3 Bronchoalveolar and Serum Markers of Lung Disease

Carlos M. Luna

There is no consensus at the moment on the meaning of the term marker. In this chapter the term marker is going to be used to designate any abnormality in serum or bronchoalveolar (BAL) fluid components, including the cellular composition of BAL, provided these components are not considered part of the classical criteria for disease diagnosis. Markers may be useful for studying diffuse lung disorders, in a number of ways; (1) screening of high risk individuals for the presence of disease, (2) diagnosing diseases, (3) monitoring the effectiveness of therapy, and (4) detecting recurrences or complications. Although experts agree that lung biopsy is necessary for an accurate diagnosis of most diffuse lung diseases, some markers may be specific for a particular type of disease, as Langerhans cells in bronchoalveolar lavage (BAL) in histiocytosis-X. More often, markers may be of help in the diagnosis of diseases, monitoring the effectiveness of therapy or detecting recurrences, when they are used together with clinical, radiological and laboratory data (e.g. serum angiotensin converter enzyme (ACE) in sarcoidosis or serum precipitating antibodies in hypersensitivity pneumonitis).

Serum Markers

Routine blood and serologic tests are often unremarkable, but can provide clues to the diagnosis of diffuse lung diseases. Because most diffuse lung diseases are inflammatory in nature, it is not surprising that patients commonly present C-reactive protein and erythrocyte sedimentation rate (ESR) increased.

High blood urea nitrogen or creatinine level disclosing the presence of renal insufficiency raises the possibility of one of the several renal-pulmonary syndromes such as Wegener's granulomatosis, Goodpasture's syndrome, systemic lupus erythematosus (SLE), idiopathic rapidly progressing glomerulonephritis or systemic necrotizing vasculitis. Survival in Wegener's granulomatosis is influenced by the presence of renal disease [1].

Other non-routinely ordered serum tests may be helpful in some diffuse lung diseases. Low-titer positivity of antinuclear antibodies (ANA), rheumatoid factor (RF), hypergammaglobulinemia and immune-complexes, are non-specific findings in a number of diffuse lung diseases such as idiopathic pulmonary fibrosis (IPF), asbestosis, silicosis, and sarcoidosis [2,3]. Depending on the cause of lung disease, some serum markers may be more useful because of their specificity for the diagnosis and follow-up (Table 3.1).

Serum Markers in Specific Diffuse Lung Diseases

In idiopathic pulmonary hemosiderosis, serum iron and iron-binding capacity alterations, characteristic of iron-deficiency anemia, usually develops [4].

M. Sperber (ed.), *Diffuse Lung Disorders*

Table 3.1. Serum markers of diffuse lung disorders

Markers	Observations
C-reactive protein and ESR	Collagen-Vascular Diseases, Vasculitis, Histiocytosis-X, Drug induced diseases, Idiopathic pulmonary fibrosis (IPF), Sarcoidosis
High serum BUN and creatinine	Renal-Pulmonary syndromes (Goodpasture's syndrome, Vasculitis, Systemic lupus erythematosus, Idiopathic rapidly progressive glomerulonephritis)
Low serum iron and iron binding capacity	Idiopathic pulmonary hemosiderosis
High level of lactate dehydrogenase	Alveolar proteinosis, *Pneumocystis carinii* pneumonia
Rheumatoid factor	IPF, Collagen-Vascular Diseases, Vasculitis
Immunecomplexes	IPF, Collagen-Vascular Diseases, Goodpasture's syndrome, Asbestosis, Berylliosis, Sarcoidosis, Silicosis
Serum precipitating antibodies	Hypersensitivity pneumonitis
High level of creatinine phosphokinase and aldolase	Dermatomyositis/Polymyositis, Mixed connective tissue disease
False positive test result for syphilis	Systemic lupus erythematosus
Hypocomplementemia	Systemic lupus erythematosus
Antineutrophilic cytoplasmatic IgG antibody (c-ANCA)	Wegener's granulomatosis
Anti-basement membrane antibody	Goodpasture's syndrome
Carcinoembrionic antigen	Primary and Metastatic lung carcinoma
CA-125	Pulmonary lymphangiomyomatosis
Hypercalcemia	Sarcoidosis
Angiotensin converting enzyme	Sarcoidosis, Berylliosis, Asbestosis, Granulomatous hepatitis, Hypersensitivity pneumonitis, Lymphoma, Milliary tuberculosis, primary biliary cirrhosis, Silicosis, Endemic mycosis
Von Willebrand factor	Acute respiratory distress syndrome
High serum level of cytokines	Acute respiratory distress syndrome, Pulmonary infections
Serologic tests for pulmonary infections	Pneumonia due to *Legionella sp., chlamydia sp., Mycoplasma pneumoniae*, virus and fungi
Blood CD4+ and CD8+ Levels	Lung infiltrates in HIV patients, Sarcoidosis, Berylliosis, Asbestosis
Neopterin and beta (Sub-2) microglobulin	Lung infiltrates in HIV patients
Hypergammaglobulinemia	IPF, Collagen-Vascular diseases, Asbestosis, Berylliosis, Sarcoidosis, Silicosis, Hypersensitivity pneumonitis

In some diffuse lung diseases, such as alveolar proteinosis and *P. carinii* pneumonia in AIDS patients, it is usual to find an elevated serum level of lactic dehydrogenase [5].

In histiocytosis X, routine laboratory tests are frequently normal; a few patients may have an elevated ESR. Elevation of alkaline phosphatase possibly signaling hepatic or bone compromise, and hypercalcemia have been described [6]. Circulating immune complexes have been found in a minority of patients [7].

Peripheral eosinophilia (>10%) may be found in Churg-Strauss syndrome, chronic eosinophilic pneumonia, or hypersensitivity pneumonitis. Precipitating antibodies to specific antigens are markers of previous exposure to inhaled organic dusts but are not diagnostic of disease. Regardless of the technique used, there is the important problem of the false positives and false negatives [8,9]. However, subjects with disease have higher titers of specific antibodies than asymptomatic, exposed individuals, and some of these patients have antigen/antibody complexes in their lungs. The absence of antibody eliminates the possibility of hypersensitivity pneumonitis to that specific agent. Unfortunately, there are many organic dusts and few commercially available antigens. No difference in pulmonary function was observed between antibody-positive and antibody-negative subgroups of patients. Therefore, hypersensitivity pneumonitis cannot be eliminated as a cause of diffuse lung disease when a standard battery of precipitating antibodies is negative [10].

There is no serologic test specific for IPF. Immune complexes have been demonstrated in the serum of some patients with the disease. Rheumatoid factor (RF) is found in 30%, with titers as high as 1/1000. Antinuclear antibodies (ANA) are found in 15%, but the percent DNA binding is normal. Seventy-five percent of patients have an associated polyclonal gammopathy but no pattern is unique to IPF. One half of patients have an elevated ESR [3].

In scleroderma, hypergammaglobulinemia is present in approximately 33%, RF is present in 25% to 35%, and elevated ANA is demonstrated in 40% to 80% of patients [11]. The pattern of ANA seen in scleroderma is the speckled pattern. In polymyositis/dermatomyositis, mild anemia and an elevated ESR are common [12]. The serum creatinine phosphokinase, glutamate oxalacetate transaminase, and aldolase are typically elevated [13]. RF and ANA assays are usually negative [11].

Pulmonary diseases are present in 60% to 90% of patients with SLE [14,15]; many laboratory tests results are associated with this disease, including positive RF (19%), false-positive test results for syphilis (15%) and hypocomplementemia. The most characteristic laboratory abnormality is an elevated ANA titer, which is found in 96% of patients. The diagnostic serologic finding is an elevation of the percent DNA binding to greater than 15%. Antihistone antibodies are present in up to 60% of patients with SLE and greater than 95% of those with drug-induced lupus syndromes. Patients with diffuse lung disease in SLE who develop lupus pneumonitis have been found to have an increased incidence of ANA to the Ro antigen [16].

Wegener's granulomatosis presents a characteristic complex of laboratory findings. Mild hyperglobulinemia, particularly involving the serum IgA fraction, occurs commonly. Almost all patients have strikingly elevated ESR, usually 100 mm h^{-1} or more. An antineutrophilic cytoplasmatic IgG antibody (c-ANCA) has been described and it is of value in the diagnosis and management of the necrotizing vasculitis syndromes. In Wegener's granulomatosis it has a sensitivity higher than 60%, with a specificity higher than 90% [17]. There is no clear evidence that ANCAs play a primary role in the pathogenesis of this vasculitis.

Specific serology for Wegener's granulomatosis and anti-basement membrane antibody testing in Goodpasture's syndrome should be ordered only in patients with compatible syndromes and not used as screening tests for all patients with diffuse lung disease.

In mixed connective tissue disease a positive ANA is seen in 100% of patients as is the ribonucleoprotein titer, but there is no evidence of the Sm antigen. A positive RF and hypergammaglobulinemia are common [18].

In lymphangiomyomatosis, surgical or chemical castration with tamoxifhen or goserelin (luteinizing-hormone-releasing hormone antagonist) [19,20] has been used in their therapy. Serum activity of the tumor marker CA-125 may be useful to monitoring the disease activity [21].

In sarcoidosis the ESR is high in about two-thirds of patients. Hypercalcemia may occur in any stage. The available evidence indicates that it is due to increased intestinal calcium absorption. Endogenous overproduction of 1,25-(OH2)-D3 by activated pulmonary macrophages seems to be the cause of increased intestinal absorption of calcium. Corticosteroids and chloroquine decrease the calcium level to normal by inhibiting the peripheral action of 1,25-(OH2)-D3 and metabolizing the compound to an inactive metabolite [22]. The hypercalcemia of sarcoidosis is frequently associated with an elevated serum angiotensin converting enzyme (ACE) level. This level is normal in patients with hypercalcemia from primary hyperparathyroidism,

malignancy, multiple myeloma, and milk and alkali syndrome [22]. ACE catalyzes the conversion of angiotensin I to vasoactive angiotensin II, the enzyme is normally primarily located in the endothelial cells of the pulmonary capillaries and epithelial cells of the proximal renal tubules. In sarcoidosis, the serum ACE level is increased in about 60% of the patients. ACE activity is higher in patients with hiliar adenopathy and pulmonary infiltration (stage II) than in either those with hiliar adenopathy alone (stage I) or pulmonary infiltrate/fibrosis (stage III/IV). The test is also positive in patients with extrathoracic sarcoidosis and a wide variety of diseases. The ACE level reflects the granuloma load in the body because it is derived from the epithelioid cells of the granulomas [23]. The diagnostic value of ACE is limited because the test has a false-negative rate of 40% and false-positive rate of 10%. This test is most useful for monitoring the clinical course of the disease. A raised ACE level occasionally antedates the clinical, roetgenographic, and physiologic alterations in sarcoidosis. Conditions associated with elevated serum ACE level likely to be confused with sarcoidosis include: asbestosis, berylliosis, granulomatous hepatitis, hypersensitivity pneumonitis, lymphoma, miliary tuberculosis, primary biliary cirrhosis, silicosis and endemic mycosis. ACE inhibitors can reduce the level of ACE. Circulating antibody production is exaggerated in sarcoidosis. Hypergammaglobulinemia occurs in perhaps half the patients and is more frequent among blacks. The prevalence of immune complexes also varies. Circulating complexes are present in about half the patients with acute sarcoidosis, particularly in those with erythema nodosum. In chronic disease, immune complexes are less frequent. Direct immunofluorescent techniques have demonstrated the complexes in cutaneous granulomas. It has been suggested that they alter the distribution and function of the helper and suppressor cells and macrophages [22].

In acute respiratory distress syndrome (ARDS) the concentration of Von Willebrand factor antigen in serum correlates with outcome and progression in some but not all studies [24]. Von Willebrand factor is between the factors that promote the platelet aggregation during acute respiratory failure. Increase of serum level of mediators of inflammation as tumor necrosis factor and other cytokines can be found in patients with ARDS. These mediators are thought to be important in the pathogenesis of the syndrome, but altering the inflammatory response to injury, by anti-inflammatory agents like corticosteroids, does not improve the outcome of patients with established disease [25].

There are no specific blood studies for drug-induced lung disease; however, several findings can be supportive of this diagnosis. For example, more than 50% of patients with amiodarone-induced lung toxicity have an elevated ESR [26]. This test may be of help in distinguishing amiodarone-induced lung toxicity from congestive heart failure.

In diffuse pulmonary infections serologic testing is an alternative approach to determine the cause of pneumonia: these tests usually provide a retrospective diagnosis. Complement fixation, indirect fluorescent antibody and immunodiffusion are the most commonly used methods. One isolated positive testing is useful exceptionally in some infectious diseases. Fourfold or higher increase of titer between acute-phase and convalescent-phase sera samples are needed for most of them [27]. Virus, *Legionella spp., Mycoplasma pneumoniae, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Aspergillus spp.* are some of the microorganisms that may produce diffuse pulmonary infiltrates and can be investigated by serologic studies. Cytomegalovirus pneumonia requires culture of lung tissue with histologic identification of viral inclusions in macrophages or pneumonocytes: serologic testing is not helpful because of the high seroprevalence of cytomegalovirus in the population [28].

Blood CD4+ lymphocytes level is a marker of importance in HIV infected patients with pulmonary infiltrates. When the level of CD4+ is less than $200 \times 10^3\ l^{-1}$, the risk for *P. carinii* pneumonia is high, while when it is higher than $300 \times 10^3\ l^{-1}$, the risk is lower than 10%. Near all the HIV patients with cryptococcal pneumonia have a CD4+ level lower than $100 \times 10^3\ l^{-1}$. Serum levels of markers as neopterin and beta (sub 2)-microglobulin have been studied in patients with HIV infection. Increased levels of both reflect the prognosis and may reflect the risk of development of pulmonary complications almost or equally as well as the reduction in the number of CD4+ T-cells [29].

Bronchoalveolar Lavage

BAL has gained popularity during the last 15–20 years in the diagnosis, staging and follow-up of diffuse lung diseases. BAL can be performed at the time of fiberoptic bronchoscopy, adding only 3–5 minutes to the procedure.

Washing of brochoalveolar specimen irrigating the lungs with a variable volume of physiological

saline has been used for more than 30 years. BAL was described as bronchopulmonar lavage in 1965 [30], as a major form of treatment for alveolar proteinosis. Alveolar surface has been estimated to be between 70 and 100 m^2 [31], and respiratory epithelium is composed of type I and type II cells and scattered neuroendocrinal cells. Different kinds of cells (including alveolar cells, macrophages, white blood cells, malignant cells, etc), microorganisms and non-cellular substances have been studied during the past two decades with the advent of widespread use of flexible fiberoptic bronchoscopy and have gained a place in the research of different pathogenic mechanisms of lung disease. The analysis of cellular and soluble components of the lavage fluid can provide information for a variety of pulmonary disorders and is used for diagnosis and monitoring of disease progression and to decide the therapeutic approach in various diffuse pulmonary diseases.

Technique of Bronchoalveolar Lavage

Today BAL is customarily performed through a fiberoptic bronchoscope. The bronchoscope is passed into the respiratory tract in the usual manner and wedged into a third-to-fourth order subsegmental bronchus prior to BAL. The procedure must be done before brushing or biopsy procedures in order to avoid contamination of the lavage fluid with excess blood, which would alter the concentration of cellular and non-cellular components. BAL can be performed in any lung area. In diffuse lung disease the bronchoscope's tip is advanced and wedged into a distal airway in the area involved by an infiltrate or into a subsegment of the lingula or the middle lobe, because it is easier to wedge it there, and because returns from the lavage of upper lobes are significantly less than from the middle or the lower lobes [32]. Nevertheless, the location of the bronchoscope has little importance in the result of BAL. Suction through the working channel of the bronchoscope before obtaining BAL sampling increases the likelihood of contamination with bacteria and bronchial or upper airway cells. Care should be taken to avoid trauma and coughing as they also may lead to excessive contamination with mucus and blood [33].

At total lung capacity, the typical lavaged zone represents about 165 ml; the residual volume of this zone is approximately 45 ml [34].

BAL is obtained by infusion and aspiration of a 0.9% sterile saline solution through the flexible wedged bronchoscope. Pre-warming of the lavage fluid to 37° is not always necessary, but may help to prevent coughing and bronchospasm. The volume infused usually ranges from 100 ml to 300 ml in each lung segment, injected in aliquots of 20–50 ml. Many of the data on BAL cells and secretions derive from lavage performed with aliquots of 20 ml and a total volume of 100 ml. Proportions and types of cells obtained in volumes ranging from 100 ml to 250 ml are comparable [35,36]. The incidence and importance of associated side effects vary according to the volume of fluid used [37]. Fluid is instilled by hand and recovered by hand or wall suction. Fifty to 80 mmHg of negative pressure is recommended for suction, as greater levels may cause distal airway collapse and lead to inadequate returns.

In some institutions lavage of different areas is routinely performed and analysed separately. There is no uniform agreement regarding variations in BAL results from different lung areas: some authors found significant interlobar variations in cell differentials, and others found no differences in BAL cell concentration or differential between the right middle lobe and the lingula [38,39].

BAL can be safely performed in immunosupressed, severely hypoxemic and/or thrombocytopenic patients [40].

Clinical Uses of BAL

BAL has a potentially important role in management of diffuse lung diseases [41]. Changes in the quantities and patterns of BAL cells and secretions have been described in several diffuse lung diseases.

BAL cellular analyses can be used as a single diagnostic tool in some selected diffuse diseases, as they are sufficiently different to provide suggestive evidence in support of a specific disease [42]. Lung infections, malignant conditions, alveolar proteinosis, histiocytosis X, and lung hemorrhage syndrome, are examples of this group of diseases (Table 3.2). In other diseases, in appropriate clinical setting, cellular lavage findings can contribute to the diagnosis of various lung disorders, provided sufficient diagnostic criteria (e.g. chest radiography, lung function or serologic parameters, etc) are available. For purposes of differential diagnosis, BAL may be helpful in excluding some diffuse lung disease or may give additional directions for further diagnostic steps. Finally, the improvement or progression of some acute or chronic diseases may be monitored by the analysis of BAL fluid (alveolitis, ARDS, malignancy, etc).

Biochemical markers in BAL such as immunoglobulins, proteases, procollagen peptides, and

Table 3.2. Common Cellular Pattern of BAL in Diffuse Lung Disorders

	Lymphocytes	Neutrophilis	Eosinophils	Mast Cells	Other
IPF	+	+++	+	N	
Sarcoidosis	++	N or +	N	N	
Hypersensitivity pneumonitis	+++	N or +	N	+	
Histiocytosis-X	N	+	+	+	Langerhans cells
Collagen-Vascular disorders	+	++	+	+	
Asbestosis	N	++	+	+	Number of asbestos bodies
Berylliosis	+++	+	N	N	
Silicosis	+	N	N	N	Silica particles by polarized light microscopy
BOOP	+	+	+	–	
ARDS	N	+++	N	N	
Pneumonia	N	+++	N	N	
Diffuse alveolar hemorrhage					Hemosiderin-laden macrophages
Carcinoma or lymphoma	++	+ or N	N	N	Malignant cells
Fat embolism and lipoid pneumonia					Neutral fat droplets in cells
Drug induced diseases	++ or N	++ or N	++ or N	N	Chemotherapeutic drug-Induced cellular atypia, alveolar hemorrhage, Foamy macrophages in patients taking aniodarone

N = normal, (+) to (++++) = increased; (–) = decreased

other serum-derived constituents show great promise as markers of disease type and progression (Table 3.3). Problems and restrictions in the detection of solute components in the BAL fluid are the major reasons why non-cellular BAL components so far cannot be used for any clinical purposes. Furthermore, BAL has tremendous potential for allowing insights into the pathogenesis of many chronic diffuse lung diseases.

Interstitial Lung Disease

In IPF there is no correlation between the percentage of various cell types found in BAL fluid and various clinical parameters, and serum, or pulmonary function tests. BAL lymphocytosis is associated with moderate-to-severe alveolar septal inflammation. On the other hand, BAL neurophilia and eosinophilia do not significantly correlate with any of the histopathological abnormalities common to IPF [43]. Although a strong correlation has been suggested between the percentage of neutrophils in lavage fluid and the prognosis in IPF [44], further investigations found no difference in the lavage fluid neutrophil percentages of patients who responded to corticosteroid therapy and those who did not [45,46]. BAL lymphocytosis at the time of presentation appears to predict corticosteroid responsiveness [45–48]. Declines in neutrophil levels occur in patients who respond to prednisolone. Patients who fail to improve maintain elevated level of neutrophils and eosinophils throughout their course [47]. There is a reduced total recovery of surfactant phospholipid, a reduction in the percentage of phosphatidylglycerol (PG), and a slight increase in the percentage of phosphatidylinositol (PI). In IPF, changes in the PG/PI ratio are predictive of cellularity and degree of fibrosis on histopathological examination [49]. In summary, although the data are limited, they appear to support the hypothesis that the initial cell counts and phospholipid content can predict the underlying histopathology. Further, monitoring serial lavage cell counts and phospholipid content in individual patients may reflect the clinical course and therefore be useful in establishing the clinical response to treatment.

BAL has proved to be useful in the diagnosis of pulmonary histiocytosis-X [50]. The total cell recovery is usually high. The differential cell count shows a high percentage of alveolar macrophages. On electron microscopy, Langerhans cells, characterized by highly specific pentalaminar structures and a tennis racket shape, constitute the specific finding [6]. A more rapid and highly specific technique using monoclonal antibodies has been developed [51]. At least 5% of Langerhans cells in the BAL fluid is required to confirm the diagnosis.

Some collagen-vascular disorders and systemic vasculitis are associated with the presence of alveolitis. Elevated neutrophil cell count in the BAL fluid is the predominant lavage pattern. Interestingly, there is evidence that intense cellular activity also can be documented in a large proportion of patients without clinical or radiologic manifestations of pulmonary involvement [52]. Increase of eosinophils and lymphocytes may be observed sometimes in collagen-vascular disorders. Cellular counts and predominance in BAL fluid analysis may have relevance in the future in monitoring their response to the therapy.

Diffuse alveolar hemorrhage may be present in patients with some collagen-vascular diseases, systemic vasculitis and primary pulmonary hemosiderosis. Hemosiderin laden macrophages, and the lack of infectious pathogens are sufficient to establish the diagnosis [53].

In hypersensitivity pneumonitis there is lymphocytosis with CD_4/CD_8 less than 1/1 [54]. Interestingly, no patient with hypersensitivity pneumonitis has been reported to show normal BAL cytology. A normal number of lymphocytes would rule out all but residual disease. However, the presence of lymphocytosis does not, by any means, establish the diagnosis because asymptomatic exposed individuals can also have increased number of lymphocytes in their BAL [55]. From the clinical point of view, BAL is more sensitive than chest radiograph for detecting alveolitis in hypersensitivity pneumonitis. Lavage fluid from these patients contains high concentrations of immunoglobulin, especially IgG and IgM. The presence of IgM is rarely found in measurable amounts both in normal lung fluid and in fluid obtained from other lung diseases [56]. Hyaluronate and type III procollagen peptide concentrations in BAL fluid might be useful in monitoring the disease in the future [57,58]. Specific precipitating antibody to inciting antigen was found in BAL fluid from a number of these patients.

In sarcoidosis, there is a significative increase in the number of T-lymphocytes in patients with active disease. The T-cell to B-cell ratio in the lung is 18 to 1, whereas the T-cell to B-cell ratio in the blood is only about 3 to 1. T-lymphocytes in lavage fluid are also increased in such conditions as hypersensitivity pneumonitis, pulmonary lymphoma and miliary tuberculosis. An elevated T-helper/T-suppressor ratio (CD4/CD8 ratio), is a characteristic finding in BAL of patients with sarcoidosis [59]. BAL is of little help in establishing the specific diagnosis of

Table 3.3. Bal Markers of Diffuse Lung Disorders

Marker	Observations
Lymphocytosis	Granulomatous diseases. In acute onset, may predict good prognosis in sarcoidosis. In IPF indicates moderate to severe Inflammation.
Neutrophilia	Usually observed in IPF and collagen-vascular disorders. In IPF does not correlate with any histopathological abnormality. Neutrophils level declines in patients responding to prednisolone. In sarcoidosis, associated with advanced disease. Common in chemotherapeutic drug-induced lung disease.
Eosinophilia	Usually seen in patients with eosinophilic lung. Advanced cases of other ILD. In IPF is associated with failure to improve.
High CD4/CD8 ratio	Sarcoidosis (diagnosis and prognosis)
Low CD4/CD8 ratio	Hypersensitivity pneumonitis, collagen vascular diseases, HIV, BOOP, drug induced diseases, silicosis
Low proportion of macrophages	BOOP
Hemosiderin laden macrophages	Difuse alveolar hemorrhage
Increase of lipid filled macrophages	Marker of dose of amiodarone but not pulmonary toxicity
Neutral fat droplets in cells	Fat embolism, Lipoid pneumonia
Langerhans cells > 5%	Histiocytosis-X
Malignant cells	Bronchioloalveolar carcinoma, carcinomatous lymphangitis, lymphomas.
Carcinoembrionic antigen, neuron specific enolase and glutathione S-'transferase isoenzymes, PGE_2	Carcinoma
Phosphatidilglycerol reduced	Probably useful in the future in monitoring hypersensitivity pneumonitis
Phosphatidilinositol increased	Probably useful in the future in monitoring hypersensitivity pneumonitis
Immunoglobulin concentration	Probably useful in the future in monitoring hypersensitivity pneumonitis
Hyaluronate and Type III procollagen increased	Probably useful in the future in monitoring IPF.
Neutrophils activating factor-1	Acute respiratory distress syndrome
Cytokines (tumor necrosis factor, interleukin-8), procollagen peptide	Acute respiratory distress syndrome
Albumin, transferrin, fibronectin, alveolar derived growth factor	Oxygen toxicity
Increased activity of proteases or decreased antiprotease activity	Emphysema, smokers, chronic bronchitis, acute respiratory distress syndrome, cystic fibrosis
Histamine, kinines prostaglandins, leukotrienes	Asthma
Bi-refringent particles	Talc induced disease

sarcoidosis; nevertheless, Winterbauer et al. recently evaluated 128 patients with 16% or more lymphocytes in the BAL fluid. They demonstrated that BAL with a CD4/CD8 ratio of 2/1 or greater, 1% or fewer neutrophils, and 1% or fewer eosinophils had essentially the same specificity and predictive positive value as multiple non-caseating granuloma on transbronchial lung specimen and that a BAL CD4/CD8 ratio of 4/1 or greater had a 100% positive predictive value in separating sarcoidosis from other diffuse lung diseases [60]. BAL cellular analysis can be used as a marker of prognosis in sarcoidosis; acute onset with increased number of lymphocytes may predict good prognosis; increased CD4/CD8 ratio predicts a good prognosis; increased number of mast cells predicts poor prognosis and increased number of neutrophils is associated with advanced disease [61–65]. ACE and mediators spontaneously released from macrophages of patients with sarcoidosis as TNF, IL-1, and PGE_2, are present in lavage fluid. Nevertheless, the amount of these substances does not positively correlate with the clinical status of the disease and they appear to be poor indicators of clinically progressive disease [66–68]. In summary, no single BAL fluid feature is diagnostic for sarcoidosis. T-lymphocyte level, CD4/CD8 ratio, increase in neutrophils, eosinophils and mast cells in BAL fluid have been associated with the progression to fibrosis [59,67]. Nevertheless these should not be used alone in making therapeutic decisions.

In ARDS, concentration of neutrophil activating factor-1, tumor necrosis factor, interleukin-8 and procollagen peptide in bronchoalveolar lavage fluid correlate with outcome and progression in some but not all studies [68,69].

In fat embolism, one of the potential causes of ARDS, the identification of neutral fat droplets by staining with oil red O within cells recovered by BAL in patients with recent trauma, may be a rapid and specific method for establishing the diagnosis [70]. Lipid stain of BAL specimen may be useful too in the diagnosis of lipoid pneumonia [71].

Considerable controversy exists regarding the value of BAL in drug-induced pulmonary diseases. Infection and malignancy are a main differential in this setting. When lymphocytes are present, infectious causes would tend to be excluded, and the presence of polymorphonuclear neutrophils commonly occurs with chemotherapeutic-induced lung disease and thus is an expected finding. Bleomycin-induced pulmonary disease may show either neutrophils, lymphocytes or eosinophils in the BAL fluid. Cancer chemotherapy agents often cause pulmonary reactions including either hypersensitivity-like reactions or cytotoxic drug reactions characterized by marked cellular atypia that may be difficult to distinguish from cellular atypia caused by viral infection or malignancy. Amiodarone produces an increase of lipid-filled macrophages: this is a marker of the dose of amiodarone taken but not of pulmonary toxicity [72]. Other miscellaneous findings include albumin, transferrin, fibronectin and alveolar-derived growth factor in oxygen toxicity and birefringent particles in talc induced disease. The presence or absence of atypia, unfortunately, has not been that sensitive in the inclusion or exclusion of chemotherapeutic lung disease.

Obstructive Lung Diseases

In bronchiolitis obliterans with organizing pneumonia *(BOOP)*, the proportion of macrophages is lower than in healthy volunteers; the lymphocytes, neutrophils, and eosinophils are higher than in normals. This mixed pattern of cellularity is thought to be characteristic of BOOP, especially when associated with multiple opacities on chest radiograph [73].

Airway inflammation has been included during the last years in the definition of asthma [74]. Samples of BAL fluid are used to study airway cell function, mediator release, mechanisms of inflammation and bronchial hyperreactivity. Histopathologic studies described the inflammatory process present in fatal asthma. Recently, histopathologic examination of endobronchial biopsy specimens from stable asthmatic subjects has shown inflammatory cell infiltration of the mucosa as a distinctive feature of mild asthma. Increased amount of mediators (histamine, prostaglandins, leukotrienes, and kinins) and increased number of cellular elements (eosinophils, lymphocytes, basophils, epithelial cells and mast cells) were reported in BAL fluid in asthmatics [75–78]. BAL of mildly asthmatic patients revealed findings consistent with active inflammation [79]. BAL may be useful in monitoring the response of asthmatic subjects to anti-inflammatory drugs such as inhaled corticosteroids and cromones.

Increased protease activity or decreased antielastase activity in BAL fluid has been described in smokers, patients with cystic fibrosis, ARDS, chronic bronchitis and emphysema. Reversal of protease-antiprotease imbalance in alveolar lining secretions after the replacement of α_1-antiprotease in emphysema patients has been used as a means of gauging long-term effects of this therapy.

In cystic fibrosis BAL is used to investigate the mechanisms of lung injury. In the future, BAL may be used in monitoring the response of bronchial epithelial cell to gene therapy [80].

Malignancies

The sensitivity of transbronchoscopic biopsy in diffuse lung malignancies is lower than its sensitivity in localized tumors, and therefore, using the measure of biochemical or immunologic markers in BAL fluid may help to diagnose diffuse lung malignances [81]. A high concentration of carcinoembryonic antigen (CEA) in BAL fluid, and a much higher CEA concentration in BAL fluid than in serum were found in patients with lung cancer [82]. There are some doubts on the specificity of CEA concentration in BAL fluid because elevated values have been found in smokers [83] and in patients with chronic bronchitis [84]. The concentration of prostaglandin E_2 (PGE_2) is increased in the BAL fluid of patients with lung cancer. PGE_2 was found to be elevated in 60% of patients with peripheral carcinoma [85,86]. Further investigations of sensitivity and specificity of measuring PGE_2 is warranted. Neuron-specific enolase and glutathione S-transferase isoenzymes B_1 and B_2 in BAL fluid were found to be valuable in the diagnosis of lung cancer. Measurement of markers in BAL has not yet achieved the status of a routine procedure in patients with suspected lung cancer.

Cytologic examination of BAL fluid shows malignant cells in most of patients with diffuse malignant lung infiltrates. BAL may be useful for the diagnosis of bronchioloalveolar carcinoma [87] and carcinomatous lymphangitis [88]. In one study BAL disclosed cancer cells in 93% of 44 bronchioloalveolar carcinomas, 83% of 69 cases with carcinomatous lymphangitis due to metastatic cancer, 67% of 15 non-Hodgkin's lymphomas and 3 of 9 cases of Hodgkin's disease with pulmonary involvement. Immunocytochemistry using monoclonal and/or polyclonal antibodies was of value in the identification and classification of cells in non-Hodgkin's lymphoma [89].

Infectious Diseases

Pneumonia sometimes has a radiographic presentation as a diffuse lung disease. BAL fluid study may be of value in determining the etiology of pneumonia in the non-immunocompromised and the immonocompromised host. Regarding the non-immunocompromised, bronchoscopy and BAL is used in mechanical ventilated patients with both community acquired pneumonia and nosocomial pneumonia. Non-immunocompromised, non-mechanically ventilated patients may sometimes require BAL fluid study to determine the infectious etiology of a diffuse infiltrate (e.g. miliary tuberculosis). Direct examination of lavage cells containing intracellular bacteria in more than 5% of the cells is sensitive and specific in predicting the bacterial etiology.

In the immunocompromised host, BAL fluid study may be useful to confirm the infectious etiology of a diffuse lung disease and determine the pathogenic microorganism or to disclose other associated condition that may have a similar clinical presentation. *Pneumocystis carinii*, cytomegalovirus, gram-negative bacteria, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Legionella pneumophila*, *Aspergillus sp*, *Histoplasma capsulatum*, *Coccidioides immitis* and *Blastomyces dermatiditis* are the commonest microorganisms isolated in the BAL fluid in the immunocompromised host. Patients with pharmacological immunosupression, bone marrow and solid organ transplants, immunodeficiency and hematological malignancy [90,91] compose this heterogeneous group. Primary or drug-induced interstitial pneumonitis may cause non-infectious diffuse lung infiltrate in AIDS and other conditions such as hematologic malignancy or collagen-vascular diseases.

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