

Non-specific pleuritis: pathological patterns in benign pleuritis



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Summary

A pleural biopsy without granulomatous inflammation or tumour cells is interpreted as 'non-specific pleuritis' (NSP), a diagnosis without any specificity, often frustrating for physicians. However, varying histological features are found in NSPs with unknown significance. The aim of this study was to describe the detailed microscopic features of NSP and correlate them with the underlying aetiology. One hundred patients diagnosed with NSP after pleural biopsy were retrospectively evaluated. A benign cause of pleural effusion was attributed. Histological features evaluated were inflammation, fibrosis, vascular proliferation, haemorrhage, fibrin, oedema and mesothelial hyperplasia. A semi-quantitative scoring was applied. Bacterial-caused and autoimmune disease-associated NSPs showed a higher score followed by viral and drug-induced conditions, while pneumothorax and cardiac-induced NSPs showed a lower score ($p < 0.0001$). The degree of fibrosis was higher in bacterial NSP, and the type of fibrosis was cellular in this group ($p = 0.006$). Vascular proliferation differed between groups ($p < 0.0001$), and was higher in bacterial NSP. Histological findings differ significantly between the varying aetiologies of NSP, and this may be used to suggest the cause of the effusion.

Key words: Non-specific; pleuritis; inflammation; vascular proliferation; effusion; fibrosis; mesothelial hyperplasia; thoracoscopy; fibrosis; pleural disease; biopsy; pleura.

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INTRODUCTION

The pleural cavity is a virtual space surrounding the lungs and containing a very small amount of fluid, normally less than 15 mL in a 70 kg individual.^{1,2} An abnormal collection of fluid within this cavity is called pleural effusion. Pleural effusion is a common presenting feature of a wide range of pleural, pulmonary or systemic diseases, benign or malignant. Standard work-up in this case includes clinical history, physical examination, blood tests, diagnostic thoracentesis, chest radiograph and computed tomography. Thoracoscopy

will be often performed as it provides the possibility to obtain pleural tissue under direct inspection of the pleural cavity.³ Diagnostic sensitivity of thoracoscopy for malignancy reaches 95%.³

However, in cases where a malignancy or a granulomatous disease is not histologically diagnosed, microscopic features for the rest of the possible aetiologies are considered largely the same, and a descriptive type of histopathological diagnosis will be employed for most of them. The term kept for these cases is 'non-specific pleuritis' (NSP). After thoracoscopy, a diagnosis of NSP is rendered in 8–38% of cases, with 25% considered 'idiopathic' with no probable cause, while almost 10% of these cases will finally reveal malignancy, particularly mesothelioma.^{4–7} This reveals the difficulties in establishing the correct diagnosis, histologically and clinically, in NSP cases but it also highlights an important absence in our knowledge concerning this entity: there are no studies describing in detail the microscopic features of NSP and their potential correlation with the underlying aetiology.

Thus, the aim of this study was to report the detailed histological features of a series of NSP in order to define differences in the histopathological pattern according to the underlying disease.

MATERIAL AND METHODS

Study group

This study used information extracted from the medical electronic files of 100 consecutive patients diagnosed with NSP after pleural biopsy for recurrent undiagnosed pleural effusion at the University Hospital of Saint-Etienne from January 2014 to January 2017. Inclusion criteria were: (1) a histological diagnosis of NSP excluding cases of neoplastic or granulomatous disease; and (2) a minimum follow up of 12 months.⁸ The study was approved by the Internal Review Board of the University Hospital of Saint-Etienne (212018/CHUSTE).

Medical files were reviewed to record demographic data, clinical features, previous clinical history and comorbidities, asbestos exposure, medications and additional laboratory and investigational data. The predominant macroscopic appearance of the pleural cavity, recorded by the thoracoscopist was also documented as: inflammatory, fibrinous, septated, haemorrhagic, or pleural plaques. All data were reviewed clinically to achieve a final aetiological diagnosis.

Histopathological evaluation

All available slides were reviewed to evaluate the following parameters: inflammation, fibrosis, vascular proliferation, oedema, fibrin, haemorrhage, and mesothelial hyperplasia. As no histological scoring system concerning the pleura has been established to date in humans, we used a system of an experimental model of pleural disease.^{9,10} According to this, a semi-quantitative system is applied for each parameter as follows: 0, absence; 1, mild; 2, moderate; 3, severe. A final score was attributed as the sum of all values.¹⁰

Furthermore, concerning inflammation, the presence of all different cellular types was recorded for each case and also the predominant inflammatory cell type (lymphocytes, plasmacytes, histiocytes, neutrophil granulocytes, eosinophil granulocytes) was separately recorded. Likewise, concerning fibrosis, this was further characterised into the following types: cellular, when a fibroblast-rich type fibrosis was found; old, when only a well-established collagenous fibrosis poor in cells was found; and mixed, when both types of fibrosis were found. Moreover, the presence of prominent layering of tissue elements was recorded.

Statistical analysis

Data were analysed using Stat View software (Abacus Concepts, USA). We used the chi-square test to explore any relationship between two groups for categorical data, and factorial analysis of variances (ANOVA) to consider the effect of at least one factor on a continuous parameter studied. For all analyses, statistical significance was set at a *p* value of <0.05.

RESULTS

Demographics

Patients' demographics are shown in Table 1. Age at diagnosis ranged from 13 to 94 years with a median of 63 years;

Table 1 Patients' characteristics (*n* = 100)

	<i>n</i> (%)
Age, years	
Median	63
Range	13–94
Sex	
Male	71 (71)
Female	29 (29)
Follow up, months	
Median	36
Range	1–48
Final aetiology	
Pneumothorax	28 (28)
Bacterial infection	27 (27)
Cardiac	10 (10)
Drug induced	7 (7)
Viral infection	7 (7)
Auto-immune disease	5 (5)
Other	16 (16)
Surgery-trauma	2
Pleural plaque	2
Dressler syndrome	1
Kidney failure	1
Pulmonary embolism	1
Radiotherapy	1
Chylothorax	1
Eosinophilic	1
Unknown-idiopathic	6
Localisation	
Left	44 (44)
Right	42 (42)
Bilateral	11 (11)
Predominant pleural aspect during thoracoscopy	
Inflammatory	40 (40)
Fibrinous	14 (14)
Fibrous	6 (6)
Septated	8 (8)
Haemorrhagic	2 (2)
Pleural plaques	2 (2)

71 patients were male and 29 were female. Median follow-up was 36 months. Eight patients died during the post-operative period or follow-up, none due to malignancy-associated pleural effusion. Overall, no pleural malignancy was revealed during follow-up.

The predominant macroscopic pattern during thoracoscopy was inflammatory in 40% of the cases, followed by fibrinous (14%), septated (8%), fibrous (6%) and haemorrhagic (2%). Pleural plaques as the predominant pattern were found in two patients (2%), whereas another 13 patients harboured histologically confirmed plaques.

Regarding final aetiological diagnosis based on all available data, this included pneumothorax in 28 patients (28%) and bacterial infection in 27 patients (27%). In the latter, the following bacterial species were found: *Pneumococcus*, *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Hemophilus*, *Escherichia*, *Neisseria*. Viral pleural effusion was separately categorised and included seven patients (7%). Cardiac-associated pleural effusion was found in 10 cases (10%), drug-induced in seven (7%) and of auto-immune aetiology in five (5%). Cases merged into the 'Other' group (*n*=16, 16%), in terms of analysis, included: cases attributed to asbestos exposure (*n*=2), chylothorax (*n*=1), post-traumatic (*n*=2), pulmonary embolism (*n*=1), Dressler syndrome (*n*=1), post-irradiation (*n*=1), kidney failure (*n*=1), eosinophilic pleuritis (*n*=1), and in six cases (6%) no possible aetiology was attributed. These 16 cases were excluded from further statistical analysis due to the very limited number with specific aetiology or their unknown aetiology.

Clinicopathological correlations

Histological findings are summarised in Table 2 and illustrated in Fig. 1–3. Association of histological findings with the aetiology of the effusion is presented in Table 3. A higher final score of pathological changes was found in bacterial and autoimmune diseases, viral and drug-induced NSPs showed a similar moderate score, while a lower score was produced by heart disease and pneumothorax (*p*<0.0001).

Seen by histological feature, degree of inflammation did not differ between the different aetiological groups (*p*=0.3); however, the predominant inflammatory cell type did differ, as in most groups lymphocytes was the predominant type while in the pneumothorax and the bacterial group, histiocytes and neutrophils, respectively, were also found (*p*=0.02). The presence of histiocytes was a feature mostly of pneumothorax and viral disease (*p*<0.0001), in comparison to other aetiologies.

Degree of fibrosis differed between aetiological groups as the bacterial-caused group showed the most severe fibrosis (*p*=0.03). Furthermore, the type of fibrosis differed as it was cellular in the bacterial-caused group in comparison to other groups, which showed an old type of fibrosis (*p*=0.006). Similarly, layering of tissue elements was more often seen with bacterial pleural effusion than the rest of the groups (*p*=0.05). Vascular proliferation and haemorrhage were mostly features of bacterial infection (*p*<0.0001 and *p*=0.02, respectively). Oedema presence did not differ between categories (*p*=0.1). Mesothelial hyperplasia was more often found with pneumothorax (*p*=0.009).

The total final score was associated with the predominant macroscopic pattern (*p*=0.002), as septated and haemorrhagic

Table 2 Histological evaluation in all patients except 'Other' group (n=84)

Parameters	n (%)
Inflammation	
No	7 (8.4)
Mild	23 (27.7)
Moderate	41 (49.3)
Severe	12 (14.4)
Predominant inflammatory cell type (n=76)	
Lymphocytes	49 (64.4)
Plasmocytes	10 (13.1)
Neutrophils	9 (11.8)
Histiocytes	7 (9.2)
Eosinophils	1 (1.3)
Fibrosis	
No	7 (8.4)
Mild	30 (36.1)
Moderate	19 (22.8)
Severe	27 (32.5)
Type of fibrosis (n=76)	
Cellular	29 (38.1)
Old	39 (51.3)
Both	8 (10.5)
Layering	
Yes	28 (33.8)
No	55 (66.2)
Vascular proliferation	
Yes: score 2 and 3	41 (49.3)
No: score 0 and 1	42 (50.6)
Oedema	
Yes: score 2 and 3	17 (20.4)
No: score 0 and 1	66 (79.5)
Haemorrhage	
Yes: score 2 and 3	19 (23.1)
No: score 0 and 1	63 (76.8)
Fibrin	
Yes: score 2 and 3	34 (40.9)
No: score 0 and 1	49 (59.1)
Mesothelial hyperplasia	
Yes: score 2 and 3	11 (13.2)
No: score 0 and 1	72 (86.7)
Number of slides examined per case	
Median (range)	4 (1–18)
Specimen size, cm	
Median (range)	7 (1–28)
Histiocytes	
Yes	24 (28.8)
No	59 (71.2)

patterns showed the higher final score (mean 5.2 ± 0.8 and 6.5 ± 0.7 , respectively), followed by fibrotic, fibrinous and inflammatory (mean 4.5 ± 1.7 , 4.7 ± 1.3 and 4.4 ± 1.5 , respectively), while pleural plaques showed a lower score (2.5 ± 2.1).

Vascular proliferation was significantly associated with fibrosis ($p<0.0001$), as it was present in biopsies with severe and moderate fibrosis and not with mild or no fibrosis. It was also significantly associated with the type of fibrosis ($p<0.0001$) as it was the cellular type that was mostly characterised by vascular proliferation. Vascular proliferation was not associated with the degree of inflammation ($p=0.1$). Inflammation was not associated with the degree of fibrosis ($p=0.08$).

According to these results and as illustrated in Table 4, we tried to define some patterns of NSP and their corresponding diagnostic efficacy in regards to underlying aetiology (Table 5). Thus, a severely fibrotic pleura, with cellular fibrosis, vascular proliferation, haemorrhage, and neutrophils is more representative of bacterial disease (Pattern A). Lymphocyte-predominant inflammation with mild/moderate old collagenous fibrosis, with no layering or vascular

proliferation, is mostly associated with viral disease (Pattern B). Moderate old collagenous fibrosis with variable degree of lymphocytic inflammation without vascular proliferation, oedema, fibrin, haemorrhage or mesothelial hyperplasia is seen with heart disease (Pattern C). Autoimmune disease presents with important cellular, layered fibrosis with moderate lymphocytic inflammation, as well as vascular proliferation, oedema and fibrin without haemorrhage (Pattern D). A similar pattern but with haemorrhage and without vascular proliferation is seen in drug-induced cases (Pattern E). In contrast to these aetiologies, pleural tissue associated with recurrent pneumothorax is characterised by numerous histiocytes and eosinophils, and by mild, if any, collagenous fibrosis (Pattern F). These patterns were significantly associated with the aetiology ($p<0.0001$) and showed interesting values of diagnostic efficacy for each pattern (Table 5).

DISCUSSION

Non-specific pleuritis is the term usually applied to a pleural effusion after biopsy has excluded a 'specific' and often definitive diagnosis, mostly malignancy or granulomatous disease.⁷ In this case, a descriptive diagnosis is given usually reporting features like inflammation or fibrosis.⁷ The aetiology hidden behind this histology is variable and impossible to define without the complete clinical data. We show in this study that the various diseases presenting with a non-specific pattern in pleural biopsy differ in their detailed histological features.

In particular, bacterial diseases present predominantly with a severely fibrotic pleura and this fibrosis is cellular, characteristically rich in fibroblasts. Vascular proliferation in the form of rich granulation tissue as well as haemorrhage and tissue layering are also frequent features of these infectious conditions. Furthermore, neutrophils as the predominant cellular type in pleural biopsy are almost exclusively seen with this aetiological group. Indeed this pattern (Pattern A in our classification) proved to have a high positive predictive value and therefore is highly specific for bacterial infection (Table 5). Pleural effusions associated with viral infections are lymphocyte-predominant in histological specimens, showing mild or moderate fibrosis, old collagenous in type and no layering of the tissue or vascular proliferation. This proposed pattern (Pattern B of our classification) presents high negative predictive value and sensitivity (Table 5). Pleural effusion associated with heart disease shows variable degrees of inflammation but always lymphocyte-predominant and moderate fibrosis, which is mostly old collagenous without vascular proliferation, oedema, fibrin, haemorrhage or mesothelial hyperplasia. The proposed Pattern C in our classification shows relatively high specificity (Table 5). Autoimmune disease presents with a moderate lymphocyte-predominant inflammation, important fibrosis cellular in type and layered, as well as vascular proliferation, oedema and fibrin without haemorrhage. This pattern (Pattern D) shows high negative predictive value and sensitivity (Table 5). A similar pattern but with haemorrhage and without vascular proliferation is seen in drug-induced cases. In these cases, the proposed Pattern E presents high specificity (Table 5). In contrast to these aetiologies, pleural tissue associated with recurrent pneumothorax is characterised by an inflammation rich in histiocytes and eosinophils, and by mild, if any, fibrosis that is old collagenous in type.

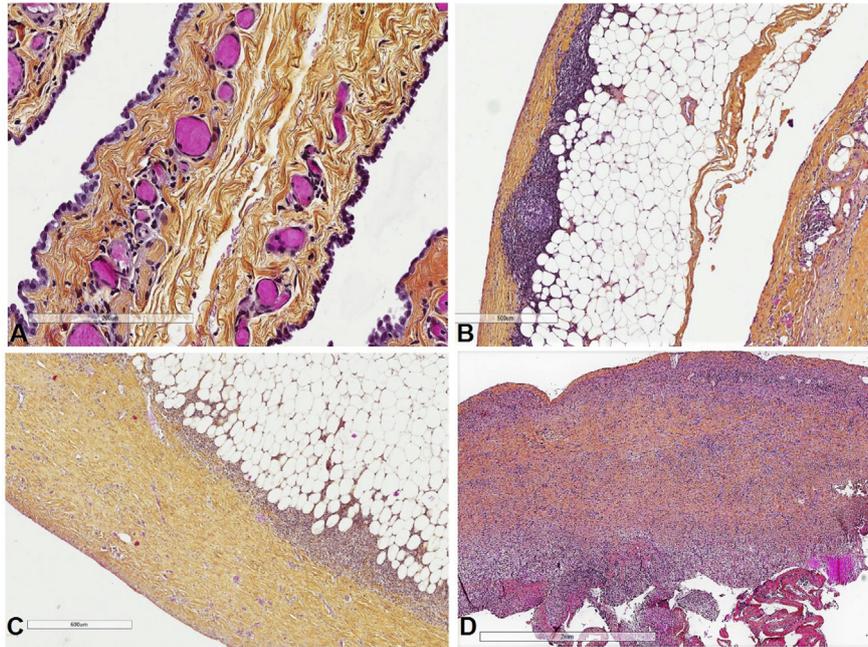


Fig. 1 Fibrosis histological assessment (haematoxylin, eosin, saffran). (A) A normal parietal pleura biopsy showing mesothelial cells and the underlying connective tissue with its vascular elements. (B) Mild collagenous fibrosis overlying parietal pleura adipose tissue and mild lymphocytic inflammation of a heart disease-associated NSP. (C) Moderate collagenous fibrosis overlying parietal pleura adipose tissue in a case of a heart disease-associated NSP. (D) Severe cellular fibrosis replacing the whole pleural membrane accompanied by haemorrhage on the cavity surface in a bacterial NSP.

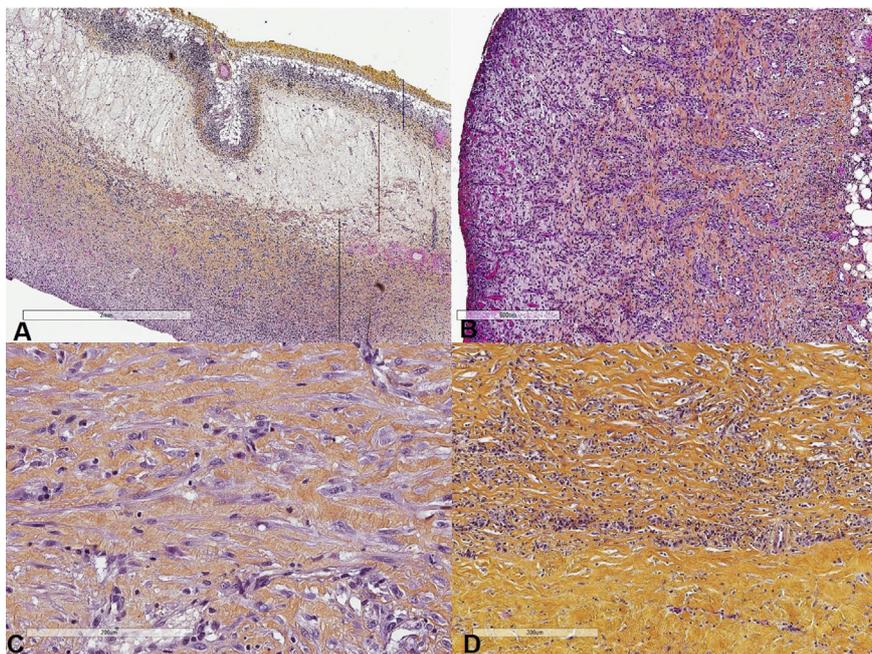


Fig. 2 Stages during inflammation/wound healing in bacterial-caused NSP (haematoxylin, eosin, saffran). (A) A biopsy showing prominent tissue layering: the initial pleural membrane with overlying inflammation (blue line), oedema (red line) and vascular-rich organisation tissue (black line). (B) Another case of tissue organisation, showing conspicuous vascular proliferation inside a fibrotic and inflammatory stroma. (C) The typical morphology of fibroblast-rich fibrosis with layering of cells. (D) For comparison, a case of viral-induced NSP showing old collagenous fibrosis at the bottom with mildly cellular fibrosis at more superficial levels (mixed fibrosis).

Interestingly, this pattern, classified as Pattern F, proved to present the highest sensitivity and specificity for diagnosis of pneumothorax (Table 5).

These differences in histological findings provide a pattern of NSP varying according to the underlying aetiology and the pathophysiology of pleural effusions. Histological changes found in the current effusions series reflect the underlying tissue remodelling seen during pleural injuries. During

pleural injury, increased microvascular permeability induces plasma extravasation and activation of tissue factor, and thus initiation of coagulation and formation of fibrin.¹¹ This disordered local fibrin turnover represents an early tissue response subject to the influence of local mediators of inflammation and of components of the fibrinolytic response and sets the stage for progressive remodelling/wound healing or fibrotic repair in the face of protracted injury.¹¹ TGF- β as

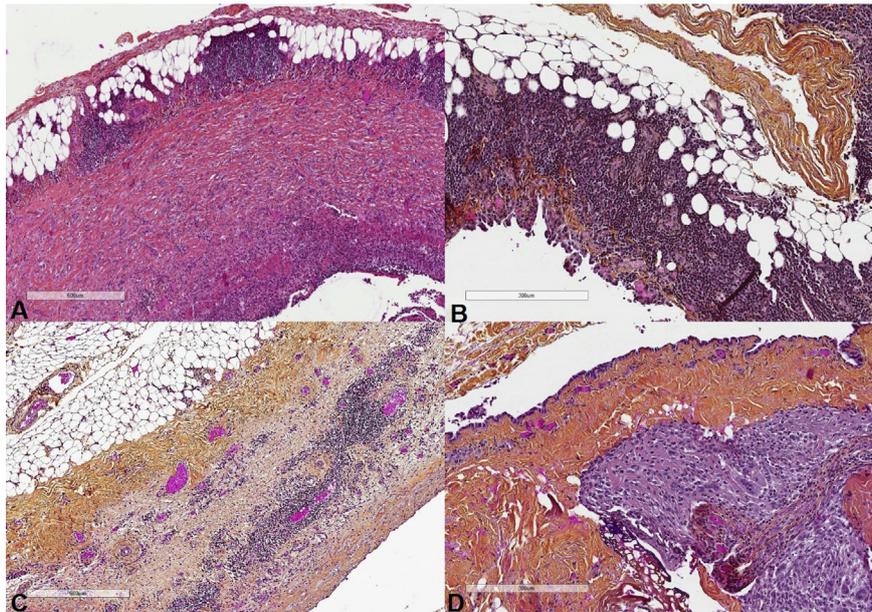


Fig. 3 Representative patterns of NSP (haematoxylin, eosin, saffran). (A) Bacteria-associated NSP showing a thickened layered fibrotic pleura with rich cellular fibrosis, inflammation and haemorrhage at the surface. (B) Viral-associated NSP showing moderate chronic inflammation, mild mesothelial hyperplasia and no fibrosis. (C) A cardiac NSP showing moderate old fibrosis and mild inflammation. (D) A pneumothorax-associated NSP showing mild old collagenous fibrosis and a rich histiocytic infiltrate, often with giant cells and eosinophilic leukocytes.

Table 3 Clinicopathological correlations

	Bacterial <i>n</i> =27	Viral <i>n</i> =7	Cardiac <i>n</i> =10	Pneumothorax <i>n</i> =28	Autoimmune <i>n</i> =5	Drug <i>n</i> =6	<i>p</i> value
Final score, mean	5.1±1.4	4.4±1.6	3.8±1.2	3.1±1.5	5.6±1.1	4±1.4	<0.0001
Inflammation							0.3
No	3	1	0	3	0	0	
Mild	6	0	3	11	0	3	
Moderate	12	4	5	13	5	2	
Severe	6	2	2	1	0	0	
Predominant inflammatory cell type							0.02
Lymphocytes	14	7	9	11	5	4	
Plasmocytes	3	0	1	5	0	1	
Neutrophils	7	0	0	1	0	1	
Histiocytes	0	0	0	7	0	0	
Eosinophils	0	0	0	1	0	0	
Fibrosis							0.03
No	2	0	2	2	0	1	
Mild	3	3	3	18	0	2	
Moderate	6	2	2	6	2	1	
Severe	15	2	3	2	3	2	
Type of fibrosis							0.006
Cellular	17	1	3	5	1	2	
Old	5	5	4	20	2	3	
Both	3	1	1	1	2	0	
Layering							0.05
Yes	13	1	4	4	3	3	
No	14	6	6	24	2	3	
Vascular proliferation							<0.0001
Yes: score 2 and 3	24	3	3	7	3	1	
No: score 0 and 1	3	4	7	21	2	5	
Oedema							0.1
Yes: score 2 and 3	7	1	0	4	2	3	
No: score 0 and 1	20	6	10	24	3	3	
Fibrin							0.1
Yes: score 2 and 3	16	2	3	7	3	3	
No: score 0 and 1	11	5	7	21	2	3	
Haemorrhage							0.02
Yes: score 2 and 3	12	1	2	2	0	2	
No: score 0 and 1	15	6	8	25	5	4	
Presence of histiocytes							<0.0001
Yes	0	3	1	20	0	0	
No	27	4	9	8	5	6	
Mesothelial hyperplasia							0.009
Yes	0	1	0	9	0	1	
No	27	6	10	19	5	5	

Table 4 Histological features according to aetiology

	Bacterial	Viral	Cardiac	Pneumothorax	Autoimmune	Drug
Inflammation	++/+++	++/+++	+/>++	+/>++	++	+/>++
Lymphocytes	++	++	++	++	++	++
Plasmacytes	+	-	-	+	-	-
Neutrophils	++	-	-	-	-	-
Histiocytes	-	-	-	++	-	-
Eosinophils	-	-	-	++	-	-
Fibrosis	+++	+/>++	++	+/>-	+++	+/>-
Cellular fibrosis	+++	+/>-	+/>-	+/>-	+/>-	+/>-
Layering	+++	+/>-	+	+/>-	+++	+++
Vascular proliferation	+++	++	+	+/>-	+	+/>-
Oedema	+	+/>-	-	+/>-	+/>-	+
Fibrin	+++	+/>-	+/>-	+/>-	++	++
Haemorrhage	+++	+/>-	+/>-	+/>-	-	+/>-
Mesothelial hyperplasia	-	+/>-	-	++	-	+/>-

-, absent; +, mildly present; ++, moderately present; +/+, usually present.

Table 5 Efficacy of the proposed patterns for diagnosing the underlying cause

	Pattern A = Bacterial	Pattern B = Viral	Pattern C = Cardiac	Pattern D = Autoimmune	Pattern E = Drug	Pattern F = Pneumothorax
PPV	100%	35%	20%	21.74%	57.14%	90.32%
NPV	84.88%	100%	90.53%	100%	96.77%	100%
Sensitivity	51.85%	100%	10%	100%	57.14%	100%
Specificity	100%	86.02%	95.56%	81.05%	96.77%	95.83%

NPV, negative predictive value; PPV, positive predictive value.

the major pro-fibrotic factor, and subpleural fibroblasts but also mesothelial cells that can undergo epithelial to mesenchymal (EMT)-like transition as the main cell targets, are the basic players in pleural fibrosis.¹¹ According to our findings, bacterial and autoimmune diseases will show the most prominent remodelling of the pleural tissue, probably reflecting an imbalance in favour of the coagulation and opposing the fibrinolytic response, while viral and cardiac aetiologies represent a more balanced response with less tissue remodelling. Chronic air trauma/local bleeding due to adhesions rupture in recurrent pneumothorax does not evoke important tissue remodelling or imbalance of the fibrinolytic/coagulation system, rather it evokes a foreign body reaction with eosinophils and histiocytes overloading the pleural surface.

From a clinical point of view, NSP often presents a management dilemma for the treating physician, as it could represent a true benign aetiology or just a sampling/diagnostic error that would then imply the need for further invasive techniques. Studies trying to answer the question of evolution of these non-specific pleuritis cases after long-term follow-up showed that in 5%⁶ to 18%^{12,13} of cases a malignancy, particularly mesothelioma, will be revealed; thus, a minimum of 1 year of clinical and imaging follow-up is recommended,^{8,14,15} as in our series. Also, past or active history of carcinoma are important criteria to facilitate the diagnosis of underlying malignancy in NSP.¹⁶ These false negative cases represent the difficulties in sampling a thickened pleura not allowing deep biopsies to be easily performed or a pleural cavity full of adhesions difficult to inspect.⁵ The endoscopic appearance of pleural lesions is suggestive of malignancy in 86% of cases and suspicious appearances include nodules, polypoid lesions, masses, malignant

thickening of the pleura, and localised 'candle wax drops'.¹⁷ However, benign conditions can be mistaken for malignancy and *vice versa*.¹⁷ False negative diagnoses could also represent cases difficult to handle histologically, as an intense fibrosing pleuritis may be difficult to discern from a sarcomatoid or desmoplastic mesothelioma.¹⁸ We have recently shown that frozen sections in pleural disease are very efficient in rapidly diagnosing malignancy¹⁹ and for tissue handling for molecular tests.²⁰

Similar to NSP cases, eosinophilic pleural effusions which are defined as effusions with 10% or more eosinophils can be attributed to many causes (air or blood in the pleural cavity, malignancy, drugs, asbestos exposure, infection, or autoimmune disease) or they can be idiopathic after exclusion of all these known aetiologies.^{21,22} Long-term follow-up of these 'idiopathic' cases has revealed a benign clinical course but this can be confirmed only after thorough thoracoscopic investigation of the pleural cavity and benign corresponding histology.²¹

To conclude, our study provides the first evidence for the microscopic features underlying benign pleural diseases, and could lead to further investigation regarding the mechanisms driving the course of disease. Our classifications may be applied in routine practice by adding a comment on the suggested pattern in the pathology report addressed to the clinician, which may be helpful in the final diagnosis of the underlying pleural disease. Indeed, although in our series all patients were found to present with benign disease, significant microscopic differences were observed, reflecting the capacity for tissue remodelling in every case. It also opens new horizons for studying pleural inflammation to establish mechanisms in the

pathogenesis of pleural involvement according to the underlying disease.

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