is ongoing. However, until now no further and more specific analysis tool can be reliably provided. Moreover, biology and dynamics of pleural metastases is still poorly understood and investigated and deserves more focus in the future.

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Abbreviation

MPM: Malignant Pleural Mesothelioma
IHC: Immunohistochemistry

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