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Bronchoalveolar Lavage in Interstitial Lung Disease: A Narrative Literature Review

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ABSTRACT

Establishing a diagnosis of interstitial lung disease (ILD) is very important because the diagnosis of ILD is often missed with other lung diseases. Apart from clinical diagnosis of ILD, other tests are also required, such as a lung biopsy, which can be done using open lung biopsy but has high mortality and morbidity rates. Apart from that, lung biopsy can be done using video-assisted thoracoscopy (VATS) and transbronchial biopsy, but it is relatively more expensive compared to examination bronchoalveolar lavage (BAL), which is another diagnostic approach of ILD. Bronchoalveolar lavage is performed using a flexible fiber bronchoscope (fiberoptic bronchoscopy), which has a lower morbidity and mortality rate.

1. Introduction

Interstitial lung disease (ILD) is a group of lung diseases characterized by parenchymal alveolitis and fibrosis, grouped because they have similarities in clinical symptoms, radiographic, physiological, and pathological. The number of ILD cases in America ranges from 14 to 42 per 100,000 people, and 15% of people require hospital treatment. Epidemiological studies in Mexico found the incidence of ILD was 31.5 per 100,000 for men and 26.1 per 100,000 for women, and idiopathic pulmonary fibrosis (IPF) reached 45% in all ILD sufferers. In general, ILD can be divided into five clinical classifications: the first is related to vascular disease, the second is due to the influence of drugs or radiation, the third is Primary or unclassified disease-related, the fourth is due to occupational or environmental influences, and the fifth idiopathic fibrosis.¹ Establishing a diagnosis of ILD is very

important because the diagnosis of ILD is often missed with other lung diseases. In addition to clinical symptoms, the diagnosis of ILD also requires other examinations, such as lung biopsy and high-resolution computed tomography (HRCT). The use of HRCT has a positive predictive value ranging from 90-100% but for a definite diagnosis of ILD lung biopsy.

To get the best tissue results, the biopsy is carried out with an open lung biopsy, but the mortality and morbidity rates are high. A lung biopsy can also be obtained by video-assisted thoracoscopy (VATS) and transbronchial biopsy procedures but is relatively more expensive compared to bronchoalveolar lavage (BAL) examination, which is another diagnostic approach for ILD.² Transbronchial and BAL procedures are performed using flexible fiber bronchoscopes which have lower morbidity and mortality rates.^{1,2} BAL examination aims to obtain cell

and component samples non-cellular from the epithelial surface of the lower airways or bronchoalveolar units, which can be used to determine the diagnosis as well as determine the stage of the disease and assess the progress of therapy in some ILD diseases.² This study discusses BAL examination techniques in general, the clinical classification of ILD, the pathogenesis of ILD in general, and the appearance of BAL in several ILD diseases.

Interstitial lung disease

Interstitial lung disease is a group of diseases consisting of approximately 200 diseases characterized by chronic alveolitis. The pathogenesis of ILD begins with injury to the alveolar epithelial layer, which results in an inflammatory process involving various inflammatory and immune effector cells in the lung parenchyma. Initiation of injury can occur through the inhalation process, such as the first inhalation of mineral fibers or mineral dust from occupational or environmental exposures; through antigen sensitization, as in hypersensitivity pneumonitis due to environmental or occupational exposure; and thirdly, through blood circulation, such as in collagen vascular disease and drug-induced ILD. The initiation of injury can cause alveolitis, resulting in changes in the alveolar structure in the form of thickening and fibrosis of the lung interstitial tissue and, ultimately, a decrease in lung function due to alveoli being unable to exchange gases.^{1,3} If the injury that occurs can be avoided or limited, the inflammatory process will not continue, so collagen deposition and fibrosis will not occur. However, if the injury continues, the inflammatory process will continue, resulting in fibroblast proliferation, collagen deposition, and blockage of interstitial capillaries. This pathogenesis applies to almost all diseases in the ILD classification with the exception of a few specific diseases, e.g., lymphangioleiomyomatosis, amyloidosis, lymphangitic carcinoma, lung interstitial tissue infiltrated by smooth muscle, amyloid fibrils, and malignant cells. On some alveolar filling disorders, before interstitial and intra-alveolar fibrosis occurs,

the alveolar space is filled with red blood cells, as in diffuse alveolar hemorrhage syndrome, eosinophilic pneumonia, alveolar proteinosis or bronchioloalveolar carcinoma.^{3,4}

Diagnosis ILD

Interstitial lung disease has clinical symptoms, such as shortness of breath, lack of breathing ability during physical exercise, hypoxemia, clubbing of the fingers, and diffuse bilateral abnormalities on thoracic CT scans. An extensive history and serologic examination are key to early diagnosis. Advanced testing, especially genetic analysis, for molecular identification and diagnosis. Comprehensive consideration of all available data and consideration of the multidisciplinary team (MDT) to arrive at the most appropriate diagnosis. This will be the basis for further management of ILD patients.⁵ The diagnostic algorithm that has been made previously for suspected ILD patients can be enforced after other diagnoses have been excluded, such as the patient immunodeficiency, heart disease, lung infections, primary ciliary dyskinesia, cystic fibrosis, repeated aspiration, and sleep-disordered breathing. Then, an examination of the family history of disease, radiation exposure, drug use, and dust exposure is carried out. In addition, serological examinations were carried out, such as inflammatory markers pANCA, GMB, GMCSF and IL2 receptor, lung function, genetics, BAL, cardiovascular, and biopsy. The ILD diagnosis algorithm can be seen in Figure 1.^{5,6}

Pathophysiology of ILD

The exact cause of ILD is not generally known, but the pathophysiology, especially the mechanism by cells, especially fibroblast cells, fibrocytes, myofibroblasts, endothelial and alveolar epithelial cells, and immune cells, will be explained in this literature review. Complex cellular interactions will cause ILD to occur, and this mechanism will be explained as follows. Fibroblasts as effector cells for fibrosis have a major role through deposits of extracellular matrix (ECM) excessively. These cells are

spindle or stellate-shaped and are joined by the smooth muscle that contains them. Smooth muscle actin (α -SMA) causes remodeling of the ILD, and on histopathological examination, fibroblast lesions that are activated and produce excessive ECM in the alveoli are found.⁷ Fibroblasts as resident cells, apoptosis, and the transition to myofibroblasts have an important role in matrix hemostasis. Fibroblasts modulate ECM turnover through the expression of matrix metalloproteinases (TIMPs) so that fibrosis is induced through cell activation, proliferation, and migration. Fibrocytes as circulating precursors and monocytes producing collagen play a role in remodeling. Several studies show that high levels of fibrocytes are found in ILD patients, and fibrocytes also play a role in cell migration to target lesions.^{5,7} Amino ethyl carbazole (AEC) is an important cell in the occurrence of ILD, acting as a chronic inflammatory response to the accumulation of abnormal cells, such as alveolar macrophages, neutrophils, and the reduced capacity of fibroblasts to synthesize prostaglandins as anti-inflammatory and anti-fibrous molecules. Amino ethyl carbazole consists of AEC type I and AEC type II. Amino ethyl carbazole type I is found on most alveolar surfaces, and when type I AECs are damaged, they will be replaced by type II AECs by proliferation of cell hyperplasia to protect the damaged cell membrane. Damaged AECs have the potential to cause pulmonary fibrosis. Pericytes and pleural mesothelial cells also play a role in the occurrence of ILD. Pericytes are mesenchymal-derived cells in the basal or perivascular area involved in healing lesions and collagen production, while mesothelial cells are involved in the transformation process into myofibroblasts and cell migration through the TGF-B1 mechanism. Endothelial cells with vascular damage to the microcirculation can cause fibrosis. Macrophages also play a role in fibrosis through monocytes and immune cells such as TGF-B, PDGF, CCL18, ROS, IL-8, and others. The role of other cells involved in fibrosis includes lymphocyte cells. Lymphocytes, especially Th

2 cells, will produce antibodies and can cause fibrosis through the excessive accumulation of lymphocyte cells, such as IL-4, IL-5, IL-6, IL-10, and IL-13. Mast cells have a role in pulmonary fibrosis, and this has been proven in ILD patients; there is an increase in mast cells.

BAL inspection procedure

Patients suspected of having ILD who will undergo BAL examination must undergo routine clinical evaluation before the procedure. This evaluation includes appropriate examination and testing for possible complications related to the procedure by identifying risk factors. American Thoracic Society issued an algorithm for the examination of patients with clinical ILD. HRCT examination can be useful for identifying ILD whether or not a BAL examination is necessary, as in patients suspected of having ILD undergoing HRCT, there is a wide honeycomb image throughout the lung field, so a BAL examination does not need to be carried out.⁸

The flexible fiber bronchoscope was first developed by Dr. Shigeto Ikeda in 1960, and the first BAL examination was carried out by Cantrell et al., namely, on healthy people who smoked and non-smokers to measure the concentration of cytosolic enzymes in alveolar macrophages. Although there have been many studies regarding the use of BAL for clinical applications in various lung diseases, there is no standard consensus regarding the use of BAL, so there are differences between various study centers regarding BAL examination techniques, BAL fluid analysis, and normal values of cellular and non-cellular components in healthy people. as well as in several ILD diseases.^{1,8,9} Bronchoalveolar lavage is an examination technique using a flexible fiber bronchoscope to obtain samples of cells and non-cellular components from the surface of the lower respiratory tract epithelium or unit bronchoalveolar.

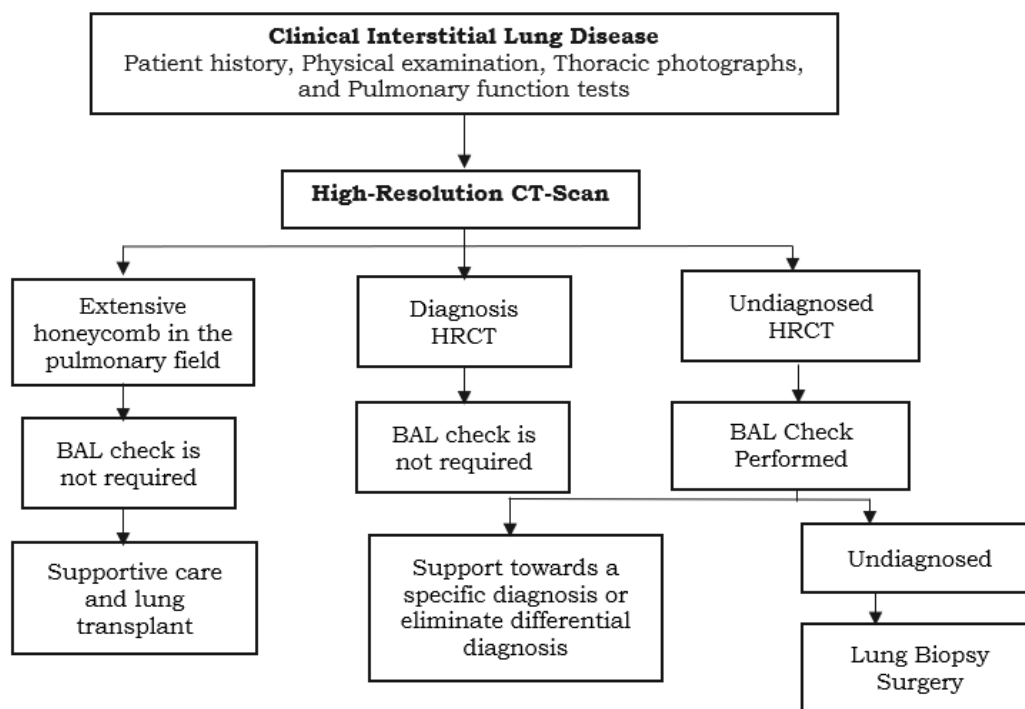


Figure 1. Supporting examination algorithm for ILD.

Bronchoalveolar lavage is performed primarily under local lidocaine anesthesia. The premedication used is usually diazepam or atropine. Atropine is used to minimize bradycardia induced by the vasovagal reflex and reduce airway secretions. A study shows that using atropine will increase the volume of BAL fluid returned, while its effect on the non-cellular components of BAL fluid is not yet known.^{10,11} The side effects of a BAL examination are almost the same as a bronchoscopy examination, namely hypoxemia, cough, fever, chills, alveolar infiltration, and temporary decrease in lung function. Side effects are mainly related to the bronchoscopy technique, the location and size of the flushed area, and the volume and temperature of the fluid installed. BAL should be performed on the middle lobe or lingula unless the lung lesion does not cover the entire lung but is localized to a particular lobe. The use of a BAL site in the middle lobe of the right lung or lingula is because, anatomically, the volume of BAL fluid and cells recovered will be greater, namely 60%, compared to the lower lobe, which is only 20%.¹²

The fluid used for BAL is 0.9% NaCl with a temperature of 37°C so that it reduces the occurrence of coughing and bronchospasm and will increase the amount of fluid recovered and the number of cells recovered. 0.9% NaCl fluid was administered as a bolus syringe at a speed of 5 ml/sec or allowed to flow with the hydrostatic force of the reservoir. The fluid is aspirated again with suction using a negative pressure of 25 – 100 mmHg or allowing it to flow using gravity. The use of mechanical suction must be careful because it can result in trauma that causes bleeding so that there are erythrocytes in the BAL fluid.¹³ The amount of fluid recovered is around 40 – 60% of the installed volume. The amount of fluid used varied between the different study centers. Most use 100 – 300 ml of fluid in each lung lobe with 20 ml of fluid per lavage. Other authors use 50 ml each time lavage. Fluid volume lavage affects the number of BAL fluid cells and other non-cellular components. The smaller the amount of fluid, the cells obtained will be more representative of bronchial cells than alveolar cells if the volume is less than 100 ml, and calculating the

amount of non-cellular components is even more difficult because the concentration of non-cellular components is very dependent on the amount of volume installed.^{9,14,15}

Patients undergoing BAL examination need to take into account their smoking status. Smoking can cause inflammation in the airways, which can affect the number of cells and non-cellular components in BAL fluid. The amount of BAL fluid obtained was measured and then centrifuged with cytospin. After centrifugation, the pellet is examined for cellular components, while the supernatant is examined for noncellular components. The existing pellets are then suspended in liquid Hank's balanced salt solution (HBSS) and centrifuged again to examine the differentiation of the cells.¹⁵ Cell differentiation examination can use immunofluorescent and immunocytochemical techniques. This technique uses monoclonal antibodies primarily to determine the type of lymphocyte. Counting the number of each cell type uses flow cytometry. Inspection of non-cellular components includes radio-immunodiffusion to calculate the amount of protein and radio-immunoassays BAL fluid to see the chemotactic activity of neutrophils, and examination of non-cellular components to detect mineral dust and certain microorganisms can use appropriate staining.¹⁵

Complications of BAL procedure

Bronchoalveolar lavage is a fairly safe procedure, but it still has the potential for serious complications, although it is rare. Several factors influence the occurrence of complications, such as patient characteristics, sedation administration, and sampling procedures. Complications resulting from sedation and anesthesia include allergic reactions, hyperventilation, and hypoxemia due to excessive sedation and respiratory depression. During the procedure, complications may occur, such as laryngospasm, respiratory failure, damage to the

mucosal surface of the airways, and vocal cord dyskinesia. After BAL procedures, the most common complication is fever. Heckner et al conducted research on 44 patients who underwent BAL procedures, of which 11 patients experienced fever after 24 hours of bronchoscopy.¹⁶

BAL examination in ILD

In 1974 Van den Bosch et al. first conducted research, namely examining BAL in normal conditions. According to the American Thoracic Society, BAL examination in normal conditions of non-smoking adults consists of several cells, namely alveolar macrophages, lymphocytes, neutrophils, eosinophils, and epithelium, which have normal values on BAL examination. The cell percentage value may be increased on BAL examination and is related to the diagnosis of specific ILD, as is the so-called increased lymphocyte value lymphocytic cellular pattern, the value of eosinophils increases the so-called eosinophilic cellular pattern, and the so-called increased neutrophil value neutrophilic cellular pattern. In addition, the comparative value of cell type counts can direct a specific diagnosis of ILD.⁸ Normal values and cell percentage values, as well as type count comparison values related to the specific diagnosis of ILD, can be seen in Table 1.

The American Thoracic Society has released a BAL examination cellular analysis algorithm. BAL examination is carried out if there are clinical symptoms, such as shortness of breath, hypoxemia, diffuse infiltrates, and HRCT examination that cannot support the diagnosis of ILD. BAL examination results are differentiated from cell types for specific diagnoses of ILD. This algorithm can be seen in Figure 7. In this literature review, we will discuss several features of BAL in ILD by looking at the percentage proportion of cell types and cell type counts in BAL, as well as non-cellular examinations that support a specific diagnosis of ILD.⁸

Table 1. Normal cellular values, cell type presentation, and cell type count in BAL.

Normal adult (non-smoker)	BAL differential cell counts
Alveolar macrophages	>85%
Lymphocytes	10-15%
Neutrophils	≤3%
Eosinophils	≤1%
Epithelium	≤5%

Interstitial lung disease		
Percentage value of cell type in BAL		
Lymphocytic cellular pattern	Eosinophilic cellular pattern	Neutrophilic cellular Pattern
Lymphocytes >15%	Eosinophils >1%	Neutrophils >3%
Sarcoidosis	Eosinophilic pneumonia	IPF
Hypersensitivity pneumonitis	Drug-induced pneumonitis	Diffuse alveolar damage (DAD)
Drug-induced pneumonitis	Churg-Strauss syndrome	Asbestosis
Collagen vascular diseases		Collagen vascular diseases

Differences in cell type count in BAL for ILD type diagnosis	
Lymphocyte differential count >25%	suspected granulomatous disease type ILD (hypersensitivity pneumonitis, or chronic beryllium disease) in sarcoidosis followed by CD4:CD8 >4 ratio.
Lymphocyte differential count >50%	suspected ILD type hypersensitivity pneumonitis or cellular nonspecific interstitial pneumonia.
Neutrophil differential count >50%	pada acute lung injury, aspiration pneumonia, or suppurative infection.
Eosinophil differential count >25%	pada ILD type eosinophilic pneumonia
Mast cells >1%, lymphocytes >50%, and neutrophils >3%	ILD type acute hypersensitivity pneumonitis.

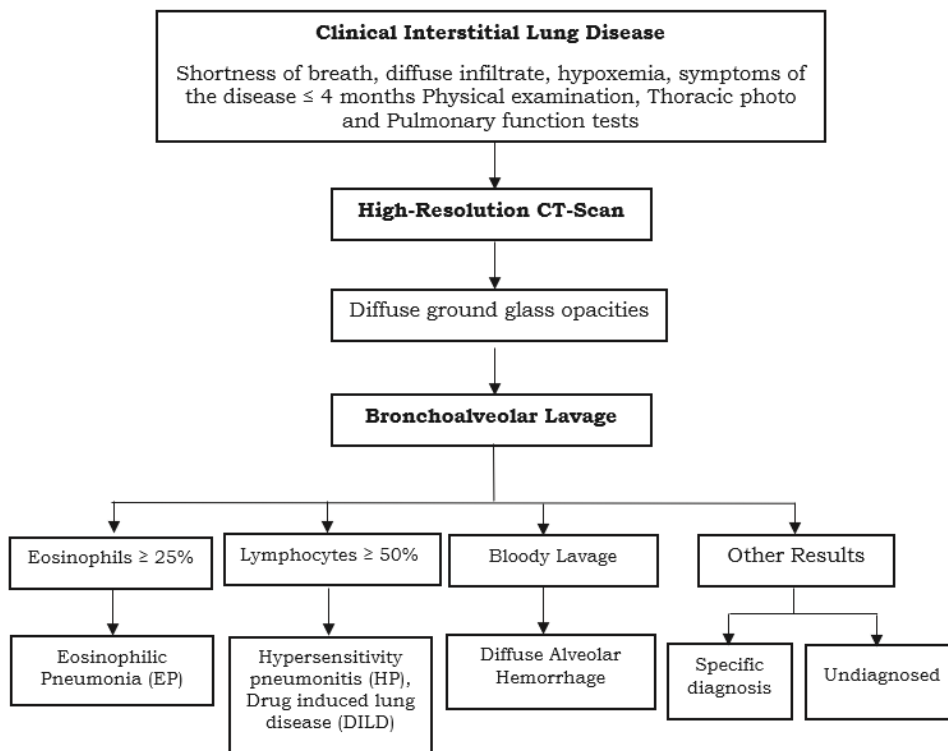


Figure 2. BAL examination algorithm for ILD.

Eosinophilic pneumonia

Eosinophilic pneumonia (EP) found a typical BAL picture in the form of eosinophil infiltration $\geq 50\%$ and macrophages in the alveoli. Although in some cases, the cause is known, such as reactions to certain drugs, fungi, parasites, and inhalation, most of them are idiopathic. In EP, peripheral blood eosinophils and increased erythrocyte sedimentation rate were found.

De Jaegher et al. found that in 5 cases of EP, there were 22-42% eosinophils before corticosteroid therapy. After therapy, the eosinophil count decreased to less than 1%. In cases of EP, lymphocytosis was also found. Lymphocytes in BAL are dominated mainly by CD4 T cells.¹⁶ BAL image on eosinophilic pneumonia can be seen in Figure 3.

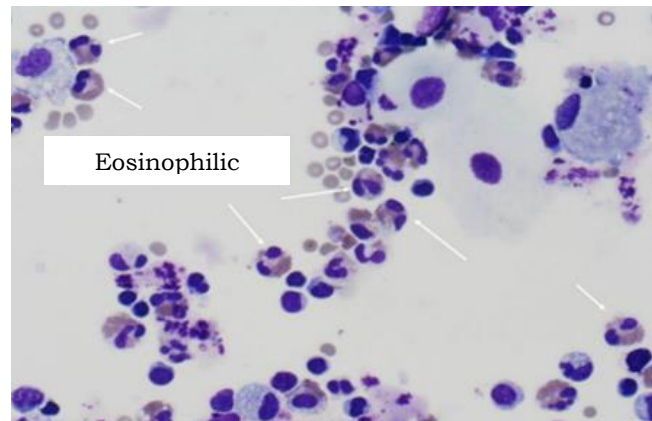


Figure 3. BAL in eosinophilic pneumonia.

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is a syndrome resulting from repeated inhalation of antigens, especially organic particles such as thermophilic bacteria, avian proteins, fungi, and chemicals. If an interaction occurs with an antigen, an antigen-antibody complex will form, which settles in the blood vessels, causing complement activation, which results in the production of IgG and IgM in the lungs. This is called the Arthus reaction. This reaction can also result in the formation of infiltrating granulomas.

macrophages and lymphocytes into the bronchiole walls and alveoli walls. The percentage of lymphocytes in BAL can increase by more than 50% and consists of T lymphocyte cells. This can be seen in Figure 4. T cell subtype analysis shows the predominance of CD8 T lymphocyte cells. Examination of BAL on HP can reveal several increased non-cellular components in BAL fluid, such as IgG, IgM, IgA, immune complexes, leukotriene C4, and b2-microglobulin. The gold standard for HP is histopathological examination.¹⁷

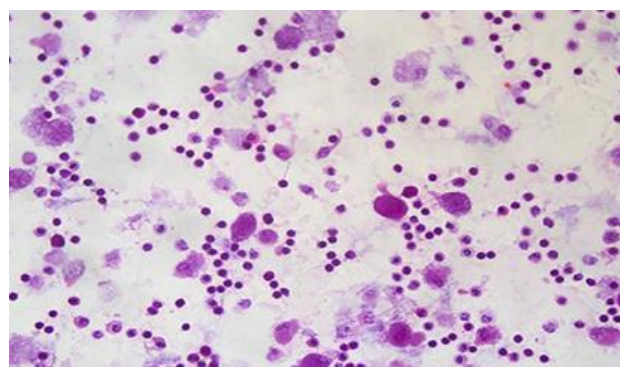


Figure 4. BAL in hypersensitivity pneumonitis.

Drug-induced lung disease

Drug-induced lung disease (DILD) does not have a typical picture in terms of symptoms, laboratory examination, or pathological examination. The diagnosis of DILD is made after excluding the possibility of malignancy, infection, pulmonary thromboembolism, and heart failure. One drug known to cause ILD is amiodarone. Amiodarone is indicated for the management of cardiac arrhythmias and is used primarily for patients who are refractory to conventional therapy. The pharmacology and toxicity of amiodarone are widely discussed in various studies. Toxic reactions to the lungs and liver are the most common non-cardiac reactions. However, the mechanism of multisystem toxicity is unknown.¹⁸ One of the consequences of using amiodarone is bovine lysosomal phospholipase, thus causing extensive phospholipids. Histopathologically, in the lungs, there is an accumulation of lymphocytes, fibroblasts, and foamy macrophage, as well as fibrosis. The image of alveolar macrophages in BAL shows vacuoles with myelin figures due to lipid accumulation. This picture is seen in patients taking both toxic and non-toxic amiodarone, so the relationship between toxicity and the BAL picture has not been proven. However, features of interstitial inflammation and fibrosis are associated with the clinical picture. The benefits of BAL examination in patients taking amiodarone may be useful in ruling out the possibility of infection. Transbronchial biopsy also shows foamy macrophages. BAL features can include an increase in the number of T lymphocytes and/or polymorphonuclear leukocytes.¹⁸

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage is part of collagen vascular disease. Patients usually complain of acute shortness of breath and hypoxemia. In supporting examinations, such as HRCT, there is an image of the area patchy or diffuse areas of ground-glass attenuation. BAL examination has an image of bloody lavage or an increase in red blood cells in BAL, which has previously been excluded as a cause of infection

and malignancy. When taking a BAL sample, you must be careful because it can injure the airway, which can cause a buildup of red blood cells, which can interfere with the assessment of the BAL examination. The gold standard diagnosis of diffuse alveolar hemorrhage is a biopsy examination.¹⁹

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is an ILD disease whose etiology is unknown, although there is an inherited form of IPF, namely the familial form. Therefore, before making a diagnosis of IPF, it is necessary to exclude causes of pulmonary fibrosis, such as sarcoidosis, eosinophilic granuloma, collagen vascular disease, pulmonary fibrosis due to infection, and aspiration. chronic and medication. In IPF there are immune complexes in the serum and lungs in the active phase of the disease. Although immune complexes can activate the complement system, there is no evidence that this process occurs in the lungs.^{3,20} Immune complexes stimulate macrophages to release various factors, including leukotriene B₄ (LTB₄), which attracts neutrophils and eosinophils. Alveolar macrophages also release oxidants which cause injury to the lung epithelium resulting in fibroblast proliferation and collagen deposits. Turner W et al conducted research on 16 IPF patients and 7 controls with the results that there was an increase in neutrophils and eosinophils in IPF compared to controls and also found that the levels of immune complexes found in BAL fluid were associated with better response to therapy with corticosteroids. However, immune complexes in BAL fluid have not been associated with a better prognosis. IPF BAL image shows a high number of neutrophils.²⁰ Turner et al. stated that serial BAL examinations can help in determining drug dosage in patients who show improvement with prednisolone and cyclophosphamide therapy. They found that there was a significant decrease in neutrophils in patients who were responsive to cyclophosphamide and a significant decrease in eosinophils in patients who were responsive to prednisolone, whereas there was an

increase in neutrophils and eosinophils in patients who were unresponsive to therapy. Apart from that, in IPF, there is also a decrease in surfactant phospholipids and a decrease in IgE, which can affect the stability of the alveoli walls. Lung tissue biopsy remains the gold standard in diagnosing IPF because it produces an accurate diagnosis and can rule out the possibility of malignancy and infection.²⁰

Sarcoidosis

Sarcoidosis is a multi-organ inflammatory disease whose cause is unknown. Antigens that have been processed by macrophages are presented to T lymphocyte cells so that they are activated and release IL-1, which will activate CD4 lymphocytes to release IL-2 so that chemotaxis occurs, which attracts lymphocyte cells from the circulation to the site of granuloma formation and mitogenesis and stimulation of T lymphocyte cells so that they proliferate at the site of granuloma formation. Compartmentalization of inflammatory cells in the lungs results in a picture of lymphocytopenia in peripheral blood and CD4 lymphocyte-rich alveolitis, also called lymphocytic alveolitis.²¹ In sarcoidosis, there is lymphocytic alveolitis with a fairly high increase in lymphocytes. If the CD4 to CD8 ratio is more than 3.5 on BAL examination for the diagnosis of sarcoidosis, the diagnostic specificity value is 94%, and the sensitivity is 52%. However, it should be noted that in sarcoidosis patients who have histopathologically proven CD4 to CD8 ratio, the ratio value is not always more than 3.5, and in a small number of other diseases, a CD4 to CD8 ratio of more than 3.5 can also be found, such as in asbestosis, tuberculosis, IPF. And hypersensitivity pneumonitis (HP).²¹ Lung biopsy remains the gold standard for diagnosis even though the CD4 to CD8 ratio is high. Evidence of histological data stating the discovery of non-caseating epithelioid cell granulomas is the gold standard, as stated by the World Association of Sarcoidosis and Other Granulomatous Diseases 1991. A report by Crystal's group at the National Institute of Health in the United States states that the prognosis of sarcoidosis is determined by the

degree of lymphocytosis, namely patients with high-intensity alveolitis, namely, BAL fluid contains >28% lymphocytes and Gallium scan positive will experience deterioration more quickly. However, in several other studies, it was said that high-intensity alveolitis found incidents of high spontaneous resolution.^{7,21} Several studies have examined the intensity of alveolitis as a guide to response to therapy. Turner et al. stated that the number of lymphocytes in BAL examination at the beginning of therapy cannot be used as a predictor of prognosis. Several studies state that analysis of lymphocyte subtypes, namely the ratio of CD4 to CD8, is a better predictor of prognosis and response to therapy than the total number of lymphocytes. Ceuppens et al. stated that a decrease in the CD4 to CD8 ratio was followed by clinical improvement in patients and improvement in radiological images.^{17,18} The role of BAL examination in sarcoidosis still requires further research, considering that there are still many contradictions between various studies, but BAL examination needs to be considered in establishing a differential diagnosis of sarcoidosis.²¹

Asbestosis

Asbestosis is a condition associated with pleural effusion, pulmonary fibrosis, malignant mesothelioma, and bronchogenic carcinoma. The pathogenesis of asbestosis is thought to be almost the same as IPF, namely that neutrophils play a major role. Asbestos can stimulate alveolar macrophages to attract neutrophils from the circulation and cause lung tissue damage due to neutrophil products such as neutrophil-specific collagenase. The typical picture of asbestosis is asbestos bodies, which can be obtained from lung tissue biopsies, sputum, bronchial lavage, and BAL fluid. Asbestos bodies in BAL fluid indicate asbestos exposure but do not predict prognosis.²² Increased polymorphonuclear cells, especially neutrophils, were seen in the BAL fluid. Other studies show normal neutrophil counts, but lymphocytosis is found at 20-28%. It is estimated that this occurs in the acute phase of lymphocytic alveolitis. However, in the later phase, fibrosis occurs,

and an increase in neutrophils is found. In a study conducted by Gellert et al., a decrease in the CD4 to CD8 ratio was found. Bell et al. found that there was a decrease in immunoglobulin levels in BAL fluid.¹³ Gaudichet et al. found an asbestos body in BAL fluid, but the gold standard for the diagnosis of asbestosis is biopsy.²²

Berylliosis

Inhalation of beryllium metal dust and dissolved beryllium salts can result in granulomatous ILD. Berylliosis is thought to be a form of HP triggered by beryllium. BAL examination shows an increase in the number of lymphocytes, especially CD4 T cells, similar to that found in sarcoidosis. The amount of BAL cell lymphocytosis is related to the degree of disease, which can help assess disease progression and response to therapy. To diagnose berylliosis, a biopsy, and histopathological examination are still carried out, especially in patients with a history of exposure to beryllium salts.²³

Rheumatoid arthritis (RA)

Rheumatoid arthritis is a symmetric inflammatory joint disease that is often found in women. Apart from articular manifestations, there are also many extra-articular manifestations, namely, 75% of RA sufferers, especially those with high rheumatoid factor titers and immune complexes in the circulation. Ellman and Ball found a relationship between ILD and RA. Garcia et al. performed BAL on 24 RA sufferers, nine sufferers with RA-ILD, and 15 RA sufferers without ILD. It turned out that in RA-ILD sufferers, there was an increase in neutrophils in BAL fluid, whereas in RA sufferers without ILD, 5 people had abnormal BAL, and the rest had normal BAL. In RA-ILD sufferers, apart from increasing neutrophils, there is also an increase in IgM levels and a decrease in the ratio of CD4 to CD8 lymphocyte cells. In RA-ILD sufferers, type I collagenase was also found. Meanwhile, in RA sufferers without ILD, lymphocytosis was found in the BAL fluid. Apart from that, there was also an increase in IgM and an increase in the CD4 to CD8 ratio, but

no collagenase was found.^{14,24}

Systemic lupus erythematosus (SLE)

In SLE, multiorgan dysfunction is found, including non-erosive arthropathy, mucocutaneous lesions, and photosensitivity. On laboratory examination, nuclear antibodies and cytoplasmic antibodies can be found. Several SLE studies conducted BAL examinations and found that the cell count was not much different from normal people, while the CD4 to CD8 ratio decreased. BAL examination on SLE is useful for finding pulmonary hemorrhage with the discovery of red blood cells and hemosiderin-laden macrophage, which appears 48 hours after the occurrence of pulmonary hemorrhage.²⁵

Progressive systemic sclerosis

Progressive systemic sclerosis or scleroderma is a systemic connective tissue disease that involves muscle tissue and internal organs, including the lungs. Scleroderma is characterized by progressive dermatologic disorders accompanied by visceral organ abnormalities due to microvascular obliteration. BAL examination in scleroderma does not show any specific abnormalities except that there is hypercellularity in all cell types, especially macrophages, neutrophils and eosinophils, compared to normal people. Some scleroderma sufferers show a picture of lymphocytosis in BAL and usually in sufferers with pulmonary symptoms for less than 1 year.²⁶ Wells et al found that patients with increased neutrophils in BAL were associated with extensive fibrotic abnormalities, whereas patients with increased eosinophils in BAL usually had less extensive lung abnormalities. Based on this, even though the BAL picture obtained is not specific, BAL can be used in patients with suspected scleroderma, and BAL can be used to monitor lung abnormalities. The gold standard for the diagnosis of Scleroderma is a histopathological examination of a tissue biopsy obtained.²⁶

Sjogren's syndrome

Sjogren's syndrome, or sicca complex, is an autoimmune endocrinopathy characterized by lymphocyte infiltration in glandular and extra-glandular organs. BAL examination in this syndrome shows lymphocytic alveolitis. Others show a mixture of neutrophilic and lymphocytic alveolitis. The ratio of CD4 to CD8 decreases when compared with sufferers of Sjogren's syndrome without alveolitis or normal people. Hatron et al. conducted a study of 29 patients with Sjogren's syndrome, and BAL examination was carried out with the results of 16 patients having alveolitis, 11 patients with lymphocytic alveolitis, and 5 patients with neutrophilic alveolitis.²⁷

Pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis is an ILD characterized by lipoprotein exudates in the alveoli of unknown etiology. The BAL fluid obtained from these sufferers is usually opaque or milky. PAS staining shows positive results, which can be seen in Figure 5. In this patient, BAL is very useful in determining the diagnosis and therapy. Whole lung lavage using a bronchoscope is a therapy for these sufferers and usually shows a significant improvement in lung function. Complications during whole lung lavage are fluid entry into the contralateral lung, atelectasis, hypotension, hydropneumothorax, bronchospasm, and pneumonia.²⁸

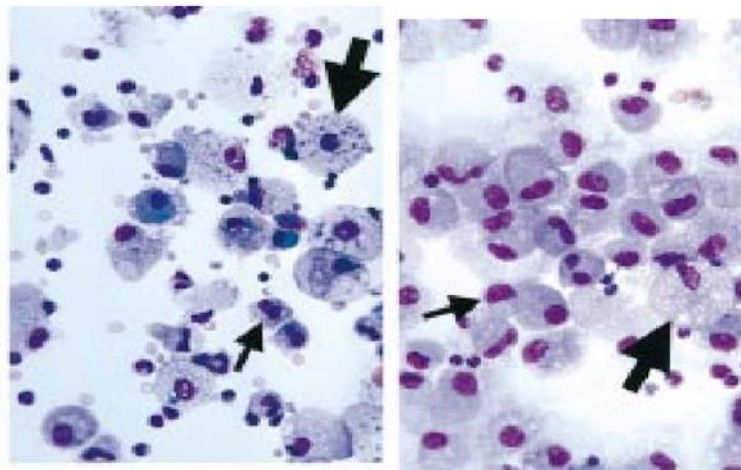


Figure 5. BAL in pulmonary alveolar proteinosis.

2. Conclusion

Interstitial lung disease is a group of lung diseases characterized by parenchymal alveolitis and fibrosis. The definitive diagnosis of ILD is by lung tissue biopsy, which can be obtained with open lung biopsy, VATS, or transbronchial biopsy. Diagnosis of ILD using BAL examination is promising because it is less invasive than using biopsy open lung biopsy and VATS. However, this requires further research, considering that there is no standardization of BAL examination techniques, analysis of BAL fluid for both cellular and non-cellular components, normal values for BAL fluid components, and standard values for ILD disease.

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