Advancements in pulmonary endosonography : the new standard to diagnose sarcoidosis and assessment of its safety profile

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1 General introduction and aims of the thesis

This thesis is about endosonography in pulmonary diseases and consists of two parts. The first part focuses on endosonography in the diagnosis of sarcoidosis. The second part includes research on the safety profile of the technique.

PART I: ENDOSONOGRAPHY IN THE DIAGNOSIS OF SARCOIDOSIS

Background of sarcoidosis

Sarcoidosis is a systemic disease that was first described in 1878 by Jonathan Hutchinson[1] that also became known as the disease of Besnier and Boeck, named after two pioneering physicians of the late 19th century.[2,3] Sarcoidosis mostly affects young adults between the age of 20 and 40 though the disease may present at any age. The disease is characterized by the formation of non-caseating granulomas (see image) and can affect virtually every organ, but most commonly affects the lungs and intrathoracic lymph nodes.

The exact pathogenesis of the disease remains unknown. Despite years of research, the stimulus that triggers the initial CD4+ T cell alveolitis, followed by the development of non-caseating granulomas is unclear. Possible etiologies include fine dust[4], infectious agents[5] and there also appears to be a genetic susceptibility.[6]

By generalized tissue accumulation of granulomas, sarcoidosis can cause a variety of symptoms of which fatigue and cough are among the most prevalent.[7] The course of the disease is variable, ranging from self-limiting complaints to progression to a chronic disease with severe symptoms resulting in death (mortality rate <5%) due to pulmonary fibrosis, cor pulmonale or cardiac arrhythmia.[8] Therapy, indicated for those patients with severe organ dysfunction, includes high dose glucocorticoids or other immunosuppressive agents.

The incidence of sarcoidosis varies between 1 to 40 per 100.000 population, depending on race and age. The disease is most prevalent in those of (northern) European and African descent, but rare in Asian, Native American and Inuit people.[9] In the Netherlands, the estimated annual incidence of sarcoidosis is 2000 patients.[10] The true prevalence of sarcoidosis is expected to be higher as sarcoidosis often manifests itself subclinical. Data from a historical cohort of more than a million US Navy recruits showed that almost 50% of patients with sarcoidosis were asymptomatic.[11]

Diagnosing sarcoidosis

There is often a great variance in the severity of symptoms in patients with sarcoidosis. Presenting symptoms include exhausting fatigue, cough, dyspnea on exertion, weight loss or night sweats, but many patients have no complaints at all and the diagnosis is made because of abnormalities found on routine x-ray or CT scan of the chest.

Generally, experts[8,12,13] state that patients with a suspicion of sarcoidosis should undergo a step-wise diagnostic approach. This includes a clinical and radiological suspicion of the disease,

a tissue confirmation of disease-specific noncaseating granulomas (Figure 1) and a follow-up period of six months in order to exclude similar presenting diseases such as tuberculosis, lymphoma and lung cancer. Patients who present with a combination of symptoms pathognomonic for sarcoidosis including Lofgren syndrome (erythema nodosum, bihilar lymphadenopathy, migratory polyarthralgia and fever) are exempted from tissue confirmation. In those specific cases a clinical/radiological diagnosis can be made without tissue confirmation. Also, in patients with Heerfordt's syndrome (uveoparotid fever) and asymptomatic bilateral hilar lymphadenopathy tissue confirmation of noncaseating granulomas is also often omitted.

Generally, whether to proceed to invasive diagnostic procedures depends on a lot of factors including patient and doctor preference, likelihood of an alternative similar presenting disease (e.g. lung cancer or tuberculosis) and the need for treatment with immunosuppressive agents.

Imaging techniques

Once the diagnosis of sarcoidosis is suspected, radiological imaging is the first step to screen for involved organs or to select a potential biopsy site.

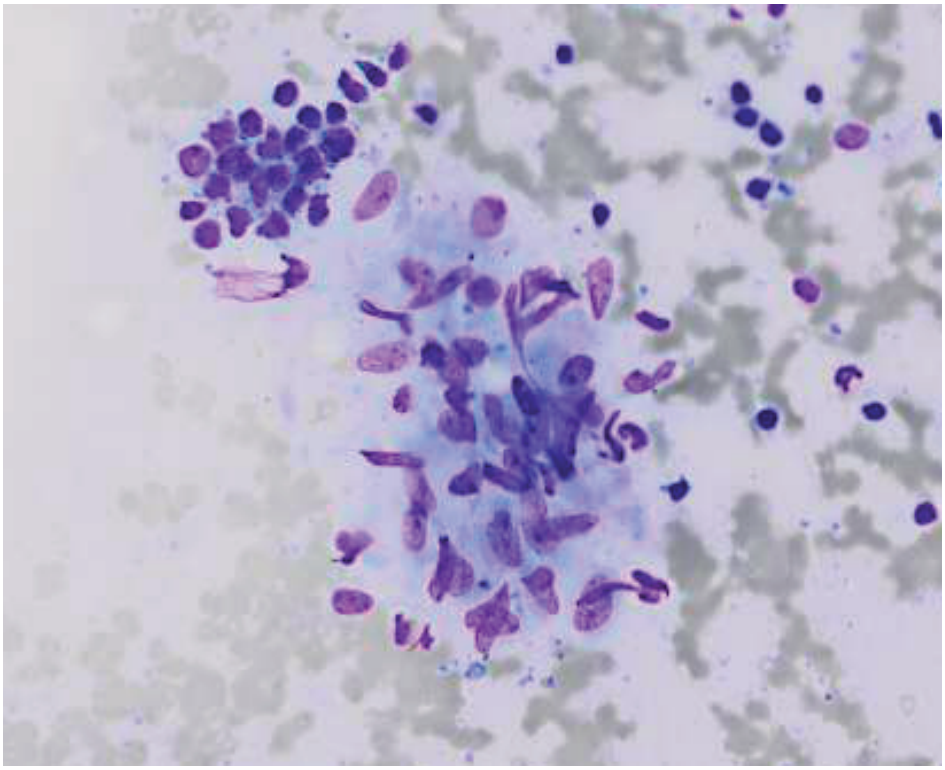

Figure 1. Cytology aspirate of a non-caseating granuloma as observed in a patient with sarcoidosis

Staging of pulmonary sarcoidosis is based on chest X-ray scanning: Stage I is defined by the presence of bihilar lymphadenopathy, stage II includes lymphadenopathy with parenchymal disease, in stage III there is only parenchymal disease and stage IV is characterized by fibrosis (Figure 2).[14] Chest X-ray scanning is widely available but has obvious imitations in image resolution.

Computed tomography (CT) offers detailed anatomical information of the lungs and mediastinum. In sarcoidosis, a chest CT scan can detect specific radiological features such as diffuse mediastinal lymphadenopathy (Figure 3), miliary and fisural nodules, ground glass opacities or alveolar opacities with satellite nodules *("galaxy sign")* but these clues can also be observed in a number of other conditions, including infections, neoplasms and occupational disorders (silicosis, chronic beryllium disease)[15] making them not very specific for a diagnosis of sarcoidosis.

Positron emission tomography (PET) is a whole body technique of functional processes in the body. When a nuclear tracer is labelled to fluorodeoxyglucose (FDG) - a glucose analogue - and subsequently injected in the body, there will be uptake of FDG in biologically active body cells (such as in the cells that form the granulomas). The biologically active cells can be visualized in a three-dimensional functional image. In patients with sarcoidosis, PET has proven

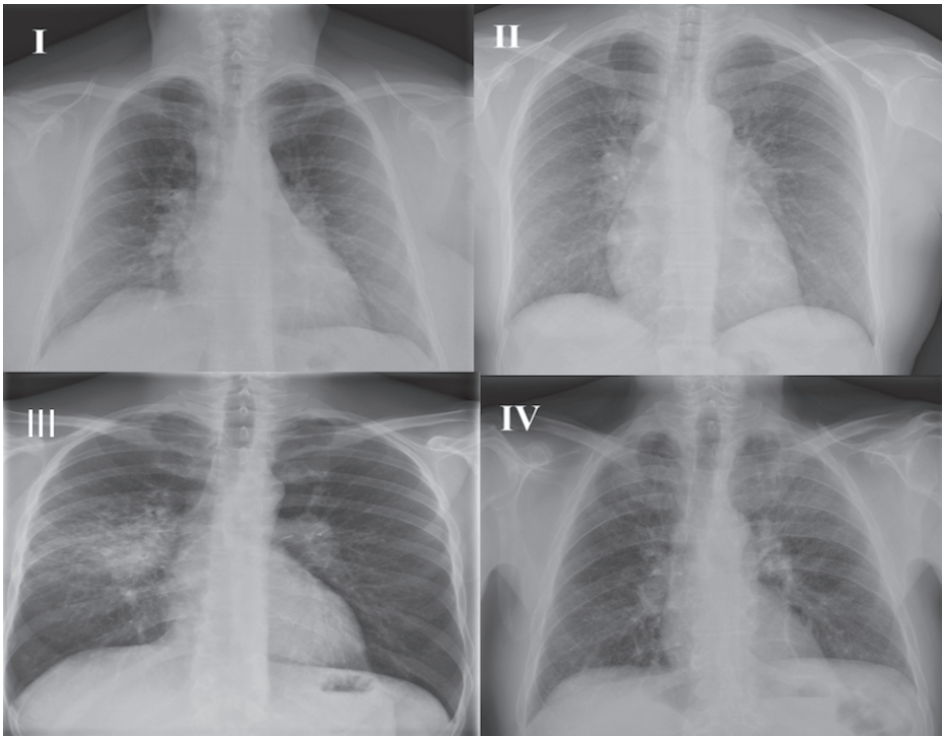

Figure 2. Chest X-ray images with sarcoidosis stage I-IV.

valuable in selecting potential sites for diagnostic biopsy[16] and it can be used as an marker of disease activity[17] but there are no disease-specific PET patterns in pulmonary sarcoidosis.

Although CT and or PET-CT imaging is helpful in the diagnostic workup of sarcoidosis, tissue sampling is often indicated to secure a final diagnosis, especially to rule out lymphoma, lung cancer or tuberculosis.

Bronchoscopic methods

The vast majority of sarcoidosis patients present with pulmonary, ocular and/or skin manifestations[7] When present, accessible lesions like peripheral lymph nodes and skin lesions should be considered first if tissue sampling is indicated.[8] But as these sites are infrequently involved, sampling of the lungs and/or intrathoracic lymph nodes is usually the next best option as >85% of sarcoidosis patients have pulmonary or mediastinal involvement.[7]

Various endoscopic techniques are available to obtain tissue to demonstrate granulomas.

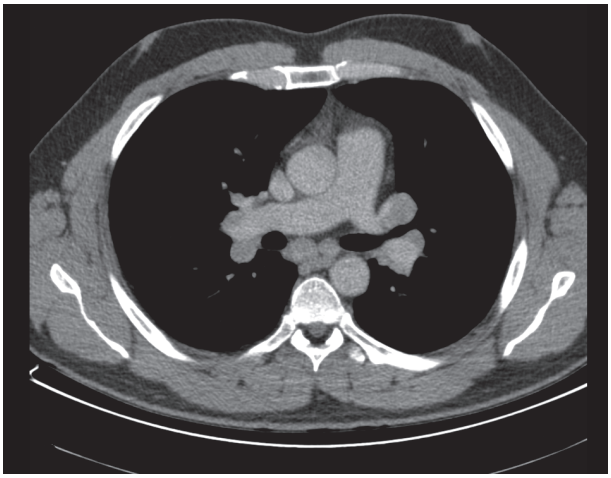

Figure 3. Computed tomography (CT) scan of the thorax displaying the heart and great vessels, the lungs and multiple enlarged mediastinal and hilar lymph nodes.

Peripheral lung biopsy (TBLB)

TBLB is one of the most commonly used bronchoscopic biopsy techniques in the diagnostic workup of sarcoidosis.However, the technique has a modest average yield (59%) of which the reported range is also variable (32%-100%).[18] Many factors are thought to contribute to the variance in yield. It may be a matter of patient selection as the accuracy of TBLB for higher stages of sarcoidosis is better.[18] Also experience with the procedure or the use of fluoroscopy may influence sensitivity in the assessment of granulomas. Moreover, the yield in trials can be somewhat optimistic due to a protocol-guided taking of a minimum number of biopsies. It has been demonstrated that at least 6 biopsies are required for stage II sarcoidosis and 8-10 in stage I to obtain the optimal yield.[19,20] Investigators often refrain from performing this amount of biopsies because of fear of severe adverse events (SAE). Generally TBLB is associated with a rate

of SAE of 3.1% including pneumothorax (2.3%; of which 1% requiring tube thoracostomy), bleeding of 40-100 ml (0.6%) and pneumomediastinum (0.2%).[18]

Endobronchial mucosa biopsies (EBB)

Endobronchial biopsy (EBB) on its own has modest value in diagnosing sarcoidosis with yields ranging from 11-49%.[21-24] Nevertheless, the risk of complications is minimal and it is good to recognize that EBB might be of value in case visible mucosal abnormalities are present and granulomas may be found in 54-91%. Also in normal appearing mucosa, granulomas may be found in 20-40%.[18]

Conventional transbronchial needle aspiration (cTBNA)

Transbronchial needle aspiration (TBNA) of mediastinal lymph nodes (Figure 4) was initially described in 1949 by Argentinian thoracic surgeon E. Schieppati when he punctured a subcarinal mass using rigid bronchoscopy.[25] The invention of the flexible bronchoscope in 1966 by dr. Ikeda further advanced diagnostic bronchoscopy, as did the development of improved optics and light sources. With TBNA, specifically the right-sided paratracheal lymph node stations 4R and the subcarinal station 7, as defined by the TNM system[26], are accessible to "conventional" transbronchial aspiration. Because of the ease of the procedure, low cost and low complication rate, TBNA is often posed as the initial procedure to assess granulomas in patients with generalized mediastinal lymphadenopathy but also to diagnose lung cancer, tuberculosis or lymphoma. The outcome of conventional TBNA in sarcoidosis, however is highly variable with a yield of 6-90% as shown by a recent meta-analysis (pooled efficacy 62%) and thus a large number of patients remain non-diagnostic after cTBNA.[18]

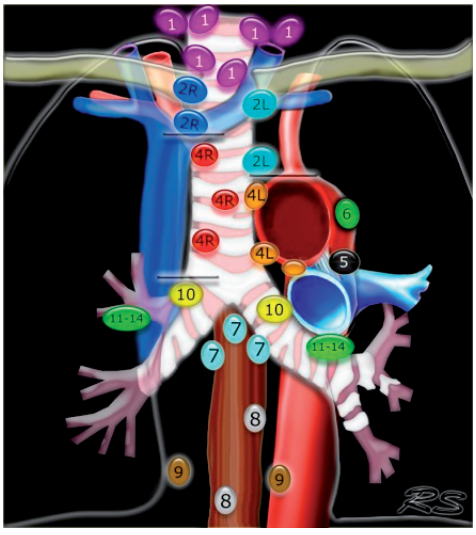

Figure 4. Regional lymph node stations adapted from the American Thoracic Society by Robin Smithuis of radiologyassistant.nl

Bronchoalveolar lavage (BAL)

Several experts suggest that bronchoalveolar lavage (BAL) should be performed in all patients suspected of having sarcoidosis as it contributes to the diagnosis process[12,13,27]

BAL determines lymphocyte subsets including the CD4/CD8 ratio, which may contribute to the diagnosis of sarcoidosis. By counting the CD4 en CD8 positive T-lymphocytes, a CD4/CD8 ratio may be calculated. A CD4/CD8 ratio > 3.5 has been reported to correspond with a high positive predictive value (PPV) (94%) for sarcoidosis and other interstitial lung diseases (ILD). However, the lavage fluid does not revenue the granulomas required for a diagnosis of sarcoidosis and with a PPV of only 50% the CD4/CD8 ratio has minimal value to distinguish sarcoidosis from non-ILDs such as lymphoma and lung cancer.[28]

Surgical biopsy

In some cases where endoscopic techniques do not provide a classifying diagnosis, surgery is performed as the next step.

Mediastinoscopy is a type of "key-hole surgery" in which the left and right paratracheal and subcarinal areas are biopsied. With a similar procedure called "extended mediastinoscopy" the aortopulmonary window (stations 5 and 6) and subcarinal station (station 7) may also be reached for tissue evaluation. By extracting lymph nodes with video-assisted mediastinal lymphadenectomy sensitivities of 90-100% may be obtained.[29,30] However, mediastinoscopy also has its downsides: Amongst others, it requires general anaesthesia, a hospital stay and increased expenses and it has a relatively high morbidity rate (1%) including recurrent laryngeal nerve injury, haemorrhage, tracheal injury and pneumothorax.[31]

Endosonography

In 1991 Danish surgeon Peter Vilmann first applied a tool that was capable of visualizing mediastinal nodes and sample them under real-time sonographic guidance. He used a modified gastroscope with a linear ultrasonic head attached, allowing visualization of the mediastinal lesions in direct proximity to the esophagus.[32] By 1996, endoscopic ultrasound (EUS) had been established as an alternative method to CT for evaluating cancers in the upper GI tract. After a working channel was incorporated in the scope it was possible to sample mediastinal masses, but also lymph nodes as small as 4 mm under real-time sonographic guidance.[33,34] Pulmonologists started to use the oesophagus as an approach route to diagnose mediastinal or centrally located pulmonary lesions, located adjacent to the oesophageal wall.

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) provides access to the lower mediastinum, home to lymph node stations 7, 8 and 9. Nodes in the aortapulmonary window (5 and 6) can be easily visualized but often sampling is difficult due to intervening vascular structures. Lymph nodes stations in direct proximity to the large airways are out of reach of EUS-FNA because of air interfering with the ultrasound signals.

In 2000 Fritscher Ravens was the first to report on EUS-FNA in investigating patients with sarcoidosis.[35]

It took some time to develop a sonographic head small enough to be fitted on the smaller bronchoscope and in 2003 Krasnik first described real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).[36] EBUS visualizes and samples the regions in the mediastinum adjacent to the large airways. The reach of EBUS-TBNA overlaps with that of mediastinoscopy and it is complimentary to that of EUS-FNA.[37] Both an EUS and EBUS investigation including multiple nodal samplings can be performed in an ambulatory setting in around 20 minutes, usually under conscious sedation.

In preliminary retrospective studies it had been shown that the detection rate of noncaseating granulomas for endosonography (EUS and EBUS) was approximately 80% with few adverse events.[38-41] This high granuloma detection rate – superior to that reported for traditional bronchoscopic sampling methods – resulted in the wish to compare endosonography to the standard bronchoscopic methods.

PART II: SAFETY OF ENDOSONOGRAPHY

When novel interventional techniques are introduced and implemented in routine clinical practice, safety issues are important. EUS-FNA and EBUS-TBNA were introduced in The Netherlands in the Leiden University Medical Center in 1999 and 2004 respectively, and are now widely available throughout the country. Mostly, literature on endosonography has focused largely on the feasibility and yield of the technique. Case reports have been reported regarding (serious) adverse events, mainly cautioning against the aspiration of mediastinal cysts and necrotic lymph nodes as increased rates of infections were observed following FNA.[42,43] Further, small retrospective (44) and prospective studies (45, 46) were published, describing low numbers of serious adverse events and no mortality. Although the safety profile seemed favourable, data outside of clinical trials or expert centres were limited.

AIMS OF THE THESIS

Part I – Endosonography in the diagnosis of sarcoidosis

At the initiation of our research, conventional bronchoscopy was regarded the first line-technique for tissue sampling in case of suspected pulmonary sarcoidosis, despite a moderate overall yield in the assessment of granulomas. The position of endosonography (EUS/EBUS) with intrathoracic lymph node sampling vs. the use of conventional bronchoscopy techniques in the workup of sarcoidosis was unknown. Within the pulmonary community, the optimal

strategy to provide tissue proof of noncaseating granulomas in a patient suspected of having sarcoidosis was often subject of debate.

Hence our primary aim was to:

Compare endosonography (EBUS/ EUS) including intrathoracic nodal sampling with conventional bronchoscopy with transbronchial and endobronchial biopsy for the diagnosis of pulmonary sarcoidosis stage I/ II

Our secondary aims were to:

- Determine whether there exists a difference in diagnostic yield between stage I and II sarcoidosis for both endosonography and conventional bronchoscopy.

- Determine the specificity of the bronchoalveolar lavage in the diagnosis of sarcoidosis and investigate whether a positive BAL obviates the need for (more invasive) tissue sampling.

- Assess safety and serious adverse events of endosonography in de diagnosis of sarcoidosis.

Part II – Safety of endosonography

Our aims in this part on the safety of endosonography were to:

- Assess morbidity and mortality rates of EUS and EBUS in pulmonary medicine in the literature and throughout the Netherlands
- To identify certain risk factors for complications or subsets of patients at risk of developing serious adverse events.

OUTLINE OF THE THESIS

Chapter 2 describes a retrospective analysis of all patients who were referred for EUS-FNA for a suspicion of pulmonary sarcoidosis in the period 2004-2009 in the Leiden University Medical Center. Besides diagnostic yield, we focussed on pathology handling, specifically on the additional value of cell-block analysis to conventional cytological smears.

Results from this paper have led to initiation of a multi-center randomized clinical trial in 14 centers in 6 countries, described in **Chapter 3** in which the diagnostic yield of endosonography (EUS and EBUS) to detect non-caseating granulomas in patients with a final diagnosis of sarcoidosis was compared to conventional bronchoscopy (TBLB and EBB). Secondary outcome measurements were the complication rates in both study arms as well as the additional value of a bronchoalveolar lavage (BAL). A specific serious adverse event of EUS-FNA in sarcoidosis patients is addressed in **Chapter 4** in where we outline the possibility of mediastinal infections following aspiration of sarcoid lymph nodes in a large retrospective cohort of patients in two Dutch hospitals. **Chapter 5** contains a systematic review of the literature of endosonography-associated complications. We aimed to assess the rate of serious adverse events and to evaluate specific associated risk factors in 16.181 patients. Subsequently, we addressed this issue by gathering original data in **Chapter 6** in where we quantified the morbidity and mortality of endosonography by conducting a retrospective nationwide survey in all Dutch hospitals. .

Chapter 7 describes a case of a serious adverse event of mediastinal-oesophageal fistulae following EUS-FNA of a subcarinal node in a patient with tuberculosis. Finally, an unconventional approach to sample lymph nodes in the aortopulmonary window by transaortic needle aspiration is discussed in a case-series in **Chapter 8.**

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