ARTICLE ORIGINAL

The place of the bronchoalveolar lavage in the diagnosis of interstitial lung disease: a descriptive and qualitative study

La place du lavage broncho-alvéolaire dans le diagnostic des pneumopathies interstitielles : une étude descriptive et qualitative

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RÉSUMÉ

Introduction : Le lavage broncho-alvéolaire (LBA) a une place importante dans l'exploration des pneumopathies interstitielles diffuses. Néanmoins son apport demeure débattu essentiellement dans le cadre des pneumopathies idiopathiques et doit s'intégrer dans un processus diagnostic multidisciplinaire.

Objectif : Etudier l'apport du LBA dans le diagnostic des pneumopathies interstitielles diffuses et d'évaluer la satisfaction des médecins traitants d'une part et des pathologistes d'autre part.

Méthodes : Il s'agissait d'une étude à la fois rétrospective, descriptive étudiant les profils de LBA colligés entre 2010 et 2018 et une étude qualitative par questionnaires adressés à aux pneumologues, réanimateurs et aux pathologistes expérimentés dans le LBA.

Résultats : Dans notre série, 2508 LBA ont été inclus. Un diagnostic précis a été possible dans 24% des cas. Une étiologie infectieuse a été évoquée dans 198 cas et une pneumopathie à éosinophiles dans 9 cas. Une hémorragie alvéolaire active a été retenue dans 295 cas, une lipoprotéinose dans 2 cas, un processus adénocarcinomateux dans 26 cas et un lymphome dans 4 cas. Le diagnostic d'histiocytose X a été confirmé dans 38 cas. Dans les autres cas, le profil cellulaire n'a pas permis d'évoquer un diagnostic précis. Les diagnostics de tuberculose ou de sarcoïdose ont été évoqués dans 316 LBA vu la formule lymphocytaire à prédominance de CD4. Les diagnostics de tuberculose ou de pneumopathie d'hypersensibilité ont été diagnostiqués dans 202 LBA présentant une formule lymphocytaire à prédominance de CD8. Concernant notre étude qualitative, 50 pneumologues et réanimateurs ont répondu au premier questionnaire. La moyenne des scores attribués était de 17,24/25 avec des extrêmes allant de 11 à 25. Concernant le deuxième questionnaire, la moyenne des scores attribués était de 24/40 et des extrêmes allant de 21 à 28.

Conclusion : Malgré la multiplicité des profils non spécifiques des LBA inclus, leur apport semble satisfaisant selon les pneumologues et les réanimateurs. Une communication de qualité entre médecins traitants et pathologistes est le seul garant pour une prise en charge optimale

Mots-clés : Lavage broncho-alvéolaire, Pneumopathies interstitielles, Anatomie pathologique

SUMMARY

Background: Interstitial lung disease represents a challenge and consists in more than 200 entities. Their diagnoses are assessed through a multidisciplinary approach including pulmonologists, radiologists, pathologists and biologists. BAL analysis is useful mainly when clinical and radiological findings aren't suggestive of an etiology. Even if, the indication of BAL is consensual, its real place as a diagnostic mean remains non consensual.

Aim: To describe the BAL findings and to analyse the perceptions of the pulmonologists, anaesthesiologists and pathologists implicated in the interpretation of the BAL data, that are related to the presentation and the validity of the results.

Methods: the authors performed a descriptive study about BAL results during an 8-year-period (2010-2018) and a qualitative study assessing the pulmonologists, anaesthesiologists and pathologists' opinions concerning the different results performed in the same institution. Two questionnaires were conceived with participation of different experts and satisfaction scores were calculated.

Results: 2508 BAL were recorded including 1320 women (53%) and 1188 men (47%) with a sex-ratio (H/F) of 0,9. The mean age of the patients was 51 years. The mean response delay was 3.25 days. An accurate diagnosis was retained in 24.3%. It consisted in infection evoked in 13.89% cases. Eosinophilic pneumonia was evoked in 0.35% cases. 15.01% cases presented erythrophagocytosis with a golde score>100 favouring active alveolar haemorrhage with occult alveolar haemorrhage. Lipoproteinosis was diagnosed in 2 cases. Adenocarcinoma was retained in 1.04% cases and lymphoma in 0.16% cases. Langerhans cell histiocytosis was confirmed in 1.51% cases. In the other cases, cellular profile was not specific evoking tuberculosis or sarcoidosis in 316 cases with a CD4/CD8 ratio superior to 1,6 and the diagnoses of tuberculosis or hypersensitivity pneumonia in 202 cases with a CD4/CD8 ratio inferior to 1,2. Concerning the questionnaire-based study, 50 pulmonologists and anaesthesiologists attributed a mean score of 7.96/10 (DS=0.55) concerning the presentation of the results and 9.28/15 (DS=0.77) concerning the quality and validity of the results. On the other hand, the mean satisfaction score rated by pathologists reached 24/40.

Conclusion: BAL results could be helpful for the management of interstitial lung disease depending on the experience of pathologists and a good communication between pulmonologists, anaesthesiologists and pathologists.

Key words: bronchoalveolar lavage, interstitial lung disease, satisfaction.

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INTRODUCTION

Interstitial lung diseases (ILD) consist in more than 200 entities (1). There are entities with known causes including pneumoconiosis, hypersensitivity pneumonitis and drug induced pneumonitis, entities of unknown causes but representing well determined entities such as sarcoïdosis, collagen vascular diseases and idiopathic ILD (1). The diagnosis of these entities has to be accurate and necessitates a multidisciplinary approach including clinical, radiological, biological and microscopic features (2). This approach is validated within multidisciplinary concertation reunions (3). Microscopic features are related to tissue and/or bronchoalveolar lavage (BAL) analysis. The latter has to be performed according to strict rules including the realization of fibroscopy and the different technical steps (4). In 2012, the American Thoracic Society (ATS) reported 3 recommendations concerning the BAL technique (4). These recommendations put emphasis on the value of BAL as a non-invasive and cost affordable exam. Whereas, the real place of BAL in the diagnosis of ILD remains non consensual and debated because of the nonspecific majority of the cellular profiles diagnosed. The authors aimed to describe the BAL findings performed in a single institution during an 8-year-period (2010-2018) and to analyse the perceptions of the pulmonologists, anaesthesiologists and pathologists implicated in the interpretation of the BAL data, that are related to the presentation and the validity of the results.

METHODS

- Type of study: the authors performed a descriptive and a qualitative study. The descriptive retrospective study was about BAL results performed during an 8-year-period (2010-2018). BAL results were analysed with focus on the sex, age, response delay, cellularity, cellular profile, immunocytochemical results and mineral study performed using a conventional microscopy for research of ferruginous bodies with typical morphology. All BAL with the items listed were included. BAL results with missed data were deleted. BAL that weren't performed during the period of study weren't included.

Besides, the authors performed a qualitative study based on questionnaires. A qualitative, inductive approach was adopted in order to ensure the spontaneity and the exhaustivity of the data. The respondents were pathologists, pulmonologists and anaesthesiologists practicing in the same institution and collaborating together. The authors didn't look for the representativeness of the sample of respondents. The analysis of the data respected the integrity of the respondents including their anonymity and freedom to answer or not to the questionnaire. The methodology used was a semi-structured individual interview. Two questionnaires were performed. The first one was dedicated to pathologists in order to assess their perception of the clinical information delivered with BAL including history, physical exam, complementary tests, diagnostic hypotheses and the second one was dedicated to pulmonologists and anaesthesiologists in order to assess their perception concerning the clarity and utility of the results.

- Conception of the questionnaires: the conception of the questionnaires started with an exhaustive literature research including manuscripts about concepts of satisfaction and validation of satisfaction questionnaires. No studies similar to this study were found. For that reason, a panel of experts including pulmonologists and pathologists were interviewed in order to assess the different satisfaction determinants.

- Presentation of the questionnaires: anonymous questionnaires were presented in a recto verso paper containing an introduction explaining the study objectives and 2 open questions related to the academic degree and the expertise. The second page contained 2 dimensions: the first dimension concerned the presentation of the results communicated to pulmonologists and anaesthesiologists and the quality of the specimen and clinical information delivered to pathologists, the second dimension was about the validity of the results according to the clinical data. Every dimension contained likert-scale questions. The questionnaire dedicated to pathologists was made available through this link: https://forms.gle/5d3De2BLQHiaHVMEA. The questionnaire dedicated to pulmonologists and anaesthesiologists was made available through this link: https://forms.gle/Ri7RwMZ1mkvS3DY79.

- Material: BAL: the different procedures of BAL performed in the pathology department consisted in the quantification and the gross evaluation of the liquid, the quantification of cellularity with Malassez slides, cytocentrifugation using a Shandon Cytospin and air drying during 1 hour. After these different steps, 3 routine stains are used: MGG, Perls and Papnicolaou stains. The interpretation of the results

was made according to the normal values of cellularity, macrophages, lymphocytes, neutrophils, eosinophils, golde score reported in the literature (5).

- Statistical tests: the different data were analysed using Microsoft Office Excel 2007. Concerning the qualitative analysis, qualitative variables (5-modality-likert-scale questions) were converted into numerical variables in order to assess scores. A score varying form 1 to 5 was attributed to each question: 1 corresponding to « totally disagree» and 5 to « perfectly agree». The mean score of a dimension (dimension related to presentation and the dimension related to the validity of the results) was the mean scores of the questions belonging to each dimension. The questionnaire dedicated to pulmonologists and anaesthesiologists contained 6 questions with a maximum score reaching 30. We considered a score superior to 15 as correlated to satisfaction. The questionnaire dedicated to pathologists contained 8 questions with a maximum score of 40. We considered a score superior to 20 as correlated to satisfaction. A logistical regression was performed in order to identify the variables influencing the satisfaction. The variables that were assessed were the experience, the specialty of pulmonologist and anaesthesiologist. The data were analysed using the free version of the XLSTAT software, Addinsoft 2014. Significant results were considered for $p< 0,05$.

- Literature research: PUBMED, EMBASE and SCOPUS databases were interrogated using these key words: « Bronchoalveolar lavage AND diagnosis », « opinions AND Bronchoalveolar lavage », « satisfaction survey AND bronchoalveolar lavage".

RESULTS

Our study contained 1320 women (53%) and 1188 men (47%) with a sex ratio of 0,9. The mean age of the patients was 51 years (average, 1 year to 92 years). Complete clinical data related to medical history, exposition, clinical findings, radiologic features and serological tests were recorded in 25 cases (5%). The response delay mean accounted for 3.25 days.

- Cellularity: hyper cellularity was recorded in 1563 cases (62.32%). 455 BAL were within normal cellularity (18.14%) and 490 BAL were hypo cellular (19.54%). Mineral study revealed ferruginous bodies in 11 cases (Figure 1a, 1b), pseudo-ferruginous bodies in 14 cases and silica mineral in 9 cases. In those cases, the exposition wasn't mentioned and no free interval was considered.

- Cellular profile: 360 BAL presented macrophage profile (14.35%) with langerhans cells present in 38 cases (1.52%) in favour of langerhans histiocytosis. Lymphocytosis was observed in 1077 BAL (42.94%). The CD4/CD8 ratio was superior to 1,6 in 316 cases (29.34%) evoking tuberculosis or sarcoidosis (Figure 1c), normal ratio in 321 cases (29.81%). The ratio was inferior to 1,2 in 202 cases (18.76%) evoking tuberculosis or hypersensitivity pneumonitis (Figure 1d). Inconclusive ratio was reported in 238 cases (22.10%).

Neutrophil polynucleosis was observed in 1425 BAL (56.82%) evoking infection in 198 cases (13.89%) (Figure 1e). Eosinophil polynucleosis was reported in 325 BAL evoking eosinophilic pneumonia in 9 cases.

- Golde score: golde score was superior to 100 in 295 cases (15.01%) associated to erythrophagocytosis evoking diffuse alveolar damage (DAD) (Figures 1f, 1g).

- Specific entities: BAL conclusion evoked lipoproteinosis in 2 cases (0.07%). Pneumocystis Jiroveci was noticed in 36 cases (1.28%) (Figure 1h), mycosis in 169 cases (13.87%) (Figure 1i) and cytopathological effect evoking cytomegalovirus infection in 1 case (0.04%). Adenocarcinoma was diagnosed in 26 cases (0.93%) (Figure 1J). Lymphoma was diagnosed in 4 cases.

- Qualitative study: 50 pulmonologists and anaesthesiologists answered the questionnaire among the 55 doctors interviewed achieving a response rate of 91%. 48 % were interns, 10% were specialists, 20% were professor assistants, 8% were professor associates and 14 % were professors. The mean experience accounted for 2,3 years for interns, 13,6 years for specialists, 2,5 for professor assistants, 3,7 years for professor associates and 12,1 years for professors. 18% and 82% of the respondents either strongly agreed or agreed with the fact that the results were clear, delivering a score of 4,18/5. 84 and 8% of the respondents estimated that the list of items represented in the results were sufficient with a score of 3,82 over 5.

Four respondents estimated the need to enlarge the conclusion's font and the necessity of explaining mineral study**.** The response delay was estimated to 10 days by pulmonologists and 24 hours by anaesthesiologists. 24% of the respondents agreed or strongly agreed with the fact that the response delay was acceptable with a score of 2,36 over 5. 66% of the respondents agreed that the conclusion helped to assess the final diagnosis with a

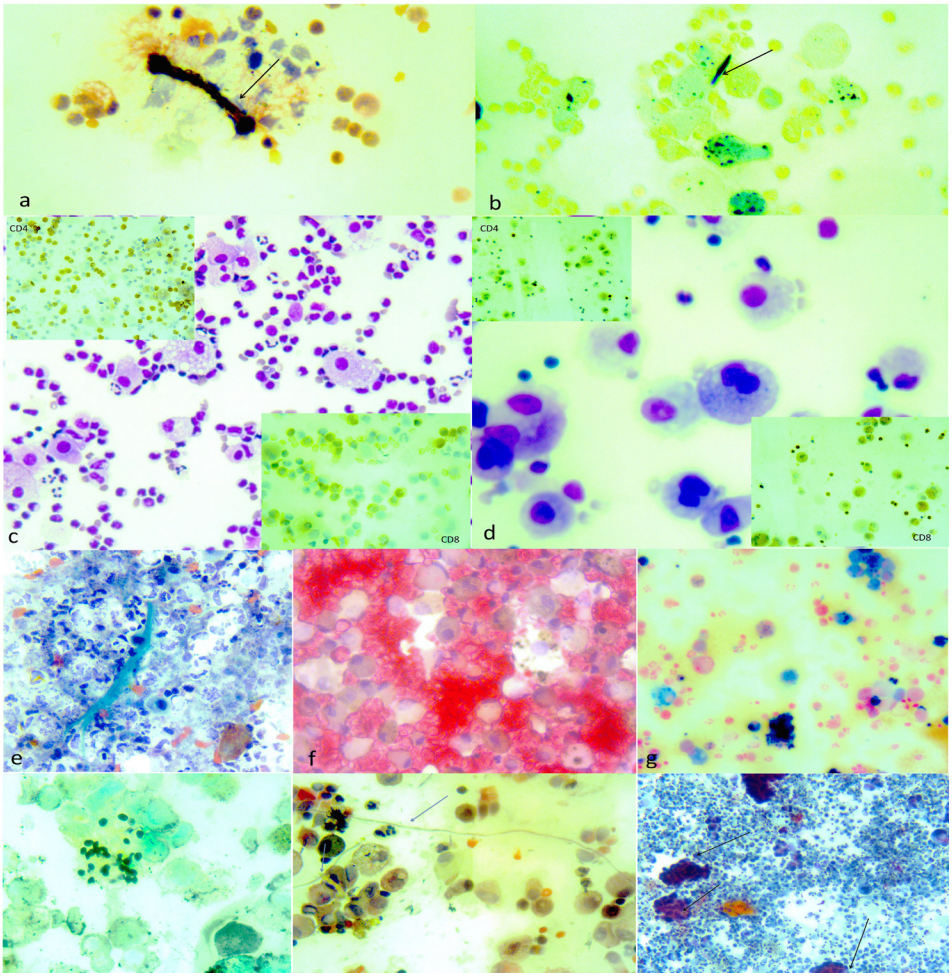

Figure 1: a/ microscopic aspect of a ferruginous body (HEx400), b/ microscopic findings of a pseudoferruginous body (HEx250), c/ lymphocytic alveolitis with a high CD4/CD8 ratio (HEx250), d/ lymphocytic alveolitis with a low CD4/CD8 ratio, e/ neutrophilic alveolitis in a case of infection (HEx250), f/ erythrophagocytosis characterized by a red cell with a macrophage (arrow), g/ Perls stain showing a high golde score compatible with an alveolar hemorrhage, h/ Characteristic aspects of pneumocystis Jiroveci mycosis (HEx400), i/ spetated pseudohyphae in a case of candidosis highlighted with papanicolaou stain (arrow) (HEx250), j/ adenocarcinomatous cells arranged into tridimensional structures (arrow) (HEx250).

score of 3,48 over 5. 58% of the respondents agreed that results were compatible with clinical data with a score of 3,38 over 5.

Concerning open suggestions, 9 respondents disapproved the delay response, 3 respondents mentioned the need for a better communication with pathologists. One respondent suggested the necessity of using mail in order to deliver fast results. 2 respondents expressed the need to enrich the conclusion with a diagnostic discussion and clinical reasoning.

The general satisfaction score was 7.96/10 concerning the presentation of BAL results and 9.28/15 concerning the validity and the utility of the results. The mean general satisfaction score reached 17.24/25. The logistical regression assessed the experience and the pulmonology and anaesthesiology as determinants of satisfaction. It revealed that all these factors didn't interfere with the ($p>0.05$). The major results are represented in table 1.

Three pathologists that used to deliver BAL results were asked to fulfil the questionnaire. The first dimension was

about the BAL reception. Two pathologists agreed that the BAL was always received not fixed and delivered a score of 4.66/5. Concerning the identification of the patients, two pathologists strongly agreed with that and one pathologist agreed also dealing with a score of 3.33/5. Respectively, two pathologists and one pathologist strongly disagreed or disagreed with the fact that clinical findings were usually complete and helped to assess the diagnosis. The question about the results of the complementary exams was given the score of 1.33/5. The question concerning the diagnoses mentioned by the treating doctor was rated a score of 2.33/5. One pathologist suggested the necessity of mentioning clinical findings and diagnostic suspicion. The score attributed to the question about the utility of the conclusion reached 2.33/5 and the one attributed to the question about the compatibility of the results with the complementary exams was 3.33/5. The mean general satisfaction score reached 24/40.

Table 1. the value of the experience (years), the specialty of pulmonology and anaesthesiology as possible determinants of satisfaction.

Variable	Value	Wald Khi²	Pr>Khi²
Experience	-0.303	1.819	0.177
Pulmonology specialty	0.00	0.04	0.842
Anaesthesiology specialty	0.064	0.04	0.842

DISCUSSION

During the period of study, 2508 BAL were recorded including 1320 women (53%) and 1188 men (47%) with a sex-ratio (H/F) of 0,9. The mean age of the patients was 51 years (average, 1 to 92 years). The mean response delay was 3.25 days. An accurate diagnosis was retained in 609 cases (24.3%). It consisted in infection evoked in 198 cases (13.89%) with a neutrophil polynucleosis and confirmed in 37 cases highlighting pneumocystis Jiroveci and cytomegalovirus cytological effect in 1 case. Eosinophilic pneumonia was evoked in 9 cases. 295 BAL (15.01%) presented erythrophagocytosis with a golde score>100 favouring active alveolar haemorrhage with occult alveolar haemorrhage. Lipoproteinosis was diagnosed in 2 cases. Adenocarcinoma was retained in 26 cases and lymphoma in 4 cases. Langerhans cell histiocytosis was confirmed in 38 cases. In the other cases, cellular profile was not specific evoking tuberculosis or sarcoidosis in 316 cases with a CD4/CD8 ratio superior to 1,6 and the diagnoses of tuberculosis or hypersensitivity pneumonia in 202 cases with a CD4/CD8 ratio inferior to 1,2. Concerning the questionnaire-based study, 50 pulmonologists and anaesthesiologists attributed a mean score of 7.96/10 (DS 0.55) concerning the presentation of the results and 9.28/15 (DS=0.77) concerning the quality and validity of the results. In open suggestions, 9 respondents noticed a long perceived delay response, 4 respondents noticed the need of a better communication with pathologists, 3 respondents noticed the need for more details in the conclusion and 3 respondents noticed the need for more details concerning the immunocytochemical and mineral study. On the other hand, pathologists questionnaire results suggested a lack of information about the clinical findings and the diagnostic hypotheses. The mean satisfaction score rated by pathologists reached 24/40. The analysis of satisfaction determinants revealed that the experience and the different specialties didn't interfere with satisfaction (p>0.05). This work seems innovating because it offers an objective view of the BAL results in the descriptive study and a qualitative view assessing the perception of the different respondents. An accurate diagnosis was possible in 24% of the cases. This percentage is due to the frequency of nonspecific cellular profiles. In fact, there are more than 200 entities in the group of ILD. According to the ATS recommendations, BAL is needed when radiologic findings are non conclusive (4). In a meta-analysis performed by Chellapandian, et al., the authors reported that BAL is more useful than biopsy when dealing with infection (6). Every cellular profile can be suggestive of many diagnoses. According to the ATS recommendations, a lymphocytosis superior to 25% is highly suggestive of giant cell pneumonia including (sarcoïdosis, hypersensitivity pneumonia, interstitial non specific pneumonia, lymphoid interstitial pneumonia, organizing pneumonia or lymphoma) and a lymphocytosis superior to 50% is suggestive of hypersensitivity pneumonia and interstitial nonspecific pneumonia in its cellular form. A neutrophil polynucleosis superior to 3% is highly suggestive of UIP, collagen vascular diseases, infections, asbestosis, diffuse alveolar damage or inhalation pneumonitis. In a study performed by Mlika M, et al., 6 patients with sarcoidosis, 1 patient

with hypersensitivity pneumonia, 1 interstitial non specific pneumonia, 1 Hodgkin lymphoma, 1 UIP and 1 infection presented a lymphocytosis superior to 25% (7). Efared B, et al., reported in a study about 151 ILD, a mixed alveolitis in 4 groups of ILD including sarcoidosis, UIP, other idiopathic ILD and collagen vascular diseases (8). They reported a lymphocytosis superior to 40% in sarcoidosis and neutrophilic polynucleosis between 5 and 20% in UIP and inferior to 5% in collagen vascular diseases. The authors concluded that BAL findings couldn't be analysed without clinical and biological findings (8). In another study, Welker, L. et al, reported an increase of the likelihood of sarcoidosis from 33.7 to 68.1% when lymphocytosis varied from 30 to 50% with a low polynucleosis. The likelihood of UIP increased from 15.8 to 33.3% with a lymphocytosis <30% and a marked neutrophil polynucleosis (9). On the other hand, Lee W, et al., reported that lymphocytosis could be useful only when suspecting sarcoidosis or eosinophilic pneumonia (10). These different results trigger every pathology department to establish its cut-offs according to the final diagnoses in order to make the results more specific even in non-specific profiles. Some authors reported that inconclusive results are generally relayed to a lack of clinical information. This fact put emphasis on the necessity of fulfilling all the clinical information needed for interpretation by pathologists. In lymphocytosis profile, the CD4/ CD8 ratio is helpful to distinguish some entities. Some authors reported the accuracy of this ratio in differentiating sarcoidosis from hypersensitivity pneumonitis (11,12). Others reported inaccurate ratios that varied according to the drug intake and the disease stage (13–15) (12,13). Inspite of some discordant results, a CD4/CD8 ratio superior to 4 is highly suggestive of sarcoidosis (4). In the study of Mlika M, et al., a CD4/CD8 ratio increased in 2 patients and was subnormal in 3 patients with sarcoidosis. It was superior to 1,6 in 4 patients: 2 sarcoïdosis and 2 infection diseases (7). These different results may be explained by the stage of the disease, the expertise of the pathologist or the diagnostic value of the technique used. Two major techniques are used: on flux cytometry and immunocytochemistry. The latter had the advantage of necessitating a few amount of liquid. The former technique simplifies the immunophenotyping making the results more reliable. The comparison of both techniques is not consensual in the literature. Some others reported discordant results between both of them (k=0,3). Thomas M, et al, reported the low number of cells interpreted with immunocytochemistry with expert-depending results (maximum of 400 elements) (16). *Diederichsen AC et al, Thalheim L et al, (17) Wenxin Ma et al (18), and Pérez-Arellano JL et al,* reported better results when using on flux cytometry (19, 20). In a comparative study performed by Mlika M, et al., the authors reported a sensitivity of 53% of the on flux cytometry and 42% of the immunocytochemistry and a specificity of 33% for on flux cytometry and 42% for immunocytochemistry (21). *Ifversen MR et al, and Paradis I., et al,* reported a better sensitivity of on flux cytometry (22, 23). *Bergmann M et al,* reported a good correlation between both techniques (r=0.96 for CD4/CD8 ratio) with a cut –off of 10% lymphocytosis (24). *Padovan CS, et al,* (25), *Lohmeyer J et al,* (26), *Smith P.A, et al*, have also reported good correlation between both techniques (27). Concerning mineral study, 2 types of studies are possible: a conventional microscopic study and electronic study (28). In this study, only conventional microscopic study was possible. It revealed ferruginous bodies in 11 cases, pseudo-ferruginous bodies in 14 cases and silica mineral in 9 cases. In those cases, the exposition wasn't mentioned and no free interval was considered. The absence of clinical information didn't allow differentiating between a true alveolar retention and a recent contamination. Even mineral study using electronic microscopy may suffer from false negative cases when particles are solubilized like Cobalt (28).

- Satisfaction questionnaire: the results of the qualitative study put emphasis on the necessity of improving the communication between pathologists and pulmonologists and anaesthesiologists. These skills aren't sufficiently taught and assessed. The importance of these skills made some authors introduce them into the curriculum in order to improve the capacity of pathologists to apologize in case of errors, to announce a bad diagnosis and to inform about critical diagnosis (29). The College of American Pathologists has reported the concept of critical diagnosis. It consists in any diagnosis which is discordant with the clinical findings or unexpected by the practitioners (30). The diagnosis of ILD can't be considered as a critical diagnosis. Nevertheless, a good communication with practitioners is compulsory. Communication skills of pathologists have been studied in numerous tumoral pathologies, or chronic inflammatory diseases of the small intestines (30–39). The different studies were questionnaire-based studies and evaluated the knowledge of pathologists or practitioners and not their perception. Communication of pathologists

with practitioners hasn't been assessed in ILD. In this study, the different results reflect a global satisfaction of the practitioners. Open suggestions consisted mainly in a long delay of response which was perceived and which was in contradiction with the real delay of 3.25 days. This perception may be explained by the delay of reception of the results of the practitioners, which is mainly attributed to pathologists. Three respondents asked for more detailed conclusion with clinical reasoning. The lack of details may be explained by the lack of clinical information delivered to pathologists, which were complete in less than 10% of the cases in this study. According to Nakhleh, et al. (37) pathologists have to answer the expectations of the practitioners and deliver detailed results with a clear checklist and using comprehensive terminologies (37, 38, 39). This may seem difficult because of the different perception of pathologist, practitioners from medical specialty and surgical specialty (40). The major limits of this work consist in the absence of correlation with the final diagnoses especially in nonspecific profiles. Besides, the qualitative study concerned only practitioners in the same institution.

This study highlighted the necessity of a good communication between pathologists and practitioners in order to deliver BAL results enriched with a clinical discussion of the major diagnoses especially in nonspecific profiles.

Conflict of interest statement: the authors declare that they have no conflict of interest.

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