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Contribution Of Pleural Adenosine Deaminase In The Diagnosis Of Tuberculous Pleurisy

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Abstract
Introduction*: In Morocco, pleurisy is one of the most frequent manifestations of tuberculosis, after pulmonary tuberculosis. It is estimated that up to 5% of tuberculosis patients will develop pleural effusion during the course of their illness. Adenosine deaminase (Ada) is a non-invasive diagnostic marker proposed for the diagnosis of tuberculous pleurisy to overcome the limitations of conventional diagnostic tools (direct examination, culture, etc.). The aim was to determine the contribution of pleural adenosine deaminase to the diagnosis of tuberculous pleurisy.*
Materials and Methods*: We report a prospective study of patients with pleurisy collected between August 2017 and February 2019 at the Pneumology Department of CHU Mohammed VI in Marrakech. In the course of the study, we performed an Ada assay in pleural fluid, using the Giusti method, in 81 patients presenting with pleurisy. We divided the patients into two groups: group "1" (tuberculous pleurisy) and group "2" (non-tuberculous pleurisy). We calculated sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), false positives and false negatives with an Ada threshold set at 40 U/L. A p-value <0.05 is considered statistically significant.*
Results*: The 81 patients had the following etiological diagnoses: tuberculous pleurisies confirmed by histological analysis of pleural biopsy +/- bacteriology (n=43) and non-tuberculous pleurisies, notably metastatic pleurisies of lung or breast cancer confirmed by cytology or histology (n=10), lymphomatous pleurisies (n=4), cardiac pleurisies (n=7), bacteriologically confirmed purulent pleurisies (n=4) and pleurisies of undetermined etiology (n=13). The mean pleural Ada level in group "1" was 55.85 ± 24.13 versus 71.00 ± 56.08 in group "2", with no significant difference between the 2 groups (p = 0.129). However, there was a significant increase (p = 0.001) in Ada activity in tubercular pleurisy (55.85 ± 24.13) versus cardiac pleurisy (31.57 ± 13.40). There was no significant difference between the tubercular pleurisy group and the rest of the groups. For a threshold value set at 40 U/L, overall diagnostic performance was as follows: Se: 95.35%; Sp: 21.05%; PPV: 57.75%; NPV: 80%; FP: 30 and FN: 2; TP: 41; NPV: 8.*
Conclusion: *Our study confirms the excellent sensitivity of Ada activity in pleural fluid. However, the specificity of the test, which is impaired by the presence of numerous false positives, mainly in purulent and neoplastic pleurisy, can be improved in practice by complementary measurement of the Ada1/total Ada ratio and by taking into account pleural fluid cytology and microbiological data. In the case of lymphocytic pleurisy, it's high NPV.*
Key Word*: pleurisy; adenosine deaminase; tuberculosis; purulent; neoplastic.*

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I. Introduction

Tuberculosis is a public health problem in Morocco. Incidence has remained relatively stable over the last decade (2006-2016) at between 86 and 91/100,000 inhabitants. Pulmonary tuberculosis (PT) accounts for 53% of all forms of tuberculosis, while extra-pulmonary tuberculosis (EPT) represents 47%, confirming the increase in the number of EPT cases observed over the years. Pleural localization ranks second after pulmonary involvement, followed by lymph node involvement (LAT 2017). After pulmonary tuberculosis, pleurisy is one of the most frequent manifestations of tuberculosis. It is estimated that up to 5% of patients suffering from tuberculosis will develop pleural effusion during the course of their illness. In high-prevalence areas, tuberculous pleurisy is the main cause of serofibrinous pleurisy [1]. In high-prevalence areas, the diagnosis of tuberculous pleurisy is usually presumptive, based essentially on epidemiological, anamnestic and clinical arguments, due to the limited accessibility of diagnostic tools, the latter also having relatively poor diagnostic performance [2, 3]. On the other hand, bacteriological diagnosis of tuberculosis as practised in laboratories always poses problems of delayed transmission of results, which are only obtained after a delay of 3 to 4 weeks, direct examination of BK rarely being positive [4, 5]. More often than not, the diagnosis of tuberculosis is only confirmed after blind pleural biopsy for histological study and culture [5]. In view of these difficulties, it is

preferable to find rapid, sensitive, simple and effective means of diagnosis at an early stage. Numerous biomarkers, including pleural adenosine deaminase (Ada) activity, have been proposed to help diagnose this clinical entity and overcome the limitations of conventional diagnostic tools (direct examination, culture, etc.). Although numerous studies have demonstrated the value of determining pleural adenosine deaminase activity, this marker remains relatively unknown. The aim of our study is to test the effectiveness of this assay in the diagnosis of pleurisy of tuberculous origin.

II. Material and Methods

Study Design: Prospective comparative study
Study Location: Pneumology Department of CHU Mohammed VI in Marrakech
Study Duration: From August 2017 to February 2019
Sample size: Total 81 adult subjects (both male and females) of aged ≥ 17 years were for in this study
Subjects & selection method: During the study, we performed an adenosine deaminase (Ada) assay in pleural fluid, using the Giusti method, in 81 patients presenting with pleurisy. Patients were classified into two groups: group "1" (tuberculous pleurisy) and group "2" (non-tuberculous pleurisy). We calculated sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), false positives and false negatives, with an Ada threshold set at 40 U/L. A p-value <0.05 is considered statistically significant.

Inclusion criteria:
The patients included in the study were all carriers of pleurisy of any etiology
Exclusion criteria:
- Patients lost to follow-up.
- Patients without the means to measure Ada in pleural fluid.

Procedure methodology :
- The patients recruited were either :
- ✓ Hospitalized in the pneumology department
- ✓ Followed in pneumology consultations, whether formerly hospitalized or followed on an outpatient basis
- ✓ Seen in the emergency department
- ✓ Hospitalized in another department
- Patients were called to the outpatient care according to a pre-programmed schedule.
- A detailed medical record was opened for each patient, including epidemiological, clinical and paraclinical information.
- Pleural samples were taken in the procedure room, including an exploratory puncture completed in most cases by a pleural biopsy.
- Patients were declared discharged on the same day and referred to the consultation for former patients, with the results of the tests requested.
- Data were collected on a detailed data sheet.
- Patients were then divided into two groups:
- ✓ Group 1: Tuberculous pleurisy
- ✓ Group 2: Non-tuberculous pleurisy

Statistical analysis:
- Data entry was carried out on Excel 2007, using a uni-variate descriptive method based on percentages.
- The software used for the p-value is epi info 6.1. A value of $p<0.05$ is considered statistically significant.
- Ada activity in pleural fluid was determined using the Giusti method. An Ada threshold was set at 40 IU/L.

Ethical considerations
- Patient consent was obtained prior to their inclusion in the research and prior to requesting Ada analysis of pleural fluid.
- Clinical data were collected with respect for patient anonymity and confidentiality.

III. Result

- Macroscopic analysis of the pleural fluid revealed a lemon-yellow fluid in 67 cases (82% of cases), serosanguineous in 10 cases (12% of cases) and cloudy in 4 cases (5% of cases).
- Chemical analysis carried out on all our patients revealed (figure 1):
- ✓ An average pleural protein level of 44 g/l.
- ✓ An average pleural protein level in group 1 of 46g/l.

- ✓ An average pleural protein level in group 2 of 38g/l.
- ✓ Transudative fluid in 7 cases (9% of cases), with an average pleural protein level of 16 g/l.
- ✓ Exudative fluid in 74 cases (91% of cases), with a mean pleural protein level of 45g/l.

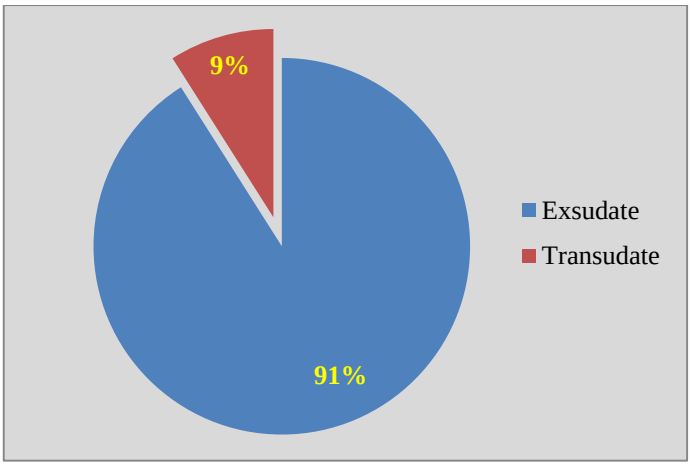

Figure 1: Graphic distribution according to the exudative or transudative nature of pleural fluid

– The determination of Ada in pleural fluid revealed (table n°1, n°2, n°3):

- ✓ A mean Ada level of 55.85 U/L± 24.13.
- ✓ A cut-off value for Ada is set at 40 U/L.
- ✓ Overall diagnostic performance was as follows: Sensitivity (Se): 35/43 = 81%; Specificity (Sp): 8/38 = 21.05%; Positive predictive value (PPV) = 53%; Negative predictive value (NPV) = 50%; False positives (FP) = **30; False negatives (FN) =8**

Table 1: Comparison of mean pleural Ada values in Group 1 and Group 2

	Group 1 Tuberculous pleurisy n= 43	Group 2 Non-tuberculous pleurisy n= 38	P-value*
Ada	55,85 ± 24,13	71,00 ± 56,08	0.129

***P<0.05 is considered significant.**

Table 2: Sensitivity, specificity, PPV, NPV, FP, FN of Ada assay in pleural fluid

	Group 1 n= 43	Group 2 n= 38
Ada> 40	41TP	30 FP
Ada <40	2 FN	8 TN

Se= 95,35% ; Sp= 21,05% ; PPV= 57,75% ; NPV= 80% ; FN= 2 ; FP= 30

Table 3: Comparison between the median Ada rate in group "1" and the various sub-groups of group "2".

P-value	Cardiac n= 7 Ada=31.57 ± 13.40	Metastatic n= 10 Ada=94.49 ± 55.63	Lymphomatous n= 4 Ada=131.35 ± 121.69	Purulent n= 4 Ada=74,25 ± 33,35	Cause undetermined n= 13 Ada=52,61 ± 20,80
Groupe 2 n = 43 Ada = 55,85 ± 24,13	0.001	0.05	0.30	0.35	0.85

– Cytological analysis performed on all our patients shows (figure n°2):

- ✓ A clear lymphocytic predominance in 77 cases (95% of cases), with a median pleural fluid lymphocyte count of 73%.
- ✓ An average lymphocyte count in group 1 of 82% versus 68% in group 2.

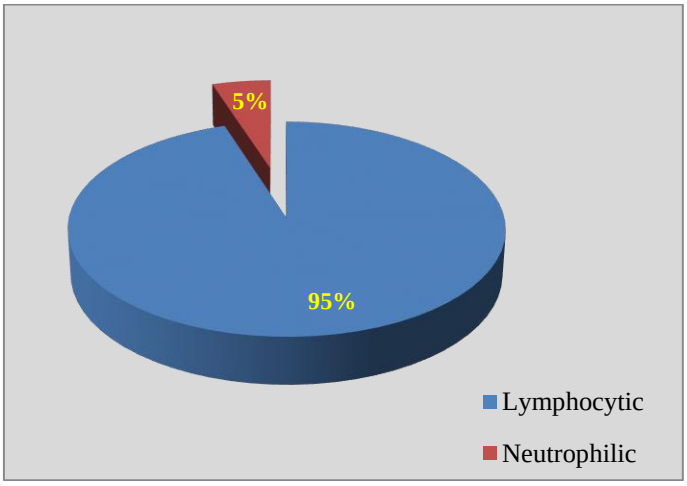

Figure 2: Graphical distribution of pleural fluid cell counts

- Cytopathological analysis of pleural fluid in 65 patients (91% of cases) revealed tumor cells in 6 cases (91% of cases).
- Bacteriological analysis of pleural fluid with culture carried out in all our patients revealed a germ in 4 cases (5% of cases).
- Direct examination and culture for AFB were negative in 67 patients (82% of cases).
- The X-pert gene in pleural fluid from 44 patients (54% of cases) was positive in just one case.
- Pleural biopsy was performed in 68 patients:

✓ Histological study of pleural fragments in 70 patients (86% of cases) revealed malignant proliferation in 3 cases (4% of cases) (including 2 cases of pulmonary adenocarcinoma and 1 case of B lymphoma), epithelio-giganto-cellular granuloma with caseous necrosis in 40 cases (49% of cases), and was inconclusive in 27 cases (33% of cases).

✓ In 51 patients (36% of cases), BK was detected by direct examination and culture of pleural fragments, and was positive in 3 cases (4% of cases).

- Bacilloscopy: Sputum BK testing was carried out in 56 patients (69% of cases) and was positive in 2 cases (2% of cases).
- Tuberculosis origin was found in 43 cases, and confirmed in all cases by pleural biopsy, including 3 cases of positive bacilloscopy (table 4).

Table 4: Distribution of patients by etiology of pleural effusion

Diagnosis	**Number of patients (n)**	**Percentage (%)**
Tuberculous pleurisy	**43**	53%
Cardiac pleurisy	**7**	9%
Metastatic pleurisy	**10**	12%
Lymphomatous pleurisy	**4**	5%
Purulent pleurisy	**4**	5%
Pleuresia of undetermined aetiology	**13**	16%

IV. Discussion

Bacteriological diagnosis of diseases involving a cellular immune response, such as tuberculosis, empyema and lymphoma, still poses problems of delay and sensitivity [7]. The assay of Ada in pleural fluid has been proposed to overcome the shortcomings of traditional methods. In 1978, Piras et al. showed that Ada activity was higher in pleural effusions of tuberculosis origin than in effusions of other etiologies. This led to large-scale prospective studies, mostly in Spain and South Africa, evaluating the diagnostic value of Ada assay in pleural tuberculosis [6, 8].

The diagnostic efficacy of this assay depends on the analytical method used in the laboratories, the discriminatory cut-off, the ethnic population and, above all, the prevalence of tuberculosis [9, 10]. However, in high TB prevalence countries with an Ada threshold ≥ 40 U/L, ranging from 40 to 60 U/L, figures vary according to studies: Se = 80-100%; Sp = 67-100; PPV = 71-100%, NPV = 85-100%; reliability = 86-100% [9, 10]. On the other hand, in countries where the prevalence of tuberculous pleurisy is lower, few studies are available [9]. Several studies have shown that the NPV of Ada, i.e. the probability that a subject with a normal

Ada level does not have tuberculosis, should remain high even in low-prevalence areas [9, 11, 12]. The results reported in our study are in agreement with those in the literature, with a sensitivity of 95.35% and an NPV of 80% for a pleural Ada threshold set at ≥ 40 U/L. These findings conclude that the Ada assay is a reliable test for ruling out tuberculosis in the presence of lymphocytic pleurisy (Table 5). In terms of specificity, only the results of Sahrma et al. [16] (Sp: 66.6) and Andriamanantena et al. [22] (Sp: 60) are close to our results (Sp: 21.05), showing that the pleural Ada assay is not specific for the diagnosis of tuberculosis, even in countries with a high prevalence of tuberculosis such as Morocco; these results contrast with most of the series reported in the literature.

Table 5: Sensitivity, specificity, PPV, NPV and cut-off values for pleural Ada in selected studies reported in the literature [10].

Authors	Country	Cut-off value (U/L)	Se (%)	Sp (%)	PPV	NPV
Aoki et al.	Japan	**45**	**81,8**	**89,3**	**75**	**93**
Teo et al.	Singapore	**50**	**96**	**81**	**65**	**98**
Reechaipichitkul et al.	Thaïland	**48**	**80**	**80,5**	**71,4**	**86,8**
Sharma et al.	India	**35**	**83,3**	**66,6**	**-**	**-**
Burgess et al.	South Africa	**50**	**91**	**81**	**84**	**89**
Banales et al.	Spain	**70**	**98**	**96**	**94**	**99**
Valdés et al.	Spain	**47**	**100**	**95**	**85**	**100**
Orphanidou et al.	Greece	**40,6**	**79**	**93,5**	**86**	**90**
Smach et al.	Tunisia	**37**	**66,6**	**81,2**	**64,3**	**82,7**
Andriamanantena et al.	France	**35**	**100**	**60**	**87**	**100**
Atmane et al. [23]	Morocco	**50**	**100**	**90**	**88**	**100**
Our study	Morocco	**40**	**95,35**	**21,05**	**57,75**	**80**

If we focus solely on lymphocytic pleurisies, as shown by 2 large Spanish series [13], false positives are rare: 8 patients/293 non-tuberculous lymphocytic pleurisies with Ada> 40 IU/L for one; and 7/410 = 1.71% with Ada> 40 IU/L for the other study where the NPV of Ada for the diagnosis of pleural tuberculosis was quantified at 99%. It should be noted that in this work, the complementary measurement of the Ada1/total Ada ratio < 0.42 corrected for false positives [13]. The results reported in our series diverge from those highlighted by these 2 Spanish series and show that false positives are fairly frequent: 30 cases/38 non-tuberculous lymphocytic pleurisies including 10 cases of metastatic pleurisies, 4 cases of lymphomatous pleurisies and 12 cases of pleurisies of undetermined etiology, with Ada ≥ 40 U/L and a VPN of 80%. This is in line with the results of Ena et al. [14], in their meta-analysis published in 1990, listed 7 studies published between 1980 and 1990. Out of a total of 760 pleurisies, 185 of which were tuberculous, with a pleural Ada threshold ranging from 33 to 79 IU/L, only 1 false negative and 40 false positives were described. The overall sensitivity of pleural Ada was calculated at 99% and specificity at 94%. This analysis was then completed by Banales et al. [15] in 1991, who found Se = 99% and Sp = 89% for 2,251 pleurisies, including 706 with tuberculosis. Among the 116 false positives = 5.7%: 52 empyemas, 20 bronchial cancers, 18 lymphomas, 6 mesotheliomas, 4 rheumatoid pleurisies and 16 idiopathic pleurisies. False negatives are rare and controversial (Table 6) [21]. Valdes et al. [28], in Spain, in 254 cases of tuberculous pleurisy, observed only one case of false negatives where Ada was < 47 U/L. In India, the results obtained by Sharma et al. [16] are lower than those reported by the Spanish (Se = 83%, Sp = 66% with a cut-off at 35 IU/L). Burgess et al. [17] in South Africa found 13 cases/143 of tuberculous pleurisy with an Ada threshold of 50 U/L (Se = 91%). Riantawan et al. [18] in Thailand reported 4 cases/100 with Ada< 47 U/L. Querol et al. [19] in Barcelona reported 11 cases/114 pleural tuberculoses with Ada< 45 U/L. In Barcelona, a team carried out a 10-year prospective study of 40 unexplained pleurisies with pleural Ada < 43 U/L: they found no tuberculosis after an average follow-up of 62 months, whereas 19 had an initial positive tuberculin TST. They felt that anti-tuberculosis treatment should not be initiated in these situations if the Ada is not elevated [20].For a threshold value of Ada < 40 U/L, false negatives were also rare in our series (2/43 tuberculous pleuresies) with a sensitivity of 95.35%. These results are in line with those reported in the literature.

Table 6: Results of the main studies carried out in countries with a high prevalence of pleural tuberculosis [21].

	N TB/N	Cut-off ADA U/L	False –	False +	Se %	Sp %	PPV %	NPV %	Reliability %
Ocana 1983	46/182	45	0	5	100	97	90	100	97
FontanBueso 1988	61/138	33	0	5	100	94	92	100	96
Baganha 1990	35/73	50	0	0	100	100	100	100	100
Banales 1991	82/218	70	1	6	98	96	94	99	97
Valdes 1993	91/405	47	0	11	100	94,9	85	100	96
Burgess 1996	143/303	50	13	7	91	81	84	89	86
Chalhoub 1996	150/221	40	—	4	93,3	93,5	97,2	85,3	—
Riantawan 1999	100/216	60	4	4	95	96	96	95	96
Perez-Rodriguez 1999	27/103	40	—	—	88,8	92	80	95,8	91,2
Gorguner 2000	36/87	47	0		100	89	86	100	89
Villegas 2000	42/140	45,5	—	10	88	85,7	79	92,3	—
Sharma 2001	48/75	35 100	—	—	83,3 40	66,6 100	82 100	69 48	—
Reechaipichitluk 2001	50/132	48	—	—	80	80,5	71,4	86,8	—

Empyemas were excluded from false positives. Abbreviations: Se = sensitivity, Sp = specificity, PPV = positive predictive value, NPV= negative predictive value, _: not specified in article or not calculable.

Burnat et al. [24], at the Paris military hospital complex, performed pleural Ada determinations in 75 (n=75) patients hospitalized for respiratory disorders of various etiologies that warranted pleural puncture. 5 groups were divided according to etiology: tuberculous pleurisy confirmed by bacteriological analysis (n = 11), metastatic pleurisy of lung cancer confirmed by cytology or histology (n = 16), purulent pleurisy confirmed bacteriologically (n = 9), cardiac pleurisy (n = 13) and pleurisy of various etiologies other than the above (n = 26). A comparison of the results obtained revealed a significant increase ($p < 0.01$) in Ada activity in tuberculous (93.6 ± 36.9) and microbial (39.8 ± 44.9) pleurisies compared with the other groups (cancer: 12.2 ± 7.7; cardiac involvement: 9.5 ± 3.8; miscellaneous: 17.1 ± 5.8). There was a significant difference between Ada activity in tubercular and bacterial pleurisy ($p < 0.05$). For a threshold value set at 45 U/L, the sensitivity and specificity percentages reported were 100% and 97% respectively. In our stud y, the mean pleural Ada level in the tuberculous pleurisy group was 55.85 ± 24.13 versus 71.00 ± 56.08 in the non-tuberculous pleurisy group, with no significant difference between the 2 groups ($p = 0.129$). On the other hand, there was a significant increase in Ada activity in tuberculous pleurisy (55.85 ± 24.13) versus cardiac pleurisy (31.57 ± 13.40; $p = 0.001$). There was no significant difference between the tubercular pleurisy group and the rest of the groups (lymphomatous: 131.35 ± 121.69; metastatic: 94.49 ± 55.63; purulent: 74.25 ± 33.35; indeterminate: 52.61 ± 20.80). Sensitivity and specificity percentages were 95.35% and 21.05% respectively. Some authors suggest associating Ada activity with other parameters. In their study, Duprat Neves et al [25] report the results of combining four indicators: Ada activity, lymphocyte percentage, pleural fluid protein concentration and patient age. The authors note that when the Ada activity value exceeds 39 U/L, the probability of tuberculous pleurisy increases from 50% to 85%, whereas when it falls below 39 U/L, the probability is reduced to 6%. This justifies the choice of a threshold value for diagnosis. The authors also highlight the value of combining these four parameters, based on the sensitivity and specificity values of different combinations: Ada activity and lymphocyte count only: 94.9% and 84.5%; Ada activity, lymphocyte percentage and protein count: 92.9% and 90.7%; integration of the four parameters: 90.9% and 93.8%. As a guide, the threshold values adopted were 39 U/L for Ada activity, age under 45 years, lymphocyte count over 81% and protein count over 41 g/L [25]. The results obtained in our series concur with those of Duprat Neves et al. (Figure3).

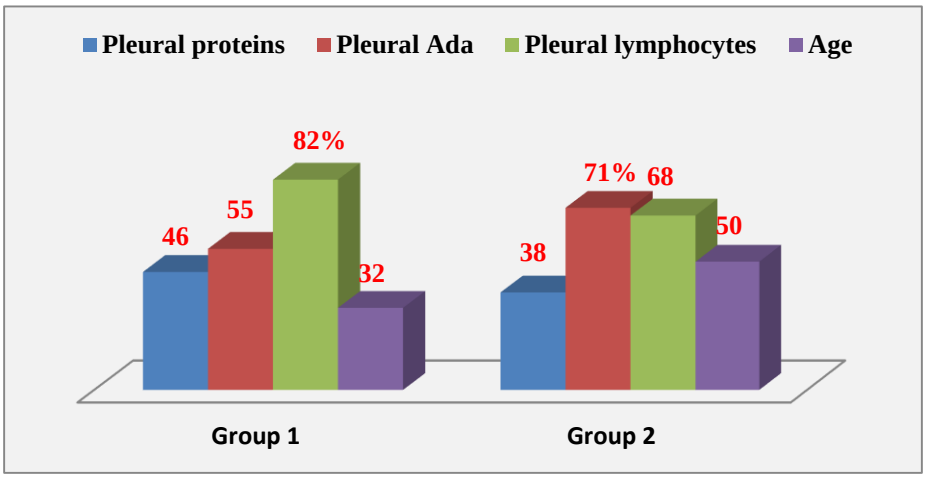

Figure 3: Graphical distribution according to age and mean values of protein, Ada and lymphocytes in pleural fluid between group 1 and group 2.

In countries where the prevalence of tuberculous pleurisy is lower, few studies are available. The Swiss retrospective study by Kuhn et al [26] included 248 pleurisies, of which only 8 were tuberculous. With a pleural Ada threshold of 50U/L, the results were disappointing, with 3 false negatives and 6 false positives (Sp= 97%; Se = 42%). Gakis et al [27], in response to the previous publication, reported the Italian study of 57 tuberculous pleurisies/185 miscellaneous pleurisies. With an Ada threshold of 50 IU/L, they found only 5 false negatives and 2 false positives, if empyemas are excluded. Although Morocco is a country with a high prevalence of tuberculosis, the results obtained in our series are partly similar to those obtained in low-prevalence countries, with a fairly high frequency of false positives. In all, 30/38 pleurisies were non-tuberculous.

Limitations of our study:
A complementary assay of the Ada1/total Ada ratio would correct the large number of false positives found in our study and consequently improve specificity.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

AUTHOR'S CONTRIBUTIONS
The authors participated in the management of the patient and the drafting of the manuscript. The final version was reviewed and approved by all the authors.

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V. Conclusion

When diagnosing pleurisy, tuberculosis should always be investigated. Despite its high diagnostic performance, validated in areas of high tuberculosis endemicity, the pleural Ada assay is not recommended by the American or French Consensus Conferences. The diagnostic efficacy of this assay depends on the analytical method used in the laboratories, the discriminatory threshold, the ethnic population and, above all, the prevalence of tuberculosis. Our study confirms the excellent sensitivity of Ada activity in pleural fluid. However, the specificity of Ada in pleural fluid is impaired by the many false-positive findings, particularly in purulent and neoplastic pleurisy, and can be improved in practice by taking pleural fluid cytology and microbiological data into account. In the case of lymphocytic pleurisy, its high NPV enables tuberculosis to be ruled out, even in areas of low prevalence.

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