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REVIEW

Subclinical alveolitis in immunological systemic disorders. Transition between health and disease?

B. Wallaert, M. Dugas, E. Dansin, T. Perez, C.H. Marquette, P. Ramon, A.B. Tonnel, C. Voisin

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ABSTRACT: A subclinical inflammatory alveolitis as assessed by BAL cell analysis may be present in a high proportion of symptomless patients with immunological systemic disorders and with normal chest roentgenogram. Subclinical alveolitis can be characterized by the relative proportions of the different cell populations comprising the alveolitis and by the activated state of the cells. Thus, subclinical alveolitis can be classified into two major groups: lymphocyte and neutrophil alveolitis. Lymphocyte alveolitis is frequently found in patients with extrathoracic granulomatosis (Crohn's disease, primary biliary cirrhosis, extrathoracic sarcoidosis) or with some collagen vascular diseases (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus). Neutrophil alveolitis is a main finding in collagen vascular diseases, especially progressive systemic sclerosis, dermatopolymyositis and mixed connective tissue disease. In addition, alveolar macrophages may be spontaneously activated and release various mediators that could be relevant to the pathogenesis of interstitial lung disease. On the other hand, some other alveolar macrophage functions (antibacterial activity may be severely impaired in some diseases, for example systemic lupus erythematosus). Alveolar inflammation is associated with an increase in the permeability of the alveolar membrane responsible for an increased influx of blood proteins in the alveolar spaces. Although subclinical inflammation may also be detected by high resolution computed tomography (HRCT) scan and/or lung permeability scintigraphic studies, the significance and prognostic value remains unclear and clearly differs according to both the disease and the pattern of alveolitis.

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It is now recognized that, independent of the type of the disease or specific aetiology, the earliest manifestation of interstitial lung disease is an alveolitis, *i.e.* an accumulation of immune and inflammatory cells within the alveolar structures [1–6]. During the last 15 years, the development of bronchoalveolar lavage (BAL) allowed quantitative and repetitive evaluation of inflammatory and immune processes in the lower respiratory tract emphasizing the concept of alveolitis associated with interstitial lung disease: 1) alveolitis is associated with chronic interstitial lung disease; 2) alveolitis precedes and may be responsible for the development of irreversible disorders of the alveolar structures [6]. Alveolitis is characterized by two main findings: an increased number of immune and inflammatory cells and an activation of one or more effector cell types. The activation of effector cells is of particular importance since it is activated cells and their products which have the potential effects to induce the development of interstitial lung disease: parenchymal injury, attraction of immune and inflammatory cells within the lung, activation of these cells, modulation of granuloma formation and derangement of the connective tissue matrix.

The concept of subclinical alveolitis

Since alveolitis is the earliest manifestation of interstitial lung disease, it seems reasonable to search for an early detection of alveolitis in patients at risk for the development of chronic interstitial lung disease in the future. In addition, BAL in symptomless patients can ethically be performed only in patients with disorders which are known to be frequently responsible for the development of interstitial lung disease. In this context, it is noteworthy that systemic disorders and particularly collagen-vascular disorders, are frequently associated with

Table 1. – Types of subclinical alveolitis observed in asymptomatic patients with various immunological systemic disorders and with normal chest roentgenogram

Systemic disorder	Subclinical alveolitis	Frequency	Reference
Extrathoracic sarcoidosis	lymphocytic	8/10	[8]
		6/12	[9]
		17/30	[10]
		14/26	[11]
		15/18	[25]
Crohn's disease	lymphocytic	11/18	[12]
		10/16	[13]
Primary biliary cirrhosis	lymphocytic	6/12	[15]
		6/10	[16]
Primary Sjögren's syndrome	lymphocytic	11/25	[17]
		7/11	[19]
		14/30	[20]
Secondary Sjörgren's syndrome	mixed*	6/8	[26]
Rheumatoid arthritis	lymphocytic	5/5	[22]
		5/12	[24]
		4/10	[52]
	neutrophilic	2/8	[23]
		3/12	[24]
Progressive systemic sclerosis	neutrophilic	6/10	[17]
		4/25	[36]
		6/20	[38]
		9/13	[39]
		4/24	[40]
		11/15	[41]
	lymphocytic	10/25	[36]
		6/20	[38]
		2/13	[39]
		1/24	[40]
		5/15	[41]
Dermatopolymyositis	neutrophilic	2/3	[17, 35]
Mixed connective tissue disease	neutrophilic	3/8	[17]
Systemic lupus erythematosus	lymphocytic	5/17	[21]
Familial idiopathic pulmonary fibrosis	neutrophilic	8/17	[44]

*mixed: lymphocytic-neutrophilic.

interstitial lung disease [7]. Thus immunological systemic disorders represent a unique opportunity to test the hypothesis that inflammation may precede fibrosis. Recently, through the work of many laboratories throughout the world, it is clear that an inflammatory alveolitis, as assessed by BAL cell analysis, may be present in a high proportion of symptomless patients with systemic disorders. Therefore, subclinical alveolitis may be defined as an accumulation of immune and inflammatory cells in the lower respiratory tract of patients with systemic immunological disorders, free of clinical pulmonary symptoms and with normal chest roentgenograms, with or without abnormalities of pulmonary function tests. It is this new concept of subclinical alveolitis that we summarize in this review article.

Cellular characteristics

Subclinical alveolitis can be characterized by the relative proportions of the different effector cell populations comprising the alveolitis and by the activated state of the cells. Currently, subclinical alveolitis in systemic disorders can be classified into two major groups: lymphocyte and neutrophil alveolitis (table 1).

Lymphocyte alveolitis

Lymphocyte alveolitis is a frequent finding in the lower respiratory tract of patients with extrathoracic granulomatosis or with collagen vascular diseases

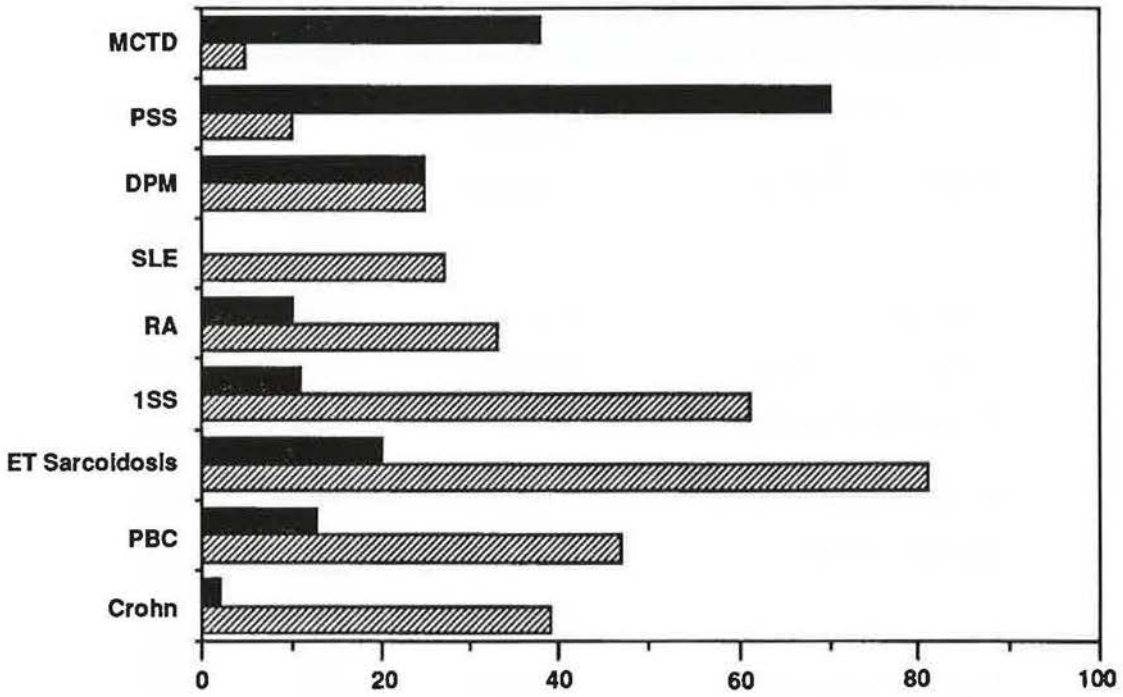

Fig. 1. – Frequency of subclinical alveolitis in various immunological systemic disorders. All patients (n=274) were asymptomatic and had normal chest roentgenogram. ET Sarcoidosis: extra thoracic sarcoidosis (n=46); Crohn: Crohn's disease (n=48); PBC: primary biliary cirrhosis (n=20); 1SS: primary Sjögren's syndrome (n=61); SLE: systemic lupus erythematosus (n=18); PSS: progressive systemic sclerosis (n=56); RA : rheumatoid arthritis (n=18); DPM: dermatopolymyositis (n=9); MCTD : mixed connective tissue disease (n=8). ▨ : lymphocyte alveolitis; ▩ : neutrophil alveolitis with or without lymphocytes.

(fig. 1). We first reported an increased percentage of lymphocytes in bronchoalveolar lavage in patients with extrathoracic sarcoidosis who had no clinical and radiological evidence of pulmonary disease [8]. Several reports also demonstrated a discrepancy between normal chest X-ray film findings and the presence of an alveolitis as determined by BAL immunological marker analysis in more than 50% of the patients with extrapulmonary sarcoidosis [9, 10]. In a recent study, a subclinical lymphocyte alveolitis was present in 14 out of 26 (54%) patients with extrathoracic sarcoidosis [11]. The mean percentage of alveolar lymphocytes (30.1±17.4%) was not significantly different from the one observed in patients with mediastino-pulmonary sarcoidosis.

Similar data have been described in Crohn's disease and in primary biliary cirrhosis [12–16]. Although the lung is usually thought to be spared in Crohn's disease, 10 out of the 18 patients initially studied showed a lymphocyte alveolitis [12]. In addition, lymphocyte alveolitis persists since it was present at the same level six months later in four tested patients.

In primary biliary cirrhosis a subclinical alveolar inflammation of the lower respiratory tract was present in six of 12 patients: evaluation of the BAL cell differential of the patients with primary biliary cirrhosis demonstrated a shift in the cell differential from that observed in the control subjects toward an increased proportion of lymphocytes (22.4±5.2% compared with the normal value of 9.9±1.5%) [15]. A recent study from SPITERI *et al.* [16] also demonstrated that a proportion of

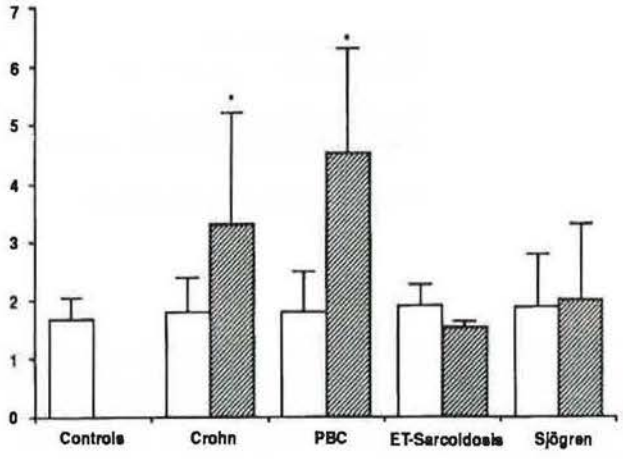

Fig. 2. – CD4/CD8 ratio in bronchoalveolar lavage from nonsmoking patients with various immunological disorders. □ : without alveolitis; ▨ : with alveolitis. for abbreviations see legeng to figure 1.

patients with primary biliary cirrhosis develop subclinical alveolitis. The alveolitis was characterized by an increased number of activated T-lymphocytes with a concomitant increase in the proportion of non-lymphoid cells with the phenotype of antigen presenting cells, despite an overall fall in macrophage proportion [16]. Although nonspecific, subclinical alveolitis is unlikely to be due to liver damage, but is more likely to be part of the underlying primary process of primary biliary cirrhosis.

Subclinical lymphocyte alveolitis has also been described in patients with primary Sjögren's syndrome [17–20], systemic lupus erythematosus [21] and rheumatoid arthritis [17, 22–24].

Characterization of lung lymphocyte subpopulations showed that the increase in lung lymphocytes was largely due to the CD4+ (helper/inducer) T-lymphocyte subset in Crohn's disease, primary biliary cirrhosis and rheumatoid arthritis, whereas blood T-lymphocyte distribution was within normal [10–16, 18, 22]. In contrast CD4+/CD8+ ratio in the lung was normal or slightly increased in extrathoracic sarcoidosis [9, 10, 25] and primary Sjögren's syndrome [26] (fig. 2). Whether lymphocytes are sequestrated in the lung or whether induced proliferation of lung lymphocyte subpopulations is induced through release of various mediators secreted by both lymphocytes and macrophages, remains to be elucidated.

It is remarkable that a similar subclinical lymphocyte alveolitis has been described in a significant number of asymptomatic subjects exposed to organic or inorganic particles or antigens [27–34]. For example, a large number of asymptomatic dairy farmers had a high percentage of lymphocytes in their bronchoalveolar lavage suggesting the presence of an ongoing subclinical alveolitis. Although subclinical alveolitis was more frequent in farmers with positive serum precipitins, the lymphocyte subpopulations were similar whether or not the subjects had positive precipitins or abnormally high percentage of lymphocytes in bronchoalveolar lavage. In addition, nonspecific lymphocytotoxicity and specific lymphocytotoxicity were not enhanced or decreased in subjects with positive precipitins compared to seronegative controls and these indices did not separate subjects who had a subclinical alveolitis from those who did not. Since farmers with acute or subacute hypersensitivity pneumonitis also have increased percentage of lymphocytes in bronchoalveolar lavage, the link between asymptomatic alveolitis and the disease is still unknown.

Neutrophil alveolitis

Neutrophil alveolitis is a main finding in collagen vascular disorders, especially progressive systemic sclerosis, dermatopolymyositis and mixed connective tissue disease (fig. 1) [17, 35]. The best characterized is progressive systemic sclerosis [17, 36–42]. Neutrophil alveolitis may be associated with lymphocyte alveolitis in cases associated with Sjögren's syndrome: the CD8+ suppressor/cytotoxic population was markedly increased in bronchoalveolar lavage from patients with alveolar neutrophilia [26]. Expansion of CD8+ lymphocyte subpopulation is of interest in the relationship to similar abnormalities in bronchoalveolar lavage from patients with overt interstitial fibrosis [43].

Similar data have been shown in unaffected family members of patients with familial idiopathic pulmonary fibrosis [44]. Despite being clinically normal in every respect, about half the first-degree relatives of patients with familial idiopathic pulmonary fibrosis (IPF) had a pattern of a neutrophilic alveolar inflammation.

Alveolar macrophage dysfunction

Since neutrophils are blood cells which are not normally found in the alveolar sructures, it was reasonable to hypothesize that they were chronically attracted to the alveolar structures. In interstitial disorders like IPF, the source for the neutrophil attraction seems to be activated alveolar macrophages that release a neutrophil chemotactic factor [45]. Several findings suggest that alveolar macrophages from patients with systemic disorders are spontaneously activated (fig. 3) and release various mediators [46, 47].

Increased chemiluminescence response of alveolar macrophages before and after stimulation by phorbol-myristate-acetate was reported in extrathoracic granulomatosis [25, 46]. The extent of chemiluminescence suppression by superoxide dismutase suggested that alveolar macrophages were activated and released increased amounts of superoxide anion. Moreover, alveolar macrophages from patients with various collagen vascular diseases spontaneously released a number of secretory products that could be relevant to the pathogenesis of interstitial lung disease, that is superoxide anion, neutrophil chemotactic activity and fibronectin [42, 47, 48]. As shown in table 2, spontaneous release of alveolar macrophage products was also shown in patients with overt interstitial lung disease as in patients with subclinical alveolitis. Similarly, in clinically normal family members of patients with idiopathic familial pulmonary fibrosis, alveolar macrophages were activated and released increased amounts of one or more neutrophil chemoattractants, alveolar macrophage-derived growth factor and, in most instances, fibronectin within the lower respiratory tract [44]. More recently, PEREZ *et al.* [49] demonstrated that alveolar macrophages from patients with rheumatoid arthritis, with or without evidence of pulmonary involvement, spontaneously released increased amounts of tumour necrosis factor but no detectable interleukin 1 activity. Spontaneous release

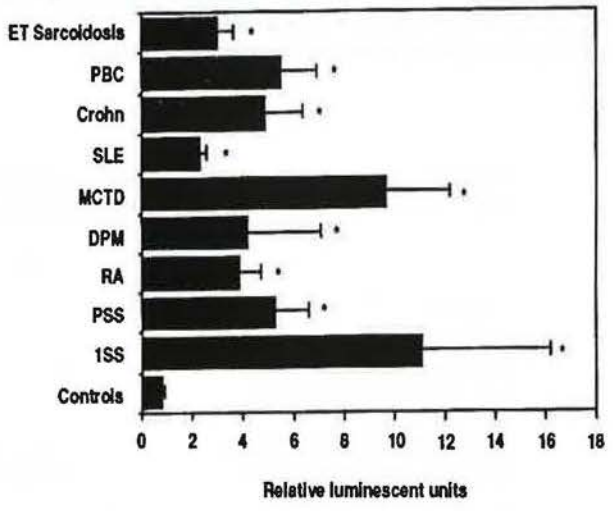

Fig. 3. – Spontaneous chemiluminescence of alveolar macrophages from patients with various immunological systemic disorders. Results are expressed as RLU (Relative Luminescent Units) per 0.5×10^6 viable alveolar macrophages. For abbreviations see legend to figure 1. Adapted from [47].

Table 2. – Spontaneous release of neutrophil chemotactic factors (NCF) of oxidants (superoxide anion) and of fibronectin by alveolar macrophages of patients with collagen vascular diseases with or without interstitial lung diseases (ILD).

Alveolar macrophage secretory products	Collagen vascular diseases with ILD (n=10)	without ILD (n=32)	Controls (n=10)
NCF	9/10	23/32	0
Fibronectin	9/10	12/32	0
Oxidants	4/10	20/32	0
Presence of out of 3 criteria activation	10/10	31/32	0/10

Adapted from [48].

of pro-inflammatory and/or profibrotic mediators by activated alveolar macrophages may play an important role in the development of lung inflammation.

On the other hand, we demonstrated that other alveolar macrophage functions, in particular antibacterial activity may be severely impaired in some, but not all, collagen-vascular diseases. Ability of alveolar macrophages from both untreated and corticosteroid-treated patients with systemic lupus erythematosus to kill *S. aureus* or *E. coli* had been shown to be severely impaired [21]. In marked contrast, antibacterial activity of alveolar macrophages from patients with progressive systemic sclerosis, dermatopolymyositis, mixed connective tissue disease or Sjögren's syndrome was within normal range [47].

Biochemical characteristics

Alveolar inflammation is associated with an increased permeability of the alveolar membrane, responsible for an increased influx of blood proteins in the alveolar spaces. In addition, various secretory products are spontaneously released by activated effector cells and can be detected in bronchoalveolar lavage fluid.

Increased levels of IgG and IgM have been demonstrated in patients with Crohn's disease with subclinical alveolitis but not in those with normal bronchoalveolar lavage [11] (table 3). Immune complexes which are thought to play a role in the development of interstitial lung disease have been demonstrated in BAL fluid from five out of eight patients with scleroderma and with normal chest roentgenograms [40]. More recently, exaggerated amounts of inflammatory mediators like plasminogen activator levels were increased in BAL fluid from patients without evidence of interstitial involvement [50] whereas high levels of fibrinopeptide A reactive procoagulant activity and histamine were found in BAL fluid subjects with rheumatoid interstitial lung disease compared to those with rheumatoid arthritis alone [51, 52].

The balance between proteases and antiproteases in the lower respiratory tract is believed to play an important role in the outcome of interstitial lung disease. However, conflicting data are found in the literature. Alpha 2 macroglobulin levels in BAL were markedly increased in patients with collagen-vascular diseases (CVD) associated with overt interstitial involvement when compared to patients with subclinical alveolitis [53]. These data may suggest that accumulation of immune and inflammatory cells in the lung of CVD patients could precede an active inflammatory process which is associated with the increased local level of antiproteases. In contrast neutrophil elastease activity was only detected in BAL fluid from 1 of 21 patients with collagen vascular disease and subclinical alveolitis whereas detectable levels were present in BAL from 8 out of 12 untreated patients with overt interstitial lung disease [50]. Similar data have been reported by Weiland *et al.* [54]: none of the five patients with rheumatoid arthritis without interstitial disease had collagenase activity in their concentrated BAL fluid whereas 4 of the 5 patients with interstitial lung disease demonstrated collagenase activity [54]. In marked contrast, collagenase activity in BAL fluid was significantly increased in those patients with scleroderma who exhibited a subclinical alveolitis [38].

Table 3. – Biochemical analysis of bronchoalveolar lavage fluid in patients with Crohn's disease, patients with pulmonary sarcoidosis and healthy controls

	IgG	IgM	α_2M	α_1AT
Controls	0.75±0.28	0.095±0.04	0.05±0.06	1.27±0.48
Crohn's disease				
Without lymphocyte alveolitis	0.72±0.4	0.03±0.02	0.06±0.05	0.72±0.04
With lymphocyte alveolitis	1.57*±0.75	0.19*±0.24	0.14*±0.08	1.35±0.9
Sarcoidosis				
Without lymphocyte alveolitis	1.22±0.41	0.17±0.7	0.09±0.03	1.11±0.48
With lymphocytes alveolitis	1.93*±0.88	0.49*±0.41	0.49*±0.39	1.98±0.77

Results are expressed as RCE (relative coefficient of excretion) calculated as follows: RCE = (protein BAL/albumin BAL)/(protein serum/albumin serum). * : $p<0.05$ when compared with controls and with patients without alveolitis; IgG: immunoglobulin G; IgM: immunoglobulin M; α_2M: alpha$_2$ macroglobulin; α_1AT: alpha$_1$ antitrypsin. Adapted from [11].

Relationship with other methods for early detection of interstitial lung disease

Over the last decade, several investigations in pulmonary medicine have been directed toward early detection of interstitial lung disorders. In the field of collagen vascular diseases, several groups, and our own, have directed their studies toward early detection of alveolar inflammation and of lung involvement. These studies have clarified the interest of each new technique and have improved our knowledge of lung involvement in systemic disorders.

Pulmonary function tests

In general, physiological studies tend to be more sensitive than chest roentgenogram in detecting parenchymal lung disease, since 7–10% of patients with interstitial disease indicated by lung function may have a normal chest roentgenogram [55]. In the past decade, a number of pulmonary function studies have shown that a high proportion of patients with collagen vascular diseases may have abnormalities in pulmonary function inspite of any clinical or roentgenographic evidence of lung disease [56–69]. For example, a reduced diffusing capacity of the lungs for carbon monoxide (DLCO) is common in rheumatoid arthritis and is characteristic of early interstitial lung disease. It is now recognized as the best single test for detecting lesions in patients with rheumatoid arthritis, even when the chest roentgenogram or other pulmonary function studies give no indications. Similarly, a diminished DLCO is a common finding in scleroderma despite minimal or absent clinical and roentgenographic evidence of pulmonary involvement. This suggests that the earliest lesion present in progressive systemic sclerosis is located in such a way as to interfere with gas exchange but that the lesions are not extensive enough to affect lung mechanics [54].

Lessons from BAL studies showed that subclinical lymphocyte alveolitis was not associated with significant abnormalities of pulmonary function tests [17]. However, obstructive ventilatory defect and impaired diffusing capacity are a frequent finding in Crohn's disease [61]. In our series of patients with Crohn's disease, pulmonary function test abnormalities are more pronounced in patients with alveolitis than in patients without alveolitis, according to smoking habits [11]. In contrast, in collagen vascular diseases, subclinical neutrophil alveolitis was frequently associated with impaired diffusing capacity and reduced vital capacity. In addition, a small percentage of patients who had normal chest X-ray and pulmonary function studies, exhibited a subclinical neutrophil alveolitis supporting the hypothesis that alveolitis may precede fibrosis [17].

CT scan

In the clinical investigation of pleuro-pulmonary disease, computed tomography (CT scan) of the thorax has been established as a valuable tool for the study of pulmonary parenchymal abnormalities [57]. In addition, the recently introduced 1mm thin cut scan, high resolution CT scan (HRCT scan) may be more sensitive for assessment of interstitial lung disease. In a group of patients with systemic sclerosis, STRICKLAND and STRICKLAND [63] demonstrated that CT scan was 24% more accurate than chest radiography in demonstrating fibrosing alveolitis, indicating that narrow section HRTC scan allows the pulmonary disease to be diagnosed before any abnormality is detectable on good quality high kV radiographs [63].

To better investigate the clinical usefulness of CT scanning of the thorax in systemic disorders, 42 patients with normal chest X-rays were examined: HRCT scan detected significant parenchymal abnormalities in 42% of patients. Abnormal HRCT scan was uncommon in extrathoracic granulomatosis whereas HRCT scan abnormalities were frequent in collagen vascular diseases, especially in patients with progressive systemic sclerosis (fig. 4) and in patients with rheumatoid arthritis [64]. HARRISON *et al.* [41]also demonstrated that peripheral parenchymal crescentic shadowing compatible with fibrosing alveolitis were present in seven of 16 (44%) patients with progressive systemic sclerosis and with normal chest roentgenogram, although changes were less extensive than in patients with ILD.

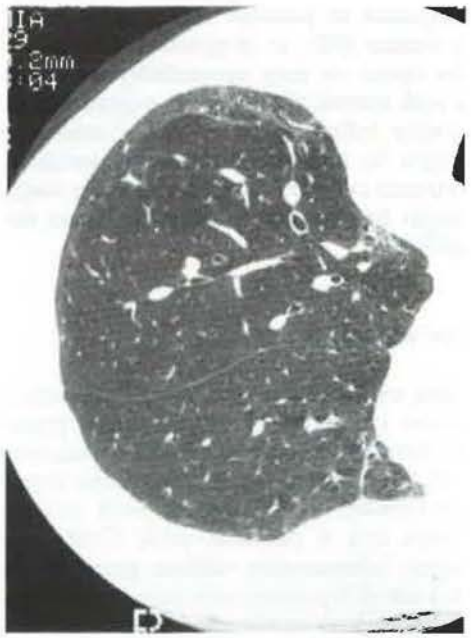

Fig. 4. – High resolution CT scan in the prone position with window setting appropriate for lung parenchyma in a patient with progressive systemic sclerosis, normal chest roentgenogram and subclinical neutrophil alveolitis. Thickened septal lines and fine honeycombing are shown. CT: computed tomography.

Scintigraphic studies

In interstitial lung diseases, Gallium-67 lung uptake reflects the inflammatory activity of effector cells and of granulomatous lesions. Ga-67 lung accumulation had been shown to correlate well with the intensity of

granulomatosis as assessed by serum angiotensin converting enzyme in pulmonary sarcoidosis [65, 66]. We have obtained Ga-67 lung scan in patients with extrathoracic sarcoidosis or with Crohn's disease. These patients did not demonstrate significant Ga-67 lung uptake [8, 12, 14] whereas increased Ga-67 uptake was detected at the sites of granulomatosis involvement suggesting that subclinical alveolar inflammation assessed by BAL was not associated with the development of interstitial granulomatosis inflammation.

Pulmonary scanning was obtained in patients with Crohn's disease including: 1) a ventilatory scan obtained in a sitting position by respiration of gaseous xenon which provided a steady-state ventilation picture; 2) a perfusion scan after slow intravenous perfusion of technetium albumin macroaggregates. The distribution of gaseous xenon and of macroaggregates was pictured so that a centre of gravity of the lung ventilation and of the lung perfusion could be determined; the distance between the two centres of gravity was markedly increased in Crohn's disease when compared to controls because of a decreased perfusion of a higher portion of lung, suggesting that lung parenchyma may be abnormal in Crohn's disease in spite of normal chest roentgenogram. In addition recent reports demonstrated that permeability of the alveolar epithelium determined by the lung to blood clearance of an inhaled radiolabelled molecule ^{99m}Tc-DTPA was severely impaired in patients with coeliac disease [67], Crohn's disease [68], or progressive systemic sclerosis [41]. The defect on lung permeability in asymptomatic patients with normal chest X-rays suggest that there is a defect and/or inflammation in the alveolar membrane which might be due to a primary abnormality or may reflect immune complex damage within the lung, both of which might be expected to cause basement membrane abnormalities.

Pathological findings

Few data are available concerning bronchial and lung parenchymal pathology of asymptomatic patients with systemic disorders without evidence of interstitial lung disease (ILD). In our series, transbronchial lung biopsies were performed in 8 patients with extrathoracic sarcoidosis and 6 patients with Crohn's disease: lymphocytic inflammation without granulomatosis was found in 5 out of 8 patients with extrathoracic sarcoidosis (fig. 5) whereas lung parenchyma was normal in the other patients. In contrast in Crohn's disease, 2 out of 6 patients with lymphocyte alveolitis showed emphysema without lymphocytic inflammation, whereas lung parenchyma was normal in the other subjects. However, it must be pointed out that no open lung biopsy was performed and only small specimens were examined.

BARIFFIE *et al.* [19] documented lymphocyte infiltration of the bronchi of patients with Sjögren's syndrome [19]. FRANK *et al.* [56] demonstrated a high frequency (53%) of lung involvement compatible with abnormalities of diffusion in asymptomatic patients with rheumatoid disease with normal chest roentgenograms. In this study, adequate tissue was obtained from seven of the eight patients who consented to the percutaneous lung biopsy and showed diffuse mild to moderate septal thickening, increased numbers of lymphocytes lying within the alveolar walls and cuboidalization of alveolar lining cells. Recently, lung biopsies were performed in 3 patients with progressive systemic sclerosis and normal chest radiograph [41], demonstrating areas of both fibrosis and interstitial inflammation indistinguishable from abnormalaties described in patients with overt ILD. Taken together, these data are consistent with the hypothesis that an alveolar and interstitial inflammation may be present in asymptomatic patients with collagen-vascular diseases.

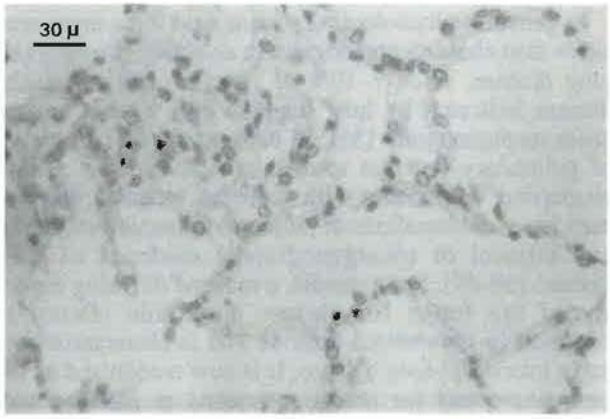

Fig. 5. – Extra thoracic sarcoidosis. Histological section of lung (transbronchial lung biopsy). Giant cells and granuloma are not seen within this area. Alveolitis is characterized by large numbers of lymphocytes and monocytes/macrophages.

Relationship with disease activity

It was tantalizing to hypothesize that subclinical alveolitis was closely related to disease activity. In extrathoracic sarcoidosis, subclinical alveolitis was present as long as extrathoracic lesions persisted; BAL were found to be normal in those patients whose extrathoracic manifestations was spontaneously cured [25]. In Crohn's disease, lymphocyte alveolitis was not correlated with clinical and biological indices of disease activity since lymphocyte alveolitis was present at the same level in the same patients during the course of the disease both in active and in quiescent phase [12, 14]. However, SMIEJAN *et al.* [13] reported an increased frequency of subclinical alveolitis in patients with active Crohn's disease.

In Sjögren's syndrome and in scleroderma, subclinical alveolitis was clearly more frequent in patients with active disease [17, 20]. In rheumatoid arthritis, neutrophil percentages in BAL did not differ significantly between patients with recent or long-term disease duration. Similarly, serum rheumatoid factor titres were unrelated to cell differential abnormalities but interestingly, patients with abnormal serum β-2-microglobulin had significantly more lymphocytes in

Table 4. – Clinical, radiological, functional, pathological and bronchoalveolar lavage findings in one patient with gastric sarcoidosis and with chronic subclinical lymphocyte alveolitis

	Before 84	After 84
Dyspnoea	No	No
Crackles	No	Yes
ACE*	37	33
Chest X-ray	Normal	Diffuse opacities
HRCT-scan	Normal	Diffuse opacities
67-Gallium scanning	Negative	Negative
BAL: Lymphocytes >18%	Yes	Yes
Neutrophilia >4%	No	Yes
CD_4+/CD_8+ >4	No	Yes
TLC <80% of predicted	No	No
FVC <80% of predicted	No	No
DLCO <80% of predicted	No	Yes
Transbronchial biopsies	Nonspecific inflammation	Granuloma and fibrosis

*ACE: angiotensin converting enzyme (normal values 15–35). Lymphocytes, neutrophilia and CD4+/CD8+ ratio were considered as abnormal when found higher than 18%, 4% and 4, respectively. BAL: bronchoalveolar lavage; TLC: total lung capacity; FVC: forced vital capacity; DLCO: diffusing capacity of the lungs for carbon monoxide. Adapted from [69].

BAL than did patients with normal β-2-microglobulin [24].

Relationship with pulmonary outcome

The observation that patients with systemic disorders frequently exhibit a subclinical alveolitis raises the question of whether these people are at risk to develop clinically apparent interstitial lung disease in the future. It is possible that the presence of subclinical alveolar inflammation may identify the patients in whom frank evidence of interstitial lung disease will eventually develop. In our own series, over a 12 month period, no patient with CVD developed clinical pulmonary symptoms or roentgenographic abnormalities. The patients with normal BAL or with subclinical lymphocyte alveolitis did not show significant deterioration over the 12 month period [17].

However, we recently reported one patient with clinically isolated gastric sarcoidosis and chronic subclinical lymphocyte alveolitis regularly followed by sequential BAL, who, after 5 years, developed an overt interstitial lung disease [69]. Characteristics of this patient are summarized in table 4. An increment of CD4+/CD8+ ratio was seen in our patient after 1984 and this may reflect a loss of immune homeostasis which may play a role in granuloma formation and the development of fibrosis. The appearance of alveolar neutrophilia after chronic lymphocyte alveolitis is also of interest: alteration of DLCO was concomitant with the influx of alveolar neutrophils suggesting that accumulation of neutrophils may play a role in the deterioration of lung function [70].

In this context, untreated patients with collagen-vascular diseases who exhibited a neutrophil subclinical alveolitis demonstrated a significant deterioration of pulmonary function tests: 7 out of 10 showed significant decrease of total lung capacity (TLC) and of DLCO compared with their baseline value (more than 10%) [17, 48]. In marked contrast, treated patients with alveolar neutrophilia did not deteriorate in pulmonary function tests (PFT) over the 12 month period: 5 out of 6 showed improvement and 1 was stable. Thus, in our study of patients with collagen-vascular diseases, although we did not find strict individual correlation, baseline value of parameters of subclinical alveolitis assessed by BAL neutrophils appeared closely related to the functional outcome of untreated patients over the subsequent 12 months. These data support the hypothesis that the neutrophil, because of its inflammatory potency, may have a major role in lung derangement [70]. In addition, recent reports suggest that continuous release of both oxidants and fibronectin by activated alveolar macrophages may be of importance in progressive deterioration of pulmonary function [71].

Conclusion

One of the purposes of this review has been to develop the concept that a subclinical alveolitis including an increased number of immune and inflammatory cells and an activated state of effector cells is a frequent finding in the lower respiratory tract of symptomless patients with immunological systemic disorders. However the significance of subclinical alveolar inflammation does not seem to be univocal and varies according to the

disease. Just how often subclinical alveolitis results in overt pulmonary disease is unknown at present, since ILD usually spreads its course over a long time. The fact that pulmonary involvement is rare during the course of extrathoracic granulomatosis like Crohn's disease or primary biliary cirrhosis and that subclinical alveolitis is frequent, suggests that alveolar inflammation may be the expression in the lower respiratory tract of the systemic immune disorder and does not necessarily precede the development of pulmonary granulomatosis. In contrast subclinical alveolitis in collagen-vascular diseases, particularly in progressive systemic sclerosis, is frequently associated with abnormalities of lung parenchyma as assessed by pulmonary function studies and HRCT scan, supporting the hypothesis that subclinical alveolitis may be associated with development of overt interstitial lung disease. Close follow-up of these patients and additional studies are needed to better determine whether subclinical alveolitis is responsible for interstitial lung disease and whether early detection of subclinical alveolitis in immunological systemic disorders may identify those patients that are at risk for the development of interstitial lung disease in the future.

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Revue générale. Alvéolite subclinique dans les maladies systémiques immunologiques. Transition entre santé et maladie. B. Wallaert, M. Dugas, E. Dansi, T. Perez, C.H. Marquette, P. Ramon, A.B. Tonnel, C. Voisin.

RÉSUMÉ: Une alvéolite inflammatoire subclinique, appréciée par l'analyse des cellules du lavage bronchalvéolaire, peut être présente dans une proportion élevée de patients asymptomatiques atteints de maladie systémique immunologique, et dont le cliché thoraciques est normal. L'alvéolaire subclinique peut être caractérisée par la proportion relative des différentes populations cellulaires constitutives de l'alvéolaire et par le degré d'activation de ces cellules. L'alvéolaire subclinique peut être classée en deux groupes majeurs: l'alvéolite lymphocytaire et l'alvéolite neutrophilique. L'alvéolite lymphocytaire est fréquente chez les patients atteints de granulomatose extra-thoracique (maladie de Crohn, cirrhose biliaire primitive, sarcoïdose extra-thoracique) ou dans certained maladies vasculaires du collagène (syndrome de Sjögren, arthrite rhumatoïde, lupus érythémateux disséminé). L'alvéolite neutrophilique est l'observation principle dans les maladies vasculaires du collagène, et principalement la sclérose systémique progressive, la dermato-polymyosite, et les connectivites mixtes. En outre, les macrophages alvéolaires peuvent être spontanément activés et produire divers médiateurs qui poirraient être importants pour la pathogénèse des maladies pulmonaires interstitielles. D'autre part, certaines autres fonctions du macrophage alvéolaire (l'activité anti-bactérienne et/ou la production du facteur de nécrose tumorale) peuvent être sévèrement réduites dans certaines maladies, par exemple dans le lupus érythémateux disséminé. L'inflammation alvéolaire est associée à une augmentation de la perméabilite de la membrane alvéolaire, responsable d'un apport accru de protéines sanguines dans les espaces alvéolaires. Quoique l'inflammation subclinique puisse également être détectée par HRCT scan et/ou par des études scintigraphiques de la perméabilité pulmonaire, la signification et la valeur pronostique en restent peu claires et sont très différentes selon le type de maladie et le type d'alvéolite. *Eur Respir J., 1990, 3, 1206–1216.*