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Bronchoalveolar Lavage and Sampling in Pulmonary Sarcoidosis

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1. Introduction

Sarcoidosis is a multisystem disorder of unknown cause. It commonly affects young and middle-aged adults and frequently it presents with bilateral hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. Other organs may also be involved. The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epitheloid cell granulomas. Granulomas of known causes and local sarcoid reactions must be excluded. Frequently observed immunological features are depression of cutaneous delayed-type hypersensitivity and increased CD4/CD8 ratio at the site of involvement. Circulating immune complexes along with signs of B-cell hyperactivity may also be detectable. The course and prognosis may correlate with the mode of the onset and the extent of the disease. An acute onset with erythema nodosum or asymptomatic bilateral hilar lymphadenopathy usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extrapulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs or other organs. Corticosteroids relieve symptoms, suppress inflammation and granuloma formation (Grutters et al., 2009). Sarcoidosis is the most frequently observed interstitial lung disease of unknown origin in Europe (Müller-Quernheim, 1998). In young adults, pulmonary sarcoidosis is the second most common respiratory disease after asthma (Rothkrantz-Kos, 2003).

The reported prevalence and presenting symptoms of sarcoidosis vary significantly by sex, racial group, and country. The true prevalence of the disease is difficult to assess because a lot of patients are asymptomatic. Estimation of radiographic population screening programmes indicates a global prevalence of 10-40 per 100 000 and an incidence of 10 per 100 000. The incidence appears to be higher in Northern European countries, Japan and African - Americans (Dements, 2001).

Sarcoidosis is a granulomatous disorder resulting from an uncontrolled cell-mediated immune reaction. Following recognition of unknown antigens, the accumulation of immunocompetent cells in the lungs, i.e. alveolitis, occurs. Although lung parenchyma normally contains only a few lymphoid elements, lymphocyte populations are strikingly compartmentalized in air spaces and interstitium in sarcoidosis. The infiltration of activated CD4 positive T-cells represents the immunological hallmark of sarcoidosis. However, many types of other immune cells, such as macrophages, are involved in the inflammatory

response of the disorder. In the lung, this accumulation in both air spaces and interstitium (alveolitis) precedes and accompanies the development of granulomas (Semenzato, 2005).

Sarcoid granulomas are immune granulomas resulting from a specific cell-mediated immune response to an antigenic antigen. The granulomas of sarcoidosis are well-formed, compact aggregates. They usually are of varying age, ranging from highly cellular lesions to collections with diminishing cellularity, some fibrosis and progressive hyalinization. Two characteristic zones can be seen in a typical, well-developed sarcoid granuloma: 1) a central zone or follicle, which is tightly packed with cells composed primarily of macrophages, multinucleated giant cells and epitheloid cells; 2) a peripheral zone consisting of a collar of loosely arranged lymphocytes, monocytes and fibroblasts. Although many microscopic features may suggest sarcoidosis, the epitheloid granulomas, especially in their earlier stages, are indistinguishable from those of other idiopathic granulomatous disorders or even granulomatous disorders of known origin, such as berylliosis, tuberculosis or hypersensitivity pneumonitis (Müller-Quernheim, 1998).

Sarcoidosis is a worldwide disease with a lifetime incidence rate of 0.85-2.4 %. It generally affects 25-40-year-old people. The clinical phenotype of sarcoidosis can be extremely diverse in terms of presentation, involved organs, duration and severity. Lung involvement is present in 86-92 % of cases according to the chest X-ray, alone or in association with extrapulmonary localizations in about 50 % of cases (Nunes, 2005). International pulmonary registries have illustrated differences in the presentation of sarcoidosis in different countries: in Asia the majority of cases presented with a radiological stage I, and a positive tuberculin skin test was found more frequently than in other countries. However, erythema nodosum has not been reported among the Japanese, is rare among African-Americans, it is the presenting symptom in 18% of cases in Finland and occurs in about 30% of British sarcoidosis patients (Dements, 2001).

Clinical features of sarcoidosis are varied. It may manifest as an acute form (Löfgren's syndrome), chronic sarcoidosis or asymptomatic disease that may be found accidentally. However, even an acute form (e.g. erythema nodosum and joint pain) of disorder, which is the most typical clinical feature of sarcoidosis, is a nonspecific one (Bourke, 2006).

There are five radiologic stages (forms) of intrathoracic changes of sarcoidosis: stage 0, normal chest radiograph; stage 1, only lymphadenopathy; stage 2, lymphadenopathy with parenchyma infiltration; stage 3, only parenchymal disease; stage 4, pulmonary fibrosis (Koyama, 2004). Sarcoidosis may present at any stage. However, a great variation of radiologic appearance in each stage has been noticed. Radiographic features of sarcoidosis may be atypical, especially in older patients (Conant, 1988). Pulmonary sarcoidosis radiologically may be indistinguishable from tuberculosis, lymphangitic carcinomatosis, pulmonary metastases or metastatic lymphadenopathy (Heo, 2005; Kaira, 2007; Thomas 2008). Furthermore, subtle radiologic changes in sarcoidosis (e.g. presence of subpleural micronodules or mild intrathoracic lymphadenopathy) may be similar to those present in healthy adults, especially smokers and/or residents of urban areas (Remy-Jardin, 1990).

Histological features of the disease are varied (Rosen, 1978). Non-necrotising granuloma, a hallmark of morphologic appearance of the disease, is not unique for sarcoidosis. The granulomas in tuberculosis, extrinsic allergic alveolitis (hypersensitivity pneumonitis) and chronic beryllium disease are often identical to those of sarcoidosis (Williams, 1967; Popper, 1999). Even if the pathologic diagnosis of sarcoidosis is confirmed by biopsy, this may not confirm that all the lesions appear because of sarcoidosis (Kaira, 2007). Usage of needle

aspirate, either transbronchial or percutaneous, provides support but never an absolute proof of diagnosis (Baughman, 2000). Sarcoid-like reactions have been reported to be associated with carcinoma and lymphoma (Brincker, 1986; Laurberg, 1975; Tomimaru, 2007). Bronchoalveolar lavage (BAL) is a method of sampling fluid and cells from a large area of the lung tissue by instilling and aspirating saline via a bronchoscope wedged in bronchi. BAL as a method of sampling cells is very useful in the diagnosis and differential diagnosis of sarcoidosis (Drent, 1993; Welker, 2004). High lymphocytosis and CD4/CD8 ratio in bronchoalveolar lavage fluid (BALF) are the main features of sarcoidosis (Poulter, 1992). In patients with a clinical picture typical for sarcoidosis, an elevated CD4/CD8 ratio in BAL fluid may confirm the diagnosis and obviate the need for biopsy (Costabel, 2001; Kvale, 2003). However, CD4/CD8 ratio in BALF is highly variable (Kantrow, 1997). BALF cell patterns, including CD4/CD8 ratio are related to radiographic stage, clinical symptoms of sarcoidosis and previous empiric treatment with corticosteroids. Optimal cutoff point for CD4/CD8 ratio is different in various manifestations of sarcoidosis (Danila et al., 2008, 2009).

Diagnosis of sarcoidosis requires a compatible clinical and radiologic picture. However, there are no specific diagnostic tests and sarcoidosis is therefore a diagnosis of exclusion (Boer, 2010). The diagnosis of sarcoidosis must always be based on summation of clinical and radiological symptoms, results of BALF examination and other findings, which include data of histological examination of the lung or lymph node biopsy material if necessary.

In this chapter the diagnostic role of bronchoalveolar lavage and other sampling methods (including endobronchial biopsy, bronchoscopic lung biopsy, transbronchial lymph node biopsy and mediastinoscopy) in various clinical situations are discussed.

2. Bronchoalveolar lavage

2.1 History of bronchoalveolar lavage

Bronchoalveolar lavage was first used at Yale in 1922 in the management of phosgene poising. This approach has been extended to cystic fibrosis and alveolar proteinosis. In 1961, Myrvik showed how this simple lavage procedure could be used in rabbits to obtain lung macrophages. This seminal observation spawned new discipline, pulmonary cell biology (Gee & Fick, 1980). With the introduction in the mid-1960's of the design of the fiberoptic bronchoscope into clinical medicine by S. Ikeda, bronchoalveolar lavage was widely used for clinical investigations and diagnostic purposes (Zizel & Müller-Quernheim, 1998). Bronchoalveolar lavage was adapted to fiberoptic bronchoscopy by Reynolds and Newball in 1974 (Winterbauer et al., 1993). Bronchoscopy and lavage procedure have been a great stimulus for lung research to have access to normal and disease-affected airways and alveolar surfaces for direct samples (Reynolds, 1992). The observation of characteristic changes in the cytology of the BAL fluid in interstitial lung diseases were first reported by Hunninghake and Crystal in 1981 (Müller-Quernheim, 1998). With the widespread use of fibreoptic bronchoscopy for diagnostic evaluation of patients with interstitial lung diseases, bronchoalveolar lavage has also become part of the procedure (Reynolds, 1992).

2.2 Technique of bronchoalveolar lavage

After the fiberoptic bronchoscope has been inserted and the search for abnormalities in the respiratory tract is complete, the tip of the bronchoscope should be advanced into the

desired bronchus as far as possible until well wedged. Biopsy and brushing should be avoided before BAL. The right middle lobe or the lingula of the left lung are the preferred sites for BAL (Emad, 1997). From these lobes, almost 20 % of more fluid and cells are recovered than from the lower lobes. However, in cases of predominant infiltrates in other lobes (e.g. upper lobe), bronchaolaveolar lavage should be done in these lobes or multiple lung segments (Cantin et al., 1983; Ziora et al. 2001).

The fluid used to perform bronchoalveolar lavage is isotonic 0,9 % NaCl solution suitable for intravenous use. Saline fluid is instilled through the working channel of the fiberoptic bronchoscope as a bolus with syringe with aliquots of 20 ml to 100 ml. The volume infused ranges from 100 ml to 300 ml. Overall, the amount of BAL fluid collected is about 40-60 % of the volume instilled (Klech & Pohl, 1989). The first neutrophil-rich aliquot, which contains the airways sample, is usually excluded from analysis of BALF differential cell count.

The information about cell types obtained in volumes of 100-250 ml is comparable, supposedly that cell populations obtained from volumes excess of 120 ml will not add to diagnostic accuracy. In most patients with sarcoidosis lavage at one site gives sufficient clinical information (Klech & Pohl, 1989; Winterbauer et al., 1993).

After measuring the recovered volume and performing total cell counts, the normal method of processing the cells from the BALF for differential counting is to prepare cytospins. The differential counts are assessed by viewing with a light microscope and counting at least 300-500 cells (Klech & Pohl, 1989). Lymphocyte subsets (CD4 and CD8) are evaluated usually using flow cytometry.

2.3 Cellular components of bronchoalveolar lavage fluid in healthy persons

The alveolar macrophages constitute the largest cell population in BALF, about 80-95 % of total recovered cells. Lymphocytes are the second major cell population in BALF .Other cells found in lavage fluid include neutrophils, occasional eosinophils, basophils and mast cells. For practical reasons the following percentages can be expected as normal within nonsmokers: lymphocytes < 20 %, neutrophils < 5 %, eosinophils < 0.5 %. T lymphocytes are the main lymphocytes, and the ratio of T-helper to T-suppressors (CD4/CD8) is approximately 1.0-3.5. Smokers usually have a decreased percentage of lymphocytes and decreased CD4/CD8 ratio (Klech & Pohl, 1989; Zizel & Müller-Quernheim, 1998).

2.4 Cellular components of bronchoalveolar lavage fluid in sarcoidosis

Bronchoalveolar lavage is thought to mirror parenchymal inflammation in the interstitial lung diseases. In sarcoidosis BAL recovers activated lymphocytes and alveolar macrophages, which are the precursors of granuloma formation (Hendricks et al., 1999). A distinct compartmentalization to the lungs of CD4 T cells has been already found in the early 1980s. The characteristic finding of lung-accumulated CD4 T cells in sarcoidosis and resulting increase in the BAL fluid CD4/CD8 ratio has come to be a clinically important marker of the disease and is used for diagnostic purposes (Grunewald & Eklund, 2007). However, cellular components and T lymphocyte profiles are related to clinical presentation, radiological stage, smoking status, and previous treatment with corticosteroids (Danila et al., 2008, 2009). Therefore, the CD4/CD8 ratio in BAL fluid may be highly variable (Kantrow et al., 1997). It should be remembered that advanced sarcoidosis may present with no increase in numbers of BAL fluid lymphocytes, and CD4/CD8 ratio can be normal.

Patients with erythema nodosum and/or arthralgia show the most marked characteristics of alveolitis, including increased percentages of T lymphocytes, the highest CD4/CD8 ratios (up to 30) in BALF samples (Ward et al., 1989; Drent et al., 1993). However, asymptomatic sarcoid patients have significantly lower BAL fluid lymphocytosis and CD4/CD8 ratio comparing with non-treated patients with sarcoidosis-related symptoms. Moreover, previously corticosteroid-treated symptomatic patients have lower BALF lymphocytosis and CD4/CD8 ratio compared to non-treated symptomatic patients (Danila et al., 2009). The increase of the macrophage and neutrophil count, decrease of lymphocyte count and CD4/CD8 ratio with increased radiographic stage of sarcoidosis in BAL fluid in patients with newly diagnosed sarcoidosis have been documented (Danila et al., 2008).

Spontaneous macrophage-lymphocytes rosettes (adherence of lymphocytes to alveolar macrophages) in BALF from active sarcoid patients have been found, probably due to active antigen presentation at the focus of inflammation (Reynolds, 1992). Macrophage-lymphocyte rosettes and giant cells (elements of immune granuloma) are found more often in BAL fluid of symptomatic patient groups compared to asymptomatic patients (Danila et al., 2008). A case of severe pulmonary sarcoidosis with intact granulomas in BAL fluid was described in medical literature (Hendricks et al., 1999). These findings may reflect still on-going inflammation in lung parenchyma.

Acute onset of the disease and high CD4/CD8 ratio is associated with good prognosis. On the other hand, increased neutrophil counts are associated with a more advanced, chronic disease course, impaired lung function, poor response to corticosteroid treatment and persisting abnormal chest radiographs. It is supposed that an increased percentage of BAL fluid neutrophils and eosinophils reflect an ongoing inflammatory process, which may result in progressive loss of lung parenchyma (Lin et al., 1985; Dren et al., 1999; Ziegenhagen et al., 2003). However, BALF lymphocyte count at diagnosis is not a valuable prognostic factor in patients with newly diagnosed sarcoidosis (Greening et al., 1984; Laviolette et al., 1991). Moreover, high lymphocyte count and high CD4 lymphocyte count (as percentage of lymphocytes) reflect an intense alveolitis at the time of the procedure, but they are not indicators of poor prognosis on which therapeutic decisions can be based (Verstraeten et al., 1990) and may be a favorable prognostic factor for lung function in pulmonary sarcoidosis (Foley et al., 1989).

Sarcoidosis patients may present with extrapulmonary lesions due to the multisystem character of the disease. In patients presenting with extrapulmonary sarcoid lesions interstitial pulmonary changes with or without hilar adenopathy may be present. There may be a normal chest X-ray film, but conclusions from roentgenographic examination may underestimate the alveolitis already present. Moreover, typical sarcoid changes in BAL fluid samples can be found even without lung field involvement shown by high-resolution computed tomography, for example in patients with only ocular findings (ocular sarcoidosis) (Hoogsteden et al., 1988; Takahashi et al., 2001).

Cigarette smoking modifies the immunologic BAL fluid sample profile and alveolitis is found to be less pronounced in smokers. Smoking results in increased total cell counts, increased CD8 lymphocytes, and less increased CD4/CD8 ratios in the BAL fluid samples in sarcoid patients. CD4/CD8 ratios are lower in smoking than in non-smoking patients (Valeyre et al., 1988; Drent et al., 1993).

2.5 Clinical role of bronchoalveolar lavage in pulmonary sarcoidosis

Several groups of investigators examined diagnostic value of the CD4/CD8 ratio of BAL lymphocytes for differentiating sarcoidosis from other causes of lung diseases. Costabel *et al.* reported that a ratio of 3.5 or greater had a sensitivity of 52 % and specificity of 94 % in 117 consecutive patients with biopsy-proven sarcoidosis (Costabel et al., 1992). Winterbauer *et al.* described that a ratio of 4.0 or greater distinguished patients with sarcoidosis from patients with other interstitial lung diseases with a sensitivity of 59 % and a specificity of 96 % (Winterbauer et al., 1993). Thomeer & Demedts found that a CD4/CD8 ratio of greater than 4.0 had a sensitivity of 55 % and a specificity of 94 % (Thomeer & Demedts, 1997). Welker *et al.* found that when the CD4/CD8 ratio is combined with lymphocyte and granulocyte numbers, the probability of sarcoidosis could exceed 85 % (Welker et al., 2004).

Group	Selected cutoff	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV %	NPV %
All patients	3.5	80	90	96	64
	4.0	76	93	97	59
	5.0	66	95	97	50
	8.0	58	99	99	37
	10.0	26	100	100	33
Asymptomatic	3.5	62	90	86	68
	4.0	57	93	89	67
	5.0	49	97	94	62
	8.0	21	99	99	54
	10.0	10	100	100	51
Symptomatic non-treated	3.5	86	90	92	90
	4.0	84	93	94	85
	5.0	81	95	95	79
	8.0	52	99	98	61
	10.0	37	100	100	55
Symptomatic treated	3.5	83	91	73	94
	4.0	77	93	77	93
	5.0	70	96	86	91
	8.0	50	99	98	85
	10.0	33	100	100	83

CI – confidence interval. PPV – positive predicted value. NPV – negative predicted value.

Table 1. Diagnostic value of sarcoid patients' bronchoalveolar lavage fluid CD4/CD8 ratio in relation to clinical symptoms (Danila et al., 2009)

Comparable results were reported by other authors (Fireman et al., 1999). CD4/CD8 ratio of less than 1.0 virtually excludes the diagnosis of sarcoidosis (Winterbauer et al., 1993).

We have found that optimal cutoff points for CD4/CD8 ratio are 3.5 and 4.0 for asymptomatic and symptomatic patients, respectively (Danila et al., 2009). Sensitivity of the optimal cutoff points (3.5 and 4.0) of CD4/CD8 ratio were lower in the asymptomatic patient groups compared to the symptomatic (non-treated and treated) patients. Sensitivity of the optimal cutoff points decreased with increased stage of sarcoidosis. The values of sensitivity, specificity and predicted values are presented in Tables 1 and 2. Normal BALF

cell counts were found in 7 % of 318 consecutive sarcoid patients with newly diagnosed disease. However, typical sarcoid BAL fluid cellular pattern (lymphocytosis and CD4/CD4 >3.5) was found in 6.2 % of all control subjects. Additionally, in 3.8 % of all control subjects BALF CD4/CD8 ratios of more than 3.5 without lymphocytosis were found.

Maximum value of BALF CD4/CD8 ratio for non-sarcoid subjects was 5.6, except for one patient with non-Hodgkin's lymphoma of low-grade malignancy (CD4/CD4 ratio = 8.8). According to the world-leading expert in interstitial lung disorders Professor U. Costabel examination of bronchoalveolar lavage fluid may be of diagnostic value in sarcoidosis, obviating need of biopsy in 40-60 % of patients (Costabel, 1997). The author's experience is in agreement with this statement. Having in mind that significant part of sarcoid patients, at least in European countries, manifested with an acute form of the disease (Löfgren's syndrome of fever, erythema nodosum, arthralgias, and bilateral hilar lymphadenopathy), even more of the patients due to very typical clinical-radiological symptoms and signs may obviate need of biopsy.

Group	Selected cutoff	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV %	NPV %
Stage 1	3.5	88	90	94	81
	4.0	85	92	95	77
	5.0	78	96	97	69
	8.0	47	99	99	52
	10.0	33	100	100	46
Stage 2	3.5	74	91	84	83
	4.0	69	92	87	80
	5.0	57	95	89	78
	8.0	25	99	95	67
	10.0	18	100	100	65
Stage 3	3.5	46	90	59	85
	4.0	42	92	64	84
	5.0	34	96	66	83
	8.0	15	99	95	80
	10.0	5	100	100	77

CI – confidence interval. PPV – positive predicted value. NPV – negative predicted value.

Table 2. Diagnostic value of sarcoid patients' bronchoalveolar lavage fluid CD4/CD8 ratio in relation to a Stage (Danila et al., 2009)

So CD4/CD8 ratio has an important role in personal diagnostic algorithms of many clinicians, although the best use of this test requires considerable experience in its application (Wells, 2010). In summary, an increased lymphocyte count with CD4/CD8 ratio > 3.5 is regarded as typical for pulmonary sarcoidosis, and is considered generally sufficient to secure the diagnosis of sarcoidosis in the appropriate clinical setting (Spagnolo et al., 2009).

2.6 Side-effects of bronchoalveolar lavage
One of the reasons why bronchoalveolar lavage is enjoying its general acceptance among scientists and clinicians is its noninvasiveness. This makes bronchoalveolar lavage possible

to perform in virtually all patients with few exceptions. Bronchoalveolar lavage is a very safe procedure. Serious complications like significant bleeding, pneumothorax and other are extremely rare (Klech et al., 1992). Fever occurred some hours after BAL in about one fifth of all patients that underwent the procedure. Side-effects can be minimized by not exceeding lavage volume of 250 ml (Klech & Pohl, 1989). At the Department headed by the author only one serious complication of bronchoalveolar lavage (performed in a patient with tuberculosis) – pneumothorax, occurred during the last fifteen years. So, the rate of serious complications is extremely small, less than 0.1 %. Usually we do not perform BAL in patients with blood platelet count below 20000 / µl. Through its safety bronchoalveolar lavage does not raise any special ethical considerations (Rennard et al., 1992).

3. Endobronchial biopsy

3.1 Airway involvement in sarcoidosis
Bronchoscopic abnormalities have been observed in up to 60 % of patients with sarcoidosis (Shorr et al., 2001). These include "retinalization" of mucosa from increased mucosal vascularity, mucosal coarseness, pallor, flat yellow mucosal plaques, wartlike excrescences, "bleb-like" formations, irregular mucosal thickening, ulceration, and atrophic mucosa. The three common findings were bronchial mucosal hyperemia or edema, distortion of the bronchial anatomy, and bronchial narrowing (due to extrinsic compression of airways by the enlarged lymphnodes, various types of mucosal involvement or airway distortion caused by parenchymal changes). The classic endobronchial sarcoidosis is characterized by mucosal islands of waxy yellow mucosal nodules, 2 to 4 mm in diameter. Bronchoscopy may reveal endobronchial occlusion by sarcoid granulomas in the submucosa or an endobronchial polyp caused by sarcoid granulomas. Lobar, segmental, subsegmental, and more distal bronchi as well as bronchioles are affected more frequently than the trachea and main bronchi (Polychronopoulos & Prakash, 2009). Rarely, sarcoidosis manifested with endoluminal stenosis of proximal bronchi (Chambellan et al., 2005). The presence of endobronchial sarcoid lesions significantly increases the risk for airway obstruction and airway hyperreactivity in patients with sarcoidosis (Lavergne et al., 1999; Shorr et al., 2001).

3.2 Technique of endobronchial biopsy
After satisfactory anesthesia is established, the lesion is visualized, biopsy forceps are passed through the working channel of the fiberoptic bronchoscopy until the forceps are just beyond the tip of the bronchoscope. The forceps are opened, advanced into the area to be biopsed, and closed firmly. The forceps should be withdrawn slowly to avoid its slipping from the tissue. The forceps may then be withdrawn through the bronchoscope (Cortese & McDougall, 1994). Biopsy is taken from most prominent lesions. If bronchial mucosa seems normal, biopsy is usually taken from the carina of segmental, subsegmental or subsubsegmental bronchus. Usually from 4 to 6 biopsy samples are taken.

3.3 Diagnostic yield of endobronchial biopsy in sarcoidosis
Although airway appearance affects the results of endobronchial biopsy (EBB), this biopsy technique may demonstrate non-necrotizing granulomas even if the airways are normal on visual inspection. EBB resulted in diagnostic tissue in 50-70 % of cases (Puar et al., 1985; Shorr et al., 2001). The results of EBB correlated with airway appearance. EBB result is more

likely to be positive if the endobronchial mucosa is abnormal. However, a normal-appearing airway mucosa does not exclude the presence of granulomas. EBB is positive in approximately 35 % of subjects with normal airway mucosa. Endobronchial biopsy increased in about 20 % in diagnostic value of fiberoptic bronchoscopy (Shorr et al., 2001).

3.4 Side-effects of endobronchial biopsy
Endobronchial biopsy is an extremely safe procedure. To the best of the author's knowledge there are no publications addressed specifically to the side-effects to endobronchial biopsy in sarcoidosis. The risk of the major complications during endobronchial biopsy, such as significant bleeding, is extremely small when a patient's blood platelets count is 50000 /μl or more. However, it should be remembered that massive or even fatal bleeding may occur after endobronchial biopsy in case of an abnormal bronchial artery of Dieulafoy's disease of the bronchus (Sweerts et al., 1995; Werf et al., 1999; Maxeiner, 2001; Stoopen et al., 2001), which may appear as submucosal smooth elevated non-pulsating lesion. At the Department for which the author works only one massive bleeding after endobronchial biopsy (presumably due to abnormal located bronchial artery) occurred during the last twenty years. There happened no other with endobronchial biopsy associated to serious complications during this period. Thus, the rate of serious complications after this procedure is less than 0.05 %.

4. Bronchoscopic lung biopsy

4.1 History of bronchoscopic lung biopsy
The ability to obtain lung tissue without subjecting a patient to an open lung biopsy is a major advance in diagnostic bronchoscopy. Bronchoscopic lung biopsy (also named as transbronchial lung biopsy) was first performed by H. Andersen in 1963, using the rigid bronchoscope. In 1974 first results of the BLB via the flexible bronchoscope were published (McDougall & Cortese, 1994). After introduction of the fiberoptic bronchoscope into clinical practice, bronchoscopic lung biopsy (BLB) during fibrobronchoscopy became a standard procedure. BLB is utilised to sample alveolar parenchyma beginning at the bronchiolar, noncartilaginous segment of the airway (Leslie et al., 2000).

4.2 Technique of bronchoscopic lung biopsy
After the inspection of the tracheobronchial tree, a bronchoscope is inserted to subsegmental or smaller bronchus until the wedging position. Under fluoroscopic control, biopsy forceps (a crocodile type biopsy forceps are usually used) are pushed forward until a peripheral position. The position of biopsy forceps is controled by two directions of chest fluoroscopy. Afterwards, the forceps are withdrawn about 2-3 cm, then opened and pushed forward. Usually this maneuver is repeated once or twice, and then the forceps are closed and withdrawn. If the patient indicates ipsilateral chest or shoulder pain then forceps are closed, and should be opened and withdrawn a few centimeters before closing or introducing to other segment or subsegment of the lung. The bronchoscope should not be removed from a wedge position until there is no evidence of significant bleeding. The BLB is usually performed after a patient's inhale (Zavala, 1978; McDougall & Cortese, 1994; Dierkesmann & Dobbertin, 1998). In the Department for which the author works for about 6 biopsies are performed in cases of suspected sarcoidosis. Most of the samples are of 1-3 mm in diameter.

4.3 Diagnostic yield of bronchoscopic lung biopsy in sarcoidosis

The specimens obtained during bronchoscopic lung biopsy are small, but in most cases permit accurate histological diagnosis. Although some authors (Roethe et al., 1980) indicated that 10 are optimal for obtaining the diagnosis in stage I and 5 biopsies in stages II and III. Most investigators (*Gilman & Wang, 1980;* Harber, 1981, Cavazza et al., 2009*)* found that 3-5 biopsies are enough when biopsy is performed by an experienced bronchoscopist.

Bronchoscopic lung biopsy has diagnostic yield of 50 % to 97 % (Mitchell et al., 1980; Roethe et al., 1980; Puar et al., 1985; Leonard et al., 1997; Boer et al., 2009). Density of the granulomas in the lung is not uniform (Rosen et al., 1977). Rosen et al. have found that nongranulomatous, nonspecific interstitial pneumonitis were predominant or prominent histopathologic findings in 62% of 128 granuloma-containing specimens from open lung biopsies obtained from patients with sarcoidosis (Rosen et al., 1978). Diagnostic accuracy is increased when biopsy is taken from the lobes with predominant involvement by chest X-ray or computed tomography scanning (Roethe et al., 1980; Boer et al., 2009).

Although the rate of positive findings on BLB is high among patients with sarcoidosis who have radiological evidence of pulmonary infiltration, it is also high (about 60 %) among patients with or even without hilar lymphadenopathy whose chest radiographs show normal lung fields (Mitchell et al., 1980; Ohara et al., 1993).

A generous transbronchial biopsy may show numerous compact, coalescent, non-necrotizing granulomas embedded within hyaline collagen, i.e. features almost diagnostic of sarcoidosis. Frequently, however, not only bronchial but also transbronchial biopsies show just a tiny granuloma, or even a single giant cell or a Schaumann body, that may be enough for the diagnosis but require a more robust clinical support. Sarcoid granulomas, although classically non-necrotizing, may show necrosis. It generally consists of tiny foci of central fibrinoid ("rheumatoid-like") necrosis, but rarely larger areas of fibrinoid, infarct, or suppurative ("Wegener-like") necrosis may be seen (Cavazza et al., 2009*)*.

Two characteristic zones can be seen in a typical, well-developed sarcoid granuloma: 1) a central zone or follicle which is tightly packed with cells composed primarily of macrophages, multinucleated giant cells and epitheloid cells; 2) a peripheral zone consisting of a collar of loosely arranged lymphocytes, monocytes and fibroblasts. Taken alone granulomas do not confirm the diagnosis of sarcoidosis, since it may also occur in tuberculosis, lymphoma or other malignant disease, berylliosis, brucellosis, extrinsic allergic alveolitis, histoplasmosis, collagen disorders, and other (Müller-Quernheim, 1998).

Specificity of noncaseating epithelioid cell granuloma in transbronchial biopsy for the distinction between sarcoidosis and other forms of diffuse lung disease may be high – about 90 % (Winterbauer et al., 1993). However, specificity of noncaseating granuloma may be less in countries with moderate or high prevalence of pulmonary tuberculosis. Our findings show that the sensitivity of non-necrotizing epithelioid cell granuloma in bronchoscopic biopsy for the diagnosis of sarcoidosis is high (94 %), as well as the negative predictive value (92 %) of this type of epithelioid cell granuloma for the exclusion of sarcoidosis. However, the specificity of epithelioid cell granuloma without necrosis in our investigated group was relatively low-only 60 %. We have found a significant overlap in types of granulomatous inflammation between tuberculosis and sarcoidosis. Moreover, non-necrotizing granulomas were found in several cases of adenocarcinoma and hematological disorder (Danila & Žurauskas, 2008).

4.4 Side-effects of bronchoscopic lung biopsy

Bronchoscopic lung biopsy is a relatively safe diagnostic method. The pneumothorax rate after BLB is 1-5% (Zavala, 1978; Cortese & McDougall, 1997; Becker et al., 1998; Ensminger & Prakash, 2006). Bleeding after the BLB for carefully selected patients is rare and not intensive. Life-threatening haemoptysis occurred in 2-5% of the BLB (Cortese & McDougall, 1997; Dierkesmann & Dobbertin, 1998). Lethal outcome mostly due to the massive bleeding, or pneumothorax, is rare, and it occurred in 0-0.2% of the cases (Schulte & Costabel, 1998).Uremia increased the risk of bleeding.

In author's institution of all the bronchoscopic lung biopsies, serious complications occurred in 2.6 % patients. Clinically significant pneumothorax requiring chest tube treatment occurred in 1.6 % patients. Non-significant pneumothorax not requiring the chest tube treatment occurred in 0.7% patients. Severe bleeding occurred in 1 % out of all BLBs. In all the cases the bleeding was stopped during the same procedure, after the bronchoscope tip in bronchus was occluded for several minutes (Danila et al., 2008). There was no lethal outcome related to BLB performed to more than 500 patients during the last fifteen years.

5. Transbronchial needle aspiration biopsy and endosonography guided needle aspiration biopsy

5.1 Standard transbronchial needle aspiration biopsy

The history of transbronchial needle aspiration (TBNA) goes back to 1949 when Eduardo Schieppat presented his new technique of endoscopical puncturing mediastinal lymph nodes across the tracheal spur (Leonard et al., 1997). In 1978, Wang with colleagues first described needle aspiration of paratracheal masses. In 1979, Oho and colleagues reported use of the first needle adapted for the flexible bronchoscope (Midthun & Cortese, 1994). To obtain cytology specimens, 20–22-gauge needles are usually used, while 19-gauge needles are needed to obtain a "core" of tissue for histology. TBNA can be performed safely and successfully during routine flexible bronchoscopy under local anaesthesia.

Selection of the proper site for needle insertion to increase diagnostic yield may be facilitated by reviewing the CT scan of the chest. The bevelled end of the needle must be secured within the metal hub during its passage through the working channel. The needle is advanced and locked in place only after the metal hub is visible beyond the tip of the working channel. The catheter can then be retracted, keeping the tip of the needle distal to the end of the fibrebronchoscope. The scope is then advanced to the target area and the tip of the needle is anchored in the intercartilaginous space in an attempt to penetrate the airway wall as perpendicularly as possible. With the needle inserted, suction is applied at the proximal port using a syringe. Aspiration of blood indicates inadvertent penetration of a blood vessel. In this case, suction is released, the needle is retracted and a new site is selected for aspiration. When there is no blood in the aspirate, the catheter is moved up and down with continuous suction, in an attempt to shear off cells from the mass or lymph node. The needle is withdrawn from the target site after the suction is released (Herth et al., 2006). Three to five passes in each location are recommended (Tremblay et al., 2009). Whenever possible, sampling of more than one nodal station is advised to increase diagnostic yield (Trisolini et al., 2008).

The diagnostic yield of conventional TBNA ranges from 54 % to 90 % (Wang et al., 1989; Trisolini et al., 2003; Oki et al., 2007; Trisolini et al., 2008; Tremblay et al., 2009).

5.2 Endobronchial ultrasonography guided transbronchial needle aspiration biopsy

The integration of ultrasound technology and flexible fibrebronchoscopy – endobronchial ultrasound (EBUS) enables imaging of lymph nodes, lesions and vessels located beyond the tracheobronchial mucosa. Recently real-time EBUS-TBNA became possible (Herth et al., 2006). EBUS-TBNA is able to sample stations that may be difficult to reach by mediastinoscopy, such as hilar nodes and posterior carinal nodes (Wong et al., 2007). EBUS-TBNA is usually performed under local anaesthesia and conscious sedation using midazolam. TBNA is performed by direct transducer contact with the wall of the trachea or bronchus. When a lesion is outlined, a 22-gauge full-length steel needle is introduced through the biopsy channel of the endoscope. Power Doppler examination may be performed before the biopsy to avoid unintended puncture of vessels. Under real-time ultrasonic guidance, the needle is placed in the lesion. Suction is applied with a syringe, and the needle is moved back and forth inside the lesion (Herth et al., 2006). Three to five passes in each location are recommended (Tremblay et al., 2009).

The diagnostic yield of EBUS-TBNA ranges from 83 % to 96 % (Wong et al., 2007; Garwood et al., 2007; Tremblay et al., 2009). The diagnostic yield significantly increased following the interpretation of the specimens by cytopathologist with expertise in lung disease for both standard and EBUS-guided TBNA (Tremblay et al., 2009).

Both conventional and EBUS-guided TBNA are safe procedures with rare complications, reported as pneumothorax, pneumomediastinum, haemomediastinum, bacteraemia and pericarditis (Herth et al., 2006; Wong et al., 2007; Garwood et al., 2007; Tremblay et al., 2009; Varela-Lema et al., 2009; Tournoy et al., 2010).

5.3 Endosonography guided needle aspiration biopsy

Initially designed for the staging of gastrointestinal malignancies, transoesophageal ultrasound-guided fine needle aspiration (EUS-FNA) has proven to be an accurate diagnostic method for the diagnosis and staging of lung cancer and the assessment of sarcoidosis. Lymph nodes in the following areas can be detected by EUS: paratracheally to the left (station 4L); the aortopulmonary window (station 5); lateral to the aorta (station 6); in the subcarinal space (station 7); adjacent to the lower oesophagus (station 8); and near the pulmonary ligament (station 9) (Herth et al., 2006). Usually, EUS-FNA is incapable of reaching lymph nodes located in the anterior mediastinum and the rest of the thorax beyond the mediastinum (Wong et al., 2007).

EUS-FNA is usually performed under local anaesthesia and conscious sedation using midazolam. The echo-endoscope is initially introduced up to the level of the coeliac axis and gradually withdrawn upwards for a detailed mediastinal imaging. Since the ultrasound waves are emitted parallel to the long axis of the endoscope, the entire needle can be visualised approaching a target in the sector-shaped sound field. Pulse and color Doppler ultrasonography imaging can be performed in cases of suspected vascular structures. For the aspirations, 22-gauge needles are standard, although smaller (25-gauge) and larger needles (19-gauge) can be used as well (Herth et al., 2006).

The diagnostic yield of EUS-FNA is of about 80 % (Annema et al., 2005), sensitivity of 89-100 % and specificity of 94-96 % (Fritscher-Ravens et al., 2000; Wildi et al., 2004).

EUS-FNA is a safe procedure with rare complications (Wildi et al., 2004; Annema et al., 2005).

It should be noted that the presence of non-necrotizing epitelioid granulomas in the specimens of the lymph nodes is not diagnostic *per se* for sarcoidosis. Specificity of the non-necrotizing epitelioid granulomas depends on prevalence of sarcoidosis and other granulomatous disorders (such as tuberculosis) in a specific geographic region.

6. Mediastinoscopy

Mediastinoscopy is a common procedure used for the diagnosis of thoracic disease and the staging of lung cancer. Since its introduction by Carlens in 1959, mediastinoscopy has become the standard to which all other methods of evaluating the mediastinum are compared (Hammound et al., 1999). Mediastinoscopy is effective in assessment of the mediastinum. Porte et al. have found that sensitivity of the mediastinoscopy was 97 % in 400 mediastinoscopes performed in 398 patients with undiagnosed mediastinal lesions (Porte et al., 1998). It is important to remember that non-necrotizing epitelioid cell granulomas may be related to carcinoma of the lung and other malignant disease. Sarcoid reactions in malignant disease appear in close association with tumors, in regional lymph nodes, or in more distant locations. They have been reported to occur in a variety of malignant diseases, with particularly high incidences in lymphoproliferative disorders (Laurberg, 1975; Brincker, 1986; Segawa et al., 1996; Tomimaru et al., 2007).

Mediastinoscopy is more invasive diagnostic method for sampling of the mediastinal lymp nodes comparing with transbronchial or transoesophageal ultrasound-guided fine needle aspiration. Carried out under general anaesthesia, it is costly, requires in-patient care (Hammound et al., 1999). Although, mediastinoscopy is a safe procedure (Venissac et al., 2003; Karfis et al., 2008), death related to mediastinoscopy is described in medical literature (Lemaire et al., 2006).

7. Diagnostic approach in suspected sarcoidosis

Presentation of sarcoidosis varied in clinical and radiological patterns. Moreover, comparative epidemiological studies have demonstrated that geographic, ethnic, and genetic factors are linked to the specific clinical characteristics of sarcoid patients (Baughman et al., 2001; Hosoda et al., 2002; Thomas & Hunninghake, 2003). Specificity of the diagnostic findings depends on other dominant diseases (e.g. tuberculosis, extrinsic allergic alveolitis, histoplasmosis) in specific population or a geographic region (Greco et al., 2005; Sibille et al., 2011). Availability of specific diagnostic techniques and patients' insurance policy differ in different countries. Thus, diagnostic pathway, which leads to confirmation of sarcoidosis, may be different.

Pathognomonic criteria or diagnostic "gold standard" are absent (Muller-Quernheim, 1998; Baughman & Iannuzzi, 2000). Most authorities thus include several clinical, radiological, immunological and histological features into their diagnostic criteria since other disease processes can simulate sarcoidosis in many ways (Muller-Quernheim, 1998; Hunninghake et al., 1999).

In principle, diagnosis of sarcoidosis may be based on typical clinical picture (symptoms of acute sarcoidosis) and typical radiological picture (Costabel, 2001; Iannuzzi et al., 2007). For the patients with no symptoms, bilateral hilar lymphadenopathy, and no other worrisome findings, close clinical observation may be sufficient (Reich et al., 1998; Kvale, 2003; Thomas & Hunninghake, 2003; Reich, 2010).

Diagnosis of sarcoidosis may be based on BAL findings (Costabel, 2001; Nunes et al., 2005). In patients with uncertain diagnosis after clinical assessment and high resolution computed tomography scanning, typical BAL cellular profiles may allow a diagnosis of sarcoidosis to be established with greater confidence (Wells et al., 2008).

In author's institution fibreoptic bronchoscopy and bronchoalveolar lavage are the first diagnostic procedures following clinical and radiological examination of the patient. Additional to BAL we perform endobronchial biopsy if bronchial mucosa seems abnormal. Examination of BAL fluid always includes microscopy and cultures for tuberculosis. Routinely, biopsy material is stained for acid-fast bacteria as well. Typical BAL fluid cellular or findings of non-necrotizing epitelioid granulomas in endobronchial biopsy material confirmed diagnosis of sarcoidosis in asymptomatic patients and patients with acute symptoms (Löfgren's syndrome). At least 60 % of all sarcoidosis cases are diagnosed this way. If BAL fluid cellular profile is non-typical and non-necrotizing epitelioid granulomas are not found, bronchoscopic forceps lung biopsy is performed. Finding of non-necrotizing granulomas confirms sarcoidosis. Practically, mediastinoscopy is performed only in exceptional cases when in patients with mediastinal lymphadenopathy the diagnosis was not confirmed by less invasive method. Routinely the 3-6 moths follow-up of our patients lasts at least up to 3 years or longer if necessary.

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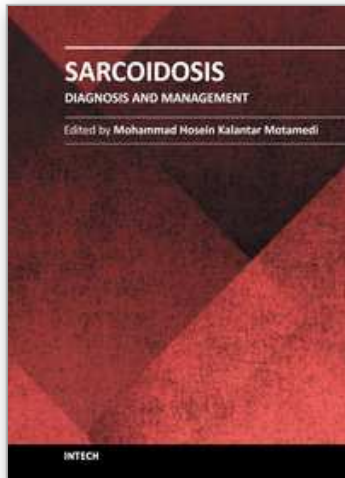
Sarcoidosis Diagnosis and Management

Edited by Prof. Mohammad Hosein Kalantar Motamedi

Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

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