Granulomatous mediastinal adenopathy: can endoscopic ultrasound-guided fine-needle aspiration differentiate between tuberculosis and sarcoidosis?

Authors A. Fritscher-Ravens[1,2,3], A. Ghanbari[1], T. Topalidis[4], M. Pelling[2], O. M. Kon[2], K. Patel[1], A. Arlt[3], A. Bhowmik[1]

Institutions Institutions are listed at the end of article.

submitted
18 September 2010
accepted after revision
25 May 2011

Bibliography
DOI http://dx.doi.org/10.1055/s-0031-1271110
Published online: 10.08.2011
Endoscopy 2011; 43: 955–961

ISSN 0013-726X

Corresponding author
A. Fritscher-Ravens, MD
Interdisciplinary Endoscopy
Department of Internal Medicine I
University Hospital Schleswig-Holstein
Campus Kiel
24105 Kiel
Germany
Fax: +49-431-5971302
Fri.rav@btopenworld.com

Background and study aims: Mediastinal lymphadenopathy may indicate diseases such as tuberculosis or sarcoidosis, and it is often difficult to establish a diagnosis when standard medical workup is inconclusive. In this study we investigated the diagnostic yield of endoscopic ultrasound-guided fine-needle aspiration (EUS – FNA) in the differentiation between tuberculosis and sarcoidosis.

Patients and methods: In this prospective study, 72 consecutive patients with mediastinal lymphadenopathy, negative endoscopic investigations including bronchoscopic procedures, and no radiological evidence of lung cancer or other malignancies on computed tomography were enrolled. EUS – FNA and subsequent cytology, microscopy for acid-fast bacilli, and culture were performed. At least 12 months' follow-up including further investigations was included to exclude tuberculosis.

Results: Adequate samples were obtained from 71/72 patients (36 male; mean age 50.2 years). No complications occurred. The final diagnosis included 30 cases of sarcoidosis, 28 of tuberculosis, four malignancies, one abscess, and nine benign lymphadenopathies. The size of lymph nodes on EUS varied from 0.5 cm to 4.2 cm. Tuberculosis nodes were significantly smaller than those in sarcoidosis. Unrelated nodes were significantly smaller than in either tuberculosis or sarcoidosis. The sensitivity, specificity, and positive and negative predictive values of EUS – FNA for tuberculosis were 86%, 100%, 100%, and 91%, respectively; those for sarcoidosis were 100%, 93%, 91%, and 100%, respectively. For culture of tuberculosis, they were 71%, 100%, 100%, and 84%, respectively. EUS – FNA led to a definite diagnosis in 64/72 cases (89%) that had not been previously diagnosed by routine methods.

Conclusion: EUS – FNA offers a high diagnostic yield for the differential diagnosis of tuberculosis and sarcoidosis that have not been diagnosed by conventional methods.

Introduction

Approximately one-third of the world's population is infected with tuberculosis, resulting in approximately 3 million deaths per year [1]. Tuberculosis is thus responsible for more than a quarter of all avoidable adult deaths in the developing world [2,3], and the number of new cases annually is still increasing [4], with 8.8 million estimated new cases of tuberculosis in the world in 2005.

The emergence of multi-resistant strains has increased the importance of an early and correct diagnosis of the disease for effective treatment [5]. In the UK the number of reported cases of tuberculosis is rising, and 40% of this national caseload is centered in London. Recent immigrants are one of the most affected subgroups [6], with a high prevalence of drug-resistant tuberculosis [5].

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology [7,8]. It is most prevalent in Afro-Caribbeans and Asians, who represent large ethnic groups in London. As tuberculosis and sarcoidosis have a high degree of overlapping clinical and diagnostic features with completely different therapeutic measures, the differential diagnosis of both diseases is of extreme importance.

The diagnosis of tuberculosis and sarcoidosis is usually made by sputum examination and culture, tuberculin skin testing, and radiological examination, the latter two being two of the many indirect tests for which tissue/cell confirmation is required. This can be achieved with bronchoscopy plus bronchoalveolar lavage, transbronchial needle aspiration or other similar techniques, culture, and histology, with a sensitivity of 72% in

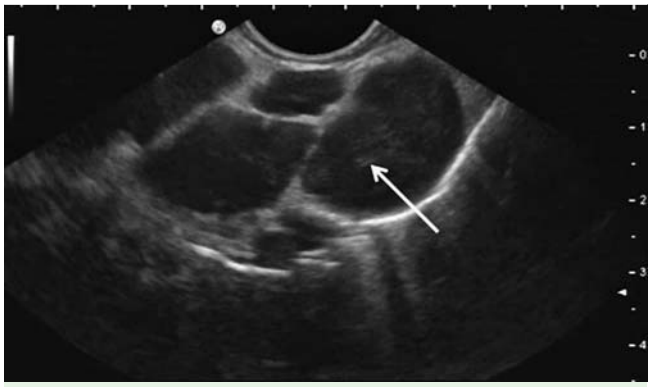

Fig. 1 Lymph node representative of sarcoidosis. Endoscopic ultrasound image of subcarinal nodes, which appear isoechoic but slightly inhomogeneous with small vessels coursing through (arrow).

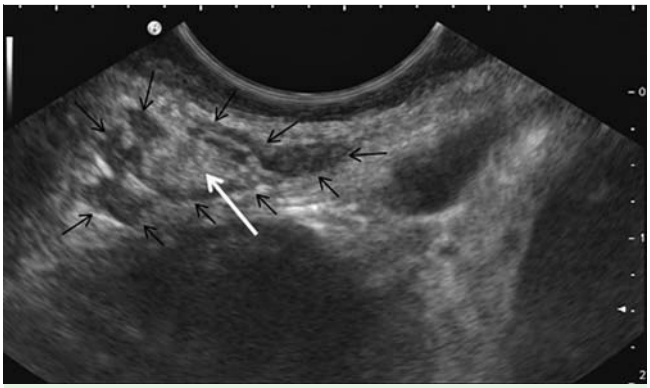

Fig. 2 Lymph node representative for tuberculosis with caseation. Endoscopic ultrasound image of a hypoechoic node (black arrows with a hyperechoic area within). This node proved to be infiltrated by tuberculosis with caseation (white arrow).

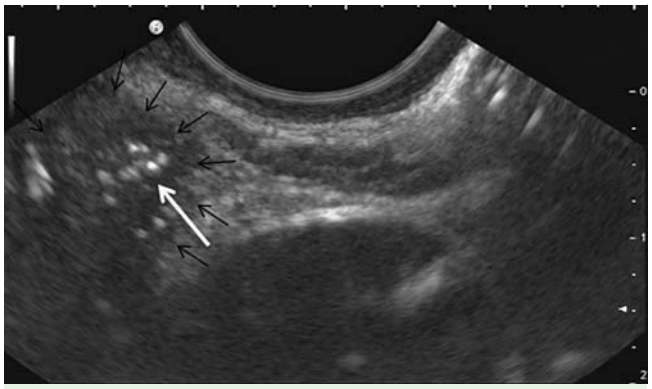

Fig. 3 A representative lymph node of calcified inactive tuberculosis. Endoscopic ultrasound image of a similar hypoechoic node (black arrows) as shown in **Fig. 2**. However, the hyperechoic material within is not one larger mass: many hyperechoic areas represent calcification of inactive tuberculosis (white arrow). In this case, cytology showed only unspecific inflammatory changes.

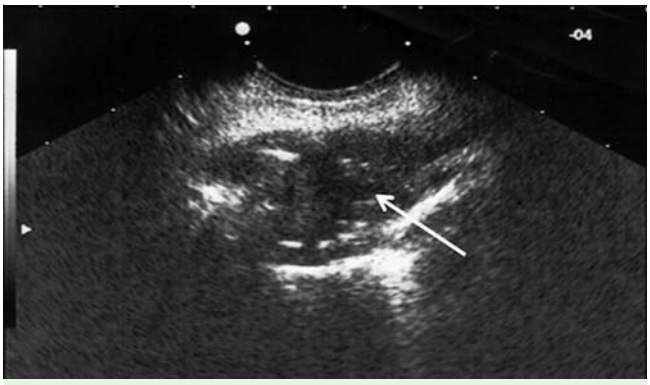

Fig. 4 Lymph node with abscess. Endoscopic ultrasound image of a large hypoechoic node (arrow) similar to Figs. 1 and 3, with acoustic shadowing representing air.

stage I sarcoidosis [9] and 83 % in tuberculosis [10].

Patients in whom a diagnosis has not been made by conventional routine work-up might benefit from new techniques such as endoscopic ultrasound-guided fine-needle aspiration (EUS – FNA) to obtain a diagnosis. EUS is able to detect pathological mediastinal lymph nodes and obtain tissue for diagnosis using FNA, with a sensitivity of more than 90 % (range 88 % – 96 %) and a specificity approaching 100 % [11 – 14]. There is some evidence that EUS – FNA can also be used to diagnose sarcoidosis [15 – 19] but little is known about the role of EUS – FNA in tuberculosis [20,21]. We therefore identified a need for a prospective study, including a large number of patients of the ethnic subgroups most affected by these two diseases, to determine the accuracy and utility of EUS – FNA in diagnosing these diseases and differentiating between them.

Patients and methods

Patients and procedure

Between March 2004 and April 2008 all patients over the age of 18 years who had been consecutively referred with mediastinal lymphadenopathy and clinical suspicion of tuberculosis or sarcoidosis, and in whom routine medical work-up had failed to achieve a diagnosis were prospectively enrolled into the study. In all patients, sputum culture, bronchoscopy with cell sampling by brushings and bronchoalveolar lavage, and thoracic computed tomography (CT) had failed to yield a diagnosis, including additional endobronchial biopsies in six and transbronchial biopsies in 11. Only those patients who had no radiological evidence of lung cancer or other malignancy on CT were included. Those who had such findings underwent EUS – FNA and other tests according to the routine work-up outside of this study. After the abovementioned tests had proven inconclusive and malignancy was not suspected, the pulmonologists in charge selected and referred the patients to the study center, where EUS – FNA was carried out by gastroenterologists who had never been involved in the care of the patients before but were aware of the possible differential diagnosis of tuberculosis /sarcoidosis.

Informed consent for the procedure as well as for the inclusion into the study was obtained before EUS and FNA were carried out with linear echoendoscopes (FG 34UA, FG 38 OUT [Pentax, Tokyo, Japan], attached to Hitachi consoles EUB 525 or 6000 [Hitachi, Tokyo, Japan]) for imaging and 22-gauge needles (Echotip; Cook Medical, Winston-Salem, North Carolina, USA) for FNA. After EUS staging of the entire dorsal mediastinum, the most prominent/suspicious nodes were selected for tissue sampling. "Suspicious" was defined as hypoechoic, inhomogeneous or having a number of vessels coursing through the node (**Fig. 1 – 4**). The needle was visualized fully as it approached a target within the sector-shaped sound field. At least two needle passes were ob-

tained for cytological and one for bacteriological analysis. The two samples were analyzed by independent cytologists and microbiologists blinded to the results of the other tests but aware of the possible differential diagnosis. Cytological differential diagnosis between sarcoidosis and tuberculosis was made after staining with May – Grünwald – Giemsa, as previously described [15]. Samples for bacteriology were flushed out of the EUS needle into a dry sterile container using sterile saline and were immediately sent for microbiological analysis including microscopy and culture for acid-fast bacilli with a view to sensitivity testing.

Cytology

Differential diagnosis of sarcoidosis and tuberculosis on cytology was made on the basis of a variety of findings described in detail in **Table 1** [15]. These include the presence of epithelioid cell granulomas on a "dirty background" representing debris (protein precipitates, caseating cell necrosis), which is suggestive for tuberculosis [11,15,22]. Sarcoidosis is suggested by epithelioid cell granulomas on a "clear background" as no bacteria are present but there are larger numbers of lymphocytes and epithelioid cells.

Prior to the study, three diagnostic categories were defined: 1) in keeping with sarcoidosis or tuberculosis; 2) indeterminate; 3) inadequate material. Only results with "in keeping with" tuberculosis or sarcoidosis were used for diagnosis.

Study aims, hypothesis, and end-points

The aim of the study was to determine the utility of EUS – FNA in the diagnosis of tuberculosis or sarcoidosis in patients with nonmalignant mediastinal lymphadenopathy in whom routine clinical investigation had failed to produce the diagnosis. We hypothesized that the material obtained by EUS – FNA could be used for cytology and bacteriology to diagnose tuberculosis as well as sarcoidosis.

The primary endpoint was the diagnosis of tuberculosis or sarcoidosis by cytology of samples obtained by EUS – FNA. The secondary endpoint was the ability of EUS – FNA and cytology plus bacteriology to differentiate between the two diseases.

Statistics

In 2004, when the study was initiated, there were no published results of EUS – FNA and tuberculosis. On the basis of the limited data available concerning EUS – FNA and sarcoidosis at the beginning of the study [15 – 17,23], we assumed that the addition of EUS – FNA to conventional work-up might increase the diagnostic yield by 20 %, from 72 % to 92 % [17,20,23]. With this assumption, a two-sided uncorrected chi-squared test with a power of 80 % and a significance level of 0.05 was carried out [24,25], which suggested that a total of 57 patients with tuberculosis or sarcoidosis was required. A study by Porte et al. using mediastinoscopy in 398 patients for undiagnosed mediastinal lesions when other methods failed to obtain a diagnosis, showed that in a subgroup of 271 patients with clinical suspicion of tuberculosis or sarcoidosis, only 80 % actually had these diseases after 53 months' follow-up [26]. Final diagnoses proved either of the two in only 217 /271 patients. The remaining diagnoses included metastases of extra-pulmonary origin (n = 20), lymphoma (n = 17), histiocytosis or anthracosis (n = 17) [26]. These data for nonlung cancer-associated lymphadenopathy [26] indicated that the actual proportion of sarcoidosis or tuberculosis present in the referred cohort would be ~ 80 %. Consequently, if a total of 57 patients with tuberculosis/sarcoidosis was required, a further 14 were necessary to replace those who would prove to have other diagnoses, to ensure that the minimum number indicated by the sample size calculation was recruited. We further added 5 % (three patients) for possible drop-outs during the follow-up period of 1 year. This resulted in a final sample size of 74 patients. The ability of cytology obtained by EUS – FNA to diagnose tuberculosis and sarcoidosis was determined by calculating sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios.

The 95 % confidence intervals (CIs) of these values were calculated using the efficient score method of Newcombe [27,28]. In order to assess the role of EUS – FNA cytology at improving the differential diagnosis, measures of agreement between EUS – FNA cytology and the final clinical and microbiological outcome in both tuberculosis and sarcoidosis were calculated using Pearson's correlation coefficient and the kappa statistic, in order to determine the strength of association between EUS – FNA cytology and the final clinical and bacteriological outcome. P values < 0.05 were taken to be significant.

Table 1 Cytological differentiation of tuberculosis and sarcoidosis in lymph nodes.*

Cells/cell types	Tuberculosis n = 24	Sarcoidosis n = 30
Amount lymphocytes (varying sizes)	+	+++
Monocytes/macrophages/histiocytes	+/+++/++	(+)/((+))/+
Neutrophil granulocytes	++	((+))
Eosinophil granulocytes	++	+
Endothelial cells/fibrocytes and fibroblasts (connective tissue cells)	++/++	+
Epithelioid cells	++	+++
Epithelioid cell granuloma	+	++ often in clusters
Langhans-type giant cells	++	–
Cell-debris/protein precipitates	+++	–
When caseous necrosis	Diagnostic	–
Background of smears†	"dirty" background*	"clear" background

– absent; ((+)) scanty or rarely present; (+) sometimes found; + regularly found; ++ frequently found, increased in number; +++ always present, must or should be present for the diagnosis.
† Dirty background represents cell debris, protein precipitates.
* May – Grünwald – Giemsa stain: blue amorphic necrosis; Papanicolaou stain: eosinophilic amorphic necrosis.

Final diagnosis

The final diagnosis of all patients not diagnosed with tuberculosis on culture was made only after 12 months of clinical follow-up, which included repeat appointments in clinics for evaluation of typical clinical features (fever, night sweats, cough, hemoptysis), blood tests including erythrocyte sedimentation rate and C-reactive protein, tuberculin skin test, repeated CT and, if considered necessary, repeat EUS – FNA. In the absence of these features and negative culture, the patients with EUS – FNA not suggestive of tuberculosis but positive for epithelioid cell granuloma were given the final diagnosis of sarcoidosis. If culture was negative, tuberculosis was still diagnosed if the patient had the typical clinical features of fever and night sweats, with/without cough or hemoptysis, moderately raised C-reactive protein, and a positive tuberculin skin test. Follow-up of all patients was continued for 12 months, looking for worsening symptoms, rising inflammatory markers or radiological features of progressive tuberculosis on CT or repeat EUS – FNA.

Table 2 Lymph node size and echo features.

	Tuberculosis n = 28	Sarcoidosis n = 30	Other n = 13
Lymph node size, cm	2.04 ± 0.59	2.4 ± 0.77	1.41 ± 0.57
Lymph node echofeatures			
Inhomogeneous, hyperechoic areas	++	–	+
Acoustic shadowing	++	–	+
Small vessels within nodes	+	+++	((+))

– absent; ((+)) rarely found; + can be found; ++ frequently found; +++ always present, must or should be present for the diagnosis.

This "clinical follow-up" or positive bacteriological culture provided the "gold standard" of the ultimate outcome and was chosen in keeping with the guidelines of the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom [29].

In no case was steroid treatment for presumed but unproven sarcoidosis started before tuberculosis was excluded by observation and follow-up of clinical features, negative tuberculin skin test, and negative acid-fast bacilli culture.

Results

Of the 75 patients enrolled in this study three were lost to follow-up, resulting in a total cohort of 72 patients studied (31 South East Asian, 26 Afro-Caribbean or African, nine Caucasian, and six Asian [36 male; mean age 50.2 years]). Lymphadenopathy was confirmed by CT images in all patients, and standard procedures failed to diagnose either tuberculosis or sarcoidosis. All patients underwent EUS – FNA, and adequate samples were obtained from 71 patients. There were no immediate or later procedure-related complications.

Lymph nodes and echo features

The overall sizes of the lymph nodes on EUS varied from 0.5 cm to 4.2 cm (short axis). Nodes related to tuberculosis were significantly smaller in size compared with those in sarcoidosis ($P < 0.02$) (**Table 2**). Nodes with conditions unrelated to these two diseases were very significantly smaller than in either tuberculosis or sarcoidosis and included three nodes < 1 cm (other nodes vs. tuberculosis: $P < 0.005$; vs. sarcoidosis: $P < 0.0001$). In all but two patients (one malignancy, one unspecific), the most prominent nodes were located in the subcarinal area and/or the aortopulmonary window. All nodes were well demarcated and isoechoic or moderately hypoechoic. Inhomogeneous, hyperechoic areas without acoustic shadowing were seen within nine of the active tuberculosis nodes (**Fig. 2**). In eight of these, caseation was proven on cytology. This EUS appearance was similar to the one abscess detected, with the exception that the hyperechoic areas in the abscess had acoustic shadowing, most likely representing gas produced by the bacteria within (**Fig. 4**). Acoustic shadowing was also seen in seven other patients. They were thought to represent calcifications of a former inactive tuberculosis (**Fig. 3**). In none of the nodes related to sarcoidosis was this feature present, but in 18/30, small vessels were coursing through the nodes (**Fig. 1**). These were only present in four of the tubercular nodes and in none of the others. The echo features are summarized in **Table 2**.

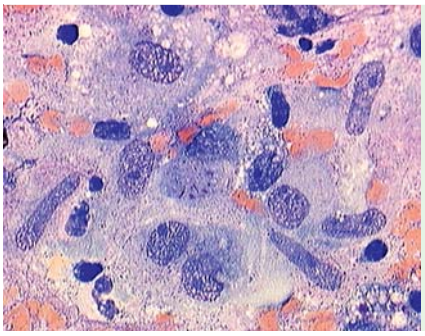

Fig. 5 Cytology representing tuberculosis. Cytology of endoscopic ultrasound-guided fine-needle aspiration samples showing epithelioid cell granulomas on a "dirty background."

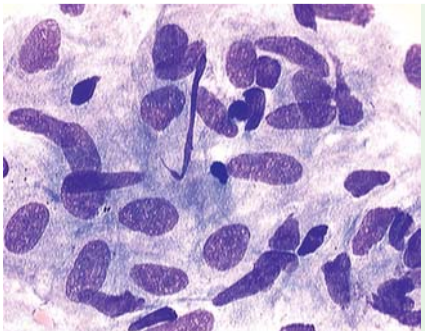

Fig. 6 Cytology representing sarcoidosis. In contrast to **Fig. 5**, on this slide the epithelioid cell granulomas are situated on a clear background representing sarcoidosis.

Cytology

Cytology (**Table 1**) revealed epithelioid cell granulomas on a "dirty background" with debris suggestive of tuberculosis (**Fig. 5**) in 24 patients, with necrosis representing caseation in eight cases. Sarcoidosis with epithelioid cell granulomas on a "clear background" was diagnosed in 33 patients (**Fig. 6**). Four patients were diagnosed on cytology as having malignancy (two lymphomas and two metastatic cancers). In the remaining 10 patients, one was found to have an abscess, one showed thymoma, and changes in the remaining eight were unspecific.

Culture

Cultures of the FNA samples for *Mycobacterium tuberculosis* were positive in 20 cases within 9 – 41 days (mean 24 days). In 3 /20, resistant strains were found. Three were misdiagnosed as sarcoidosis on cytology. Cultures of the remaining 51 EUS – FNA samples were negative. The final diagnosis of tuberculosis was made in a further eight patients after at least 12 months' "follow-up" following anti-tuberculous chemotherapy, which had been initiated due to very strong clinical suspicion in correlation with positive findings on cytology (n = 7). Overall, culture of FNA samples for tuberculosis had a sensitivity of 71 % (95 %CI 0.53 – 0.85), a specificity of 100 %, a positive predictive value of 100 % (95 %CI 0.8 – 1.00), and a negative predictive value of 84 % (95 %CI 0.71 – 0.93) (**Table 3**).

Final diagnosis

The final diagnosis after "clinical follow-up" of at least 12 months was tuberculosis in 28 patients and sarcoidosis stage I and II in 30. While cytology revealed tuberculosis in 24 cases, three further cases were detected on culture of EUS – FNA. These had been misdiagnosed as sarcoidosis on cytology as only a few slides were available with scanty material. In one case, follow-up showed an increase in symptoms and node size and repeat EUS – FNA culture performed 6 weeks later proved the diagnosis of tuberculosis. In this case, which was diagnosed as unspecific on cytology, no sign of possible tuberculosis was found at re-evalua-

Table 3 Endoscopic ultrasound-guided fine-needle aspiration cytology and bacteriology results.

	Tuberculosis				Sarcoidosis	
	Bacteriology		Cytology		Cytology	
	Total	95% CI	Total	95% CI	Total	95% CI
Total number of patients*	71		71		71	
Positive	24		20		33	
Negative	47		51		38	
Sensitivity, n/N (%)	20/28 (71)	0.53 – 0.85	24/28 (86)	0.66 – 0.95	30/30 (100)	0.86 – 1.00
Specificity, n/N (%)	43/43 (100)	0.92 – 1.00	43/43 (100)	0.90 – 1.00	38/41 (93)	0.79 – 0.98
Positive predictive value, n/N (%)	20/20 (100)	0.80 – 1.00	24/24 (100)	0.83 – 1.00	30/33 (91)	0.75 – 0.98
Negative predictive value, n/N (%)	43/51 (84)	0.71 – 0.93	43/47 (91)	0.79 – 0.97	38/38 (100)	0.89 – 1.00
Positive likelihood ratio	Infinity	NaN	Infinity	NaN	13.7	4.60 – 40.60
Negative likelihood ratio	0.29	0.16 – 0.51	0.14	0.06 – 0.35	0	NaN

* Data for culture of tuberculosis (column "bacteriology") and for cytology (columns "cytology") are shown. The final diagnosis was 28 for tuberculosis and 30 for sarcoidosis.
NaN, calculation cannot be performed because the values entered include one or more instances of zero.

tion of the first set of specimens and culture was negative. This may indicate that a reactive nontuberculosis node was biopsied.
In summary, EUS – FNA with cytology and microbiology was able to associate the lymph-node findings to a disease or condition in 71/72 cases (99%) and led to a definite diagnosis in 64/72 cases (89%). The remaining seven cases showed unspecific lymphadenopathy.
The statistic values for EUS – FNA (**Table 3**) show that this technique has high sensitivity and specificity with a low false-negative rate and high positive predictive value for diagnosing both tuberculosis and sarcoidosis. A kappa measure of agreement of 0.88 and a Pearsons correlation coefficient of 0.89 suggests that the strength of association is very high, indicating that tuberculosis and sarcoidosis can be reliably distinguished from one another by cytology obtained by EUS – FNA.

Discussion

In this study, we have demonstrated for the first time the value of EUS – FNA in the diagnosis of sarcoidosis and tuberculosis and show that a definitive diagnosis was achievable in the vast majority of patients studied when routine diagnostic procedures had failed. In addition, four underlying malignant diseases and one abscess were detected.
In general, the diagnosis of tuberculosis is made in about 85% of cases with sputum smear microscopy plus culture, culture of bronchoalveolar lavage fluid and of other clinical samples. The choice of patients for this study included only those in whom all these tests had not led to a diagnosis and therefore represents the group of patients who would benefit most from a new procedure providing further material. But because in many cases the accepted "gold standard" (culture) was not available to serve this role, the results obtained may lead to some dispute, as there was no easy way to assess the usefulness of EUS – FNA. We were forced to choose an unconventional "gold standard," which was drawn from the UK NICE guidelines for tuberculosis in which this problem was acknowledged: "the gold standard (culture) against which diagnostic tests for tuberculosis are usually compared, is not perfect as it might be negative in tuberculosis due to paucibacillary disease, sampling error or technical problems. In these cases, the standard against which a diagnostic test might be compared could be response to treatment, clinical features or a positive culture in the future. A tuberculosis diagnosis in this population would be achieved on a case-by-case basis and this has thus not been the subject of many studies" [29]. The NICE guidelines further quote a controlled trial of 3-, 6-, and 12-month regimens of chemotherapy for sputum-smear negative pulmonary tuberculosis, in which eventual confirmation of active disease requiring treatment in 57% of 173 patients was obtained, 43% during the first 12 months. Confirmation of tuberculosis was by culture from sputum, or by radiographic or clinical deterioration (bacteriological confirmation 41%) [30]. The trial also did not encourage routine polymerase chain reaction studies, and therefore we did not do this analysis in our study.
Thus, the final diagnoses made in our study were made in accordance with the NICE guidelines on tuberculosis, confirming or refuting the diagnosis of tuberculosis by the composite end-point of culture, radiographic appearances (i.e. repeated CT scan), repeated EUS – FNA where thought to be necessary, and clinical deterioration as determined over a 12-month follow-up period, in which the patients were seen in clinic and re-evaluated on a very regular individual basis.
EUS – FNA can be performed using various needle sizes and shapes for cytology and histology. We chose a 22-gauge needle and cytology, which we have used for many years with diagnostic yields of > 90% [15]. However, as the outcome of EUS – FNA is also dependent upon the interpretation of the material obtained (i.e. on the skills of the available cytopathologist or histopathologist), the choice of needle, and work-up of the samples might vary from hospital to hospital and be dependent upon the local expertise available. In many cases, where no well-trained cytopathologist is available, the use of 19-gauge needles and core-biopsies for histology might be a viable option, offering comparable results [31 – 33]. In a recent study, Song et al. achieved a diagnostic yield of 90.0% with a 22-gauge FNA needle for cytology and 78.6% with trucut biopsy in patients from an area with intermediate tuberculosis burden [34]. It was further shown that the addition of cell-block analysis to EUS – FNA samples could reduce the false-negative rate of suspected sarcoidosis I by 33% [19]. These alternatives might offer an equal or possibly even better option when compared with our choice of a routine 22-gauge needle and cytology in this challenging clinical scenario.
In our study, EUS – FNA cytology alone led to a diagnosis of tuberculosis in 24/28 cases resulting in a sensitivity and specificity of 71% and 100%, respectively. When bacteriological studies were taken into account, EUS – FNA provided a diagnosis in 27/28 cases, which were previously not diagnosed.

Out of the 20 cases with a positive tuberculosis culture, three patients were diagnosed with resistant strains. The ability to obtain bacteriology, which includes the identification of multi-drug resistant tuberculosis, is of great benefit as this result changes the management considerably. Further testing to investigate whether the diagnostic yield for bacteriology could be improved by using larger-diameter needles, trucut biopsies or just by increasing the number of needle passes might improve results. However, the uncertainty over whether the "right" node containing tuberculosis was sampled remains unsolved, as can be seen in our study, where initially one reactive node was sampled instead of the nearby infiltrated one.

It is generally recommended that patients with suspected sarcoidosis have histopathological confirmation. The usual first-line investigation is a transbronchial lung biopsy. Depending on the experience of the operator and the number of biopsies taken, its diagnostic yield varies from 38% to 90% [8]. In another study, the diagnostic yield increased from 73% using transbronchial biopsy alone to 88% when additional endobronchial biopsies were performed [35]. However in stage I disease where only mediastinal lymphadenopathy is present, transbronchial needle aspiration can be unhelpful and a direct sampling of the nodal involvement is essential. In our study 33/30 patients were diagnosed with sarcoidosis on cytology. Although three samples proved to be a tuberculosis on bacteriology, the sensitivity and specificity to diagnose sarcoidosis was 100% and 93%, respectively. The sensitivity of 100% appears rather unrealistic and would most likely be reduced to above 90%, as was recently published [19] in a larger cohort study. The fact that three of the patients with tuberculosis were misdiagnosed as sarcoidosis on EUS–FNA cytology highlights the importance of culture of the specimen [36], as treatment of a supposed sarcoidosis with steroids would be detrimental if the patient actually had tuberculosis. These findings also highlight that the diagnosis of sarcoidosis cannot be made on cytological/histological demonstration of noncaseating granulomas alone, but needs a compatible clinical picture and exclusion of other diseases capable of producing a similar histological or clinical appearance [37].

Overall, EUS–FNA with cytology and microbiology led to a definite diagnosis of a condition requiring treatment in 64 out of 72 cases. After follow-up of the nine cases with benign inflammatory changes, no serious diagnosis was made and in one, the EUS findings led to further work-up and the diagnosis of a thymoma. EUS–FNA achieved a diagnosis in 71 of the 72 cases. These data are in line with other studies showing the value of EUS–FNA in the diagnosis of mediastinal lymphadenopathy and especially tuberculosis [12,16,19–21,34,38].

In general, cytology may not be regarded as sufficient to differentiate between tuberculosis and sarcoidosis, as epithelioid cell granulomas are present in both scenarios and the interpretation of the "dirty background" may be difficult [22]. However, strength of association within the whole cohort as assessed by the kappa statistic and Pearson's correlation coefficient suggests that cytology obtained by EUS–FNA is a viable method for reliably differentiating between the two diseases.

This is the first study to use EUS–FNA and cytology and bacteriology to diagnose either tuberculosis or sarcoidosis and to differentiate them from each other. It was performed on patients in whom all prior efforts to obtain diagnosis with conventional methods had failed to establish a diagnosis. The true percentage of the patients in whom this was the case out of all with such a diagnosis cannot be stated, as the patients were sent from a multitude of other local institutions to our centers. But reviewing the literature of negative outcome with other methods, the numbers of patients in whom this could be of benefit if other methods fail, ranges from 28% in stage I sarcoidosis to 17% in tuberculosis [9,10]. But for the future, it needs to be discussed whether EUS–FNA should be performed much earlier in the work-up of those patients, as is the case already in the work-up of lung cancer and mediastinal lymphadenopathy. This procedure is likely to significantly reduce the morbidity and cost associated with more invasive mediastinal lymph node sampling procedures.

Competing interests: None

Institutions
[1] Homerton University Hospital NHS Foundation Trust, London UK
[2] St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK
[3] Interdisciplinary Endoscopy, Department of Internal Medicine I, University Hospital Schleswig-Holstein, Campus Kiel, Germany
[4] Cytologic Institute, Hannover, Germany

References

1 *Raviglione MC*, *Snider Jr DE*, *Kochi A*. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA 1995; 273: 220–226
2 *Chan ED*, *Iseman MD*. Current medical treatment for tuberculosis. BMJ 2002; 325: 1282–1286
3 Joint Tuberculosis Committee of the British Thoracic Society. prevention of tuberculosis in the United Kingdom: code of practice 2000. Control and Thorax 2000; 55: 887–901
4 *Maher D*, *Dye C*, *Floyd K et al.* Planning to improve global health: the next decade of tuberculosis control. Bull World Health Organ 2007; 85: 341–347
5 *Ormerod LP*, *Prescott RJ*. The management of pulmonary and lymph node tuberculosis notified in England and Wales in 1998. Clin Med 2003; 3: 57–61
6 *French CE*, *Kruijshaar ME*, *Jones JA*, *Abubakar I*. The influence of socioeconomic deprivation on tuberculosis treatment delays in England, 2000-2005. Epidemiol Infect 2009; 137: 591–596
7 *Baughman RP*, *Lower EE*, *du Bois RM*. Sarcoidosis. Lancet 2003; 361: 1111–1118
8 Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999; 160: 736–755
9 *Trisolini R*, *Lazzari Agli L*, *Cancellieri A et al.* The value of flexible transbronchial needle aspiration in the diagnosis of stage I sarcoidosis. Chest 2003; 124: 2126–2130
10 *Bilaceroglu S*, *Gunel O*, *Eris N et al.* Transbronchial needle aspiration in diagnosing intrathoracic tuberculous lymphadenitis. Chest 2004; 126: 259–267
11 *Fritscher-Ravens A*, *Sriram PV*, *Bobrowski C et al.* Mediastinal lymphadenopathy in patients with or without previous malignancy: EUS-FNA-based differential cytodiagnosis in 153 patients. Am J Gastroenterol 2000; 95: 2278–2284
12 *Vilmann P*, *Puri R*. The complete "medical" mediastinoscopy (EUS-FNA + EBUS-TBNA). Minerva Med 2007; 98: 331–338
13 *Vilmann P*, *Annema J*, *Clementsen P*. Endosonography in bronchopulmonary disease. Best Pract Res Clin Gastroenterol 2009; 23: 711–728
14 *Micames CG*, *McCrory DC*, *Pavey DA et al.* Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: a systematic review and metaanalysis. Chest 2007; 131: 539–548
15 *Fritscher-Ravens A*, *Sriram PV*, *Topalidis T et al.* Diagnosing sarcoidosis using endosonography-guided fine-needle aspiration. Chest 2000; 118: 928–935
16 *Annema JT*, *Veselic M*, *Rabe KF*. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. Eur Respir J 2005; 25: 405–409
17 *Wildi SM*, *Judson MA*, *Fraig M et al.* Is endosonography guided fine needle aspiration (EUS-FNA) for sarcoidosis as good as we think? Thorax 2004; 59: 794–799

18 *Iwashita T*, *Yasuda I*, *Doi S et al.* The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis. Endoscopy 2008; 40: 400 – 405
19 *von Bartheld MB*, *Veselic-Charvat M*, *Rabe KF*, *Annema JT*. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. Endoscopy 2010; 42: 213 – 217
20 *Khoo KL*, *Ho KY*, *Nilsson B*, *Lim TK*. EUS-guided FNA immediately after unrevealing transbronchial needle aspiration in the evaluation of mediastinal lymphadenopathy: a prospective study. Gastrointest Endosc 2006; 63: 215 – 220
21 *Khoo KL*, *Ho KY*, *Khor CJ et al.* First endoscopic procedure for diagnosis and staging of mediastinal lymphadenopathy. World J Gastroenterol 2009; 15: 6096 – 6101
22 *Koo V*, *Lioe TF*, *Spence RA*. Fine needle aspiration cytology (FNAC) in the diagnosis of granulomatous lymphadenitis. Ulster Med J 2006; 75: 59 – 64
23 *Fritscher-Ravens A*, *Soehendra N*, *Schirrow L et al.* Role of transesophageal endosonography-guided fine-needle aspiration in the diagnosis of lung cancer. Chest 2000; 117: 339 – 345
24 *Dupont WD*, *Plummer Jr WD*. Power and sample size calculations for studies involving linear regression. Control Clin Trials 1998; 19: 589 – 601
25 *Dupont WD*, *Plummer Jr WD*. Power and sample size calculations. A review and computer program. Control Clin Trials 1990; 11: 116 – 128
26 *Porte H*, *Roumilhac D*, *Eraldi L et al.* The role of mediastinoscopy in the diagnosis of mediastinal lymphadenopathy. Eur J Cardiothorac Surg 1998; 13: 196 – 199
27 *Julious SA*. Two-sided confidence intervals for the single proportion: comparison of seven methods by Robert G. Newcombe, Statistics in Medicine 1998; 17: 857 – 872 . Stat Med 2005; 24: 3383-3384.
28 *Newcombe RG*. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998; 17: 857 – 872
29 *Wiselka M*. 2006: a year for cautious optimism in tuberculosis. J Infect 2006; 53: 1 – 4
30 Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 60 months. Am Rev Respir Dis 1984; 130: 23 – 28
31 *Berger LP*, *Scheffer RC*, *Weusten BL et al.* The additional value of EUS-guided Tru-cut biopsy to EUS-guided FNA in patients with mediastinal lesions. Gastrointest Endosc 2009; 69: 1045 – 1051
32 *Storch I*, *Shah M*, *Thurer R et al.* Endoscopic ultrasound-guided fine-needle aspiration and Trucut biopsy in thoracic lesions: when tissue is the issue. Surg Endosc 2008; 22: 86 – 90
33 *Saftoiu A*, *Vilmann P*, *Guldhammer Skov B*, *Georgescu CV*. Endoscopic ultrasound (EUS)-guided Trucut biopsy adds significant information to EUS-guided fine-needle aspiration in selected patients: a prospective study. Scand J Gastroenterol 2007; 42: 117 – 125
34 *Song HJ*, *Park YS*, *Seo DW et al.* Diagnosis of mediastinal tuberculosis by using EUS-guided needle sampling in a geographic region with an intermediate tuberculosis burden. Gastrointest Endosc 2010; 71: 1307 – 1313
35 *Armstrong JR*, *Radke JR*, *Kvale PA et al.* Endoscopic findings in sarcoidosis. Characteristics and correlations with radiographic staging and bronchial mucosal biopsy yield. Ann Otol Rhinol Laryngol 1981; 90: 339 – 343
36 *Sriram PVJ*, *Kaffes AJ*, *Rajasekhar P et al.* EUS features of mediastinal tuberculosis: a PCR based cytodiagnosis by trans-esophageal EUS-FNA. Gastrointest Endosc 2004; 59: 216
37 *Costabel U*, *Hunninghake GW*. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J 1999; 14: 735 – 737
38 *Puri R*, *Vilmann P*, *Sud R et al.* Endoscopic ultrasound-guided fine-needle aspiration cytology in the evaluation of suspected tuberculosis in patients with isolated mediastinal lymphadenopathy. Endoscopy 2010; 42: 462 – 467