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Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis

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ABSTRACT: The objective of the current study was to assess the yield of endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) for the diagnosis of sarcoidosis in a large patient group.

Bronchoscopy with transbronchial lung biopsy (TBLB) is nondiagnostic in 30% of patients with suspected sarcoidosis and has a risk of pneumothorax and haemoptysis. In order to obtain a diagnosis, mediastinoscopy is often performed as the next diagnostic procedure. EUS-FNA provides a nonsurgical alternative for the demonstration of noncaseating granulomas by aspirating mediastinal lymph nodes from the oesophagus.

In total, 51 patients with suspected sarcoidosis stage I and II underwent EUS-FNA. Thirty-six patients (71%) previously underwent a nondiagnostic bronchoscopy. All patients were clinically followed (median 18 months) and surgical–pathological verification occurred in those patients with EUS aspirates that contained unrepresentative material.

EUS-FNA demonstrated noncaseating granulomas without necrosis in 41 of 50 patients (82%) with the final diagnosis of sarcoidosis. Specific ultrasound features of clustered, well-demarcated iso-echoic lymph nodes were observed in 64% of patients with sarcoidosis. No complications occurred.

Endoscopic ultrasound-guided fine-needle aspiration has a high yield in diagnosing sarcoidosis and qualifies as the next diagnostic step after a nondiagnostic bronchoscopy. The current authors expect that endoscopic ultrasound-guided fine-needle aspiration will reduce the number of mediastinoscopies for the diagnosis of sarcoidosis dramatically.

KEYWORDS: Endoscopic ultrasound-guided fine-needle aspiration, mediastinal lymph nodes, sarcoidosis

In patients with suspected sarcoidosis a tissue diagnosis is strongly recommended to exclude malignant diseases or tuberculosis, especially when treatment is considered [1]. Biopsy specimens should be obtained from the most readily accessible organ using the least invasive method [1]. Bronchoscopy with transbronchial lung biopsy (TBLB) is the initial technique of choice [2] and has a yield of ~65% (range 40–90%) in demonstrating noncaseating granulomas [3, 4]. Currently, approximately one-third of bronchoscopies for suspected sarcoidosis remain nondiagnostic. As intrathoracic lymphadenopathy is common in sarcoidosis, with radiographic evidence of hilar node enlargement in up to 90% of patients [1], lymph nodes (LNs) are a likely target to confirm the diagnosis.

Mediastinoscopy is currently regarded as the next diagnostic step after a nondiagnostic bronchoscopy in these patients [2, 5]. Although high yields of 82–97% in demonstrating noncaseating granulomas are reported [5–7], mediastinoscopy is invasive, requires general anaesthesia, often clinical admission and has a morbidity of 2% [8].

Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) is an accurate technique for the analysis of mediastinal LNs from the oesophagus, especially for those LNs located subcarinally, the aortopulmonary window and the lower mediastinum [9, 10]. Due to its high accuracy, safety and minimally invasive nature, EUS-FNA is increasingly used for the diagnosis and staging of lung cancer [9–12]. In a preliminary report in patients with suspected sarcoidosis, EUS-FNA has also been shown to be accurate in demonstrating noncaseating granulomas [13].

In this large prospective study, patients with suspected sarcoidosis underwent EUS-FNA. The vast majority of patients previously underwent a nondiagnostic bronchoscopy. The current authors

For editorial comments see page 400.

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hypothesised that EUS-FNA has a high yield in demonstrating noncaseating granulomas and, therefore, that surgical interventions, such as mediastinoscopy, could be prevented.

PATIENTS AND METHODS

Study design

Patients with suspected sarcoidosis with enlarged (>1 cm) hilar or mediastinal LNs on chest computed tomography (CT), were eligible for this study. All patients underwent EUS-FNA for diagnostic purposes and were clinically followed. Mediastinoscopy was performed if EUS-FNA did not deliver representative material.

Patients

In total, 51 consecutive patients with the differential diagnosis of sarcoidosis were included in this study. Patients were either symptomatic or malignant disease or tuberculosis had to be excluded. The mean age of the study population was 42 yrs (range 23–81) and 63% were male. Patients had suspected sarcoidosis stage I (n=32) or II (n=19). Altogether, 36 patients (71%) had previously undergone a nondiagnostic bronchoscopy. Informed consent was obtained from all patients.

Endoscopic ultrasound-guided fine-needle aspiration

EUS-FNA examinations were performed at the Dept of Pulmonary Medicine, Leiden University Medical Center (LUMC), Leiden, the Netherlands. The LUMC is a teaching and tertiary care hospital and the pulmonary dept is a referral site for the analysis of mediastinal lesions by EUS-FNA. An echo-endoscope (FG 34 UX; Pentax, Tokyo, Japan) with a longitudinal convex ultrasound transducer with an adjustable ultrasonic frequency of 5, 7.5 or 10 MHz was used, in combination with an ultrasound scanner (EUB 6500; Hitachi, Tokyo, Japan). EUS-FNA was performed, on an outpatient basis under conscious sedation using midazolam (1–5 mg *i.v.*). Prior to EUS-FNA, a recent CT scan of the chest was available to the investigators. Ultrasound features of mediastinal LNs were described and videotaped, and aspirates were obtained under EUS guidance from the oesophagus with a 22-gauge needle (Hancke/Vilmann; GIP/MEDI-Globe, Achenmühle, Germany). The aspirated material was examined on site by one of the investigators who were trained by pathologists to judge samples for its adequacy. Once granulomas were identified in one specimen, the procedure was stopped. There was no pathologist present during the procedure itself. After the procedure, all slides were examined by an experienced cytopathologist (M. Veseliç). Patients were observed for 2 h after the procedure. They were instructed to contact the hospital in the case of chest discomfort or complaints.

Data analysis

In all patients the diagnosis of sarcoidosis was suspected based on clinical and radiological criteria. The final diagnosis was based on LN aspirates obtained by EUS revealing noncaseating granulomas without necrosis (fig. 1), clinical and radiological follow-up, and histology in those cases where mediastinoscopy was performed. Based on the number of patients with the final diagnosis of sarcoidosis, the proportion of patients in which EUS demonstrated noncaseating granulomas was calculated *versus* the total number of patients with sarcoidosis.

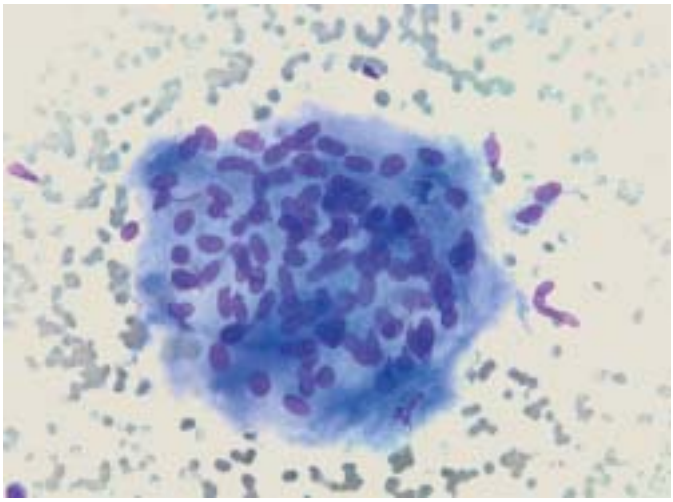

FIGURE 1. Endoscopic ultrasound-obtained lymph node aspirate demonstrating a noncaseating granuloma without necrosis, as seen in sarcoidosis.

RESULTS

Endoscopic ultrasound-guided fine-needle aspiration

EUS detected mediastinal LNs in all patients with a mean size of 25 mm (range 5–40 mm). In 32 patients (63%) a typical pattern of clustered, well-demarcated LNs with a homogeneous iso-echoic echo texture (fig. 2) was observed. In 50 patients (98%), a mean number of three biopsies (range 1–7) were performed. LNs were located paratracheally on the left (n=1), the aortopulmonary window (n=2), subcarinally (n=32), the lower para-oesphageal region (n=1), both paratracheally on the left as well as subcarinally (n=5) and both in the aortapulmonary window as well as subcarinally (n=9). Noncaseating granulomas without necrosis were found in 41 patients (82%), giant cells in one (2%), reactive LN tissue in five

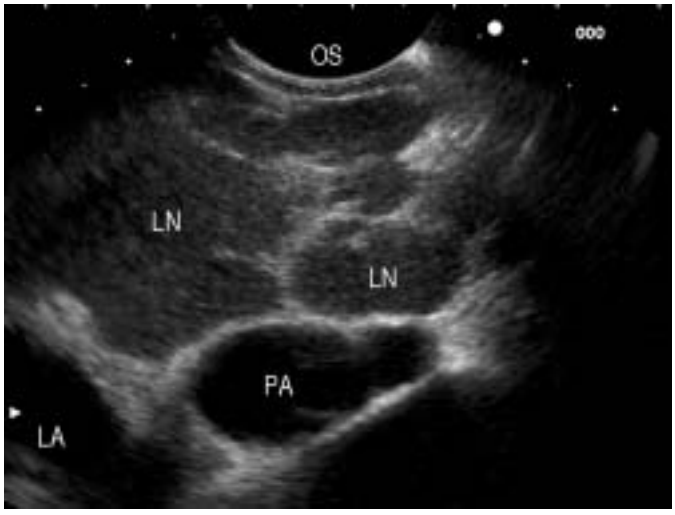

FIGURE 2. Endoscopic ultrasound image in a patient with sarcoidosis demonstrating multiple, well demarcated lymph nodes (LN) located between the oesophagus (OS), left atrium (LA) and pulmonary artery (PA).

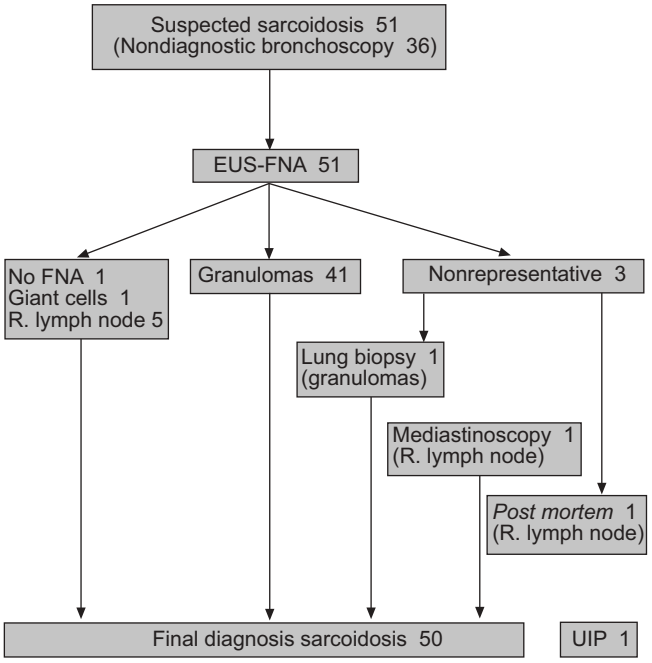

FIGURE 3. Scheme of study conduct. Numbers refer to the number of patients. EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; granulomas: noncaseating granulomas without necrosis; R. lymph node: reactive lymph node tissue; UIP: usual interstitial pneumonia.

(10%) and nonrepresentative material (squamous cell epithelium) in three patients (6%) (fig. 3). A mean number of three needle passes occurred for both patients with suspected sarcoidosis stage I and II. In one patient, a flat 5-mm LN was detected but not aspirated by EUS. PCR and culture for mycobacterium tuberculosis of LN aspirates was performed in 10 patients and were negative in all. No complications, such as pneumothorax, bleeding or fever, occurred.

EUS-FNA findings of noncaseating granulomas were confirmed in all five patients that underwent mediastinoscopy (n=4) or thoracotomy (n=1). Of the three patients in whom EUS-FNA revealed nonrepresentative material, one had fibrotic LNs without granulomas (mediastinoscopy), one had granulomas in a lung nodule (CT guided lung biopsy) and one patient had reactive LNs (*post mortem* examination). All patients were clinically and radiologically followed for a median of 18 months (range 2–54).

The final diagnosis sarcoidosis was given to 50 patients, based on clinical and radiological features, the presence of noncaseating granulomas without necrosis (in 42 patients), as well as clinical and radiological follow-up. EUS-FNA demonstrated noncaseating granulomas without necrosis in 41 of 50 patients (82%) in patients with suspected sarcoidosis. In eight patients no tissue proof of noncaseating granulomas was available. One patient was diagnosed *post mortem* with a usual interstitial pneumonia (fig. 3).

DISCUSSION

EUS-FNA demonstrated noncaseating granulomas in 82% of patients with suspected sarcoidosis stage I or II. The most frequently seen ultrasound pattern of mediastinal LNs was clustered, well-demarcated LNs with an iso-echoic texture, in 64% of patients.

Data from this large prospective study (n=51) confirm the results of the preliminary study by FRITSCHER-RAVENS *et al*. [13] in 19 patients, who found a sensitivity and specificity of EUS-FNA in diagnosing sarcoidosis of 100% and 94% respectively. This corresponds with the results of a recently published study in patients with enlarged mediastinal LNs of unknown origin where the sensitivity and specificity for EUS-FNA was 89% and 96% [14]. Limitations of the latter study are its retrospective design and the fact that in addition to 28 patients with the final diagnosis of sarcoidosis, the final diagnosis was indefinite in 16 patients. The somewhat lower yield found in the current study cohort might be due to large number of patients with sarcoidosis stage II (37%) who tend to have more fibrotic LNs compared with stage I. In three of the nine patients in whom EUS-FNA did not assess granulomas, a significant resistance was experienced when trying to advance the needle in the LN. Histopathological examination of one of these LNs demonstrated a node with extensive fibrosis without granulomas. In these particular cases EUS-FNA did not provide representative material. In the patients in whom EUS obtained aspirates demonstrated only giant cells (n=1) or reactive LN tissue (n=5), granulomas were possibly missed due to a sampling error. As surgical verification of these LNs was not available it is possible that these nodes were truly negative for granulomas. However, as the clinical picture was compatible with sarcoidosis the current authors regarded EUS results in these patients as false negative. In 64% of patients with the final diagnosis of sarcoidosis, multiple, clustered LNs, with a homogenous iso-echoic echo texture with well-demarcated margins (fig. 2) were observed, as described in seven patients by MISHRA *et al*. [14]. To the current authors, these EUS features are highly predictive for sarcoidosis as they are different from those of malignant LNs but further studies have to confirm these findings. The current authors did not notice hyper-echoic central foci [15] or atypical vessels [13], as observed by others in some patients with sarcoidosis. The yield of at least 82% in demonstrating granulomas in sarcoidosis found in the current study is comparable to the yield of EUS-FNA in diagnosing LN metastases (88%) in lung cancer staging [10].

How does EUS-FNA compare with other techniques in the diagnosing of sarcoidosis and when should it be used? According to the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders statement [2] the diagnosis of sarcoidosis needs a compatible clinical picture, as well as tissue demonstrating noncaseating granulomas without necrosis and other diseases with these features have to be excluded. Although the need for a tissue diagnosis is under debate in asymptomatic patients, as spontaneous remission occurs in up to two-thirds of patients [2], in symptomatic patients tissue diagnosis is needed before possible treatment and to rule out other diseases, such as LN metastases, lymphoma or tuberculosis [1]. Tissue specimens should be obtained from the most readily accessible organ with the least invasive method [1]. TBLB is the procedure of choice in most cases [1, 2]. The yield of ~65% (range 40–90%) [3, 4, 16–19] is operator-dependent and optimal results are achieved if 4–5 biopsies are taken for stage II [3, 19] and up to 10 biopsies for stage I [19].

Transbronchial needle aspiration (TBNA) in patients with suspected sarcoidosis revealed noncaseating granulomas in 66% of patients using rigid [20] and 50–72% patients using flexible bronchoscopy [16, 18, 21]. The diagnostic yield of TBNA and TBLB combined is significantly higher than TBNA or TBLB alone [16, 17, 21], reaching up to 80–90% [16–18, 21]. Maximum yield is acquired if endobronchial mucosal biopsies are taken as well [17]. TBLB has a risk of pneumothorax in 5% and pulmonary haemorrhage in 2% of patients with sarcoidosis [17]. In daily practice, the reported success rate of bronchoscopy in patients with suspected sarcoidosis is often not achieved due to an inadequate number of transbronchial lung biopsies and under use of transbronchial needle aspiration. In the future, endobronchial ultrasound-guided FNA, a novel technique by which lesions adjacent to the trachea and main bronchi can be aspirated under real-time ultrasound guidance from the airways, might also be an alternative in increasing the diagnostic yield of bronchoscopy in the diagnosis of sarcoidosis [22]. The use of bronchoalveolar lavage with assessment of CD4/CD8 ratios differs widely by region due its low sensitivity (<60%) for diagnosing sarcoidosis.

In patients with suspected sarcoidosis and enlarged mediastinal LNs, mediastinoscopy is regarded as the next diagnostic step [2]. Although its diagnostic yield of 82–97% [5–7] is high, mediastinoscopy has a morbidity of 2% [8], and requires general anesthesia, operating facilities and clinical admission in most hospital settings. Additionally, this generally young patient population ends up with scarring to the neck.

EUS-FNA in the current study has a comparable yield, compared with both bronchoscopy (with both TBLB and TBNA adequately performed) and mediastinoscopy in the diagnosis of sarcoidosis, but EUS-FNA is safer, as no complications in the analysis of mediastinal LNs have yet been reported [9, 10]. An additional advantage of EUS-FNA lies in the fact that LN tissue is obtained, an important fact in those patients with a previous or suspected malignancy. Whether in the future a CT scan of the thorax is still necessary in patients with suspected sarcoidosis who are referred for EUS-FNA remains an open question. Although not proven, the current authors hypothesise that it will be feasible to perform EUS-FNA without a CT scan.

Several limitations apply to the current study. Only patients with suspected sarcoidosis stage I and II were included and conclusions, therefore, only apply to this group. EUS-FNA was performed with a 22-gauge needle that provides cytological material, and only a fraction of the study cohort underwent histological verification of the EUS-FNA results, as most referring physicians considered it unethical to have the diagnosis confirmed by mediastinoscopy. FNA of LNs has previously been shown to be accurate in demonstrating noncaseating granulomas [23, 24]. It should be noted that as with histological biopsies, the presence of noncaseating epitheloid cells granulomas without necrosis alone is not diagnostic for sarcoidosis. Other granulomatous diseases were excluded before deciding on the final diagnosis of sarcoidosis. In the current study, in 10 patients with a slight suspicion of tuberculosis, PCR and culture of LN aspirates were performed, which were all negative. The current authors are well aware that in their region histoplasmosis is not endemic and the prevalence of tuberculosis is low. Whether the results of the current study are applicable to regions with a high prevalence of tuberculosis or histoplasmosis has yet to be established. Pneumoconioses, such as berylliosis, were excluded in the absence of any occupational risk factor. Sarcoid-like lesions in regional LNs to carcinoma or lymphomas were considered unlikely due to the long-term follow-up of 18 months median. It should be clear that granulomatous reactions to malignancies should always be taken into account and in patients with suspected malignancy additional LN analysis by mediastinoscopy should be considered. In none of the patients in the current study did the final diagnosis sarcoidosis have to be changed during follow-up. The current authors are well aware that the pre-test probability of sarcoidosis was very high, which might be a bias toward the high yield obtained in this study. Furthermore, only one patient in the current study had another disease besides sarcoidosis. Finally, the technique of EUS-FNS is clearly operator-dependent, requires specific expertise and is currently only available in a few specialised hospitals.

In conclusion, endoscopic ultrasound-guided fine-needle aspiration has a high yield in demonstrating noncaseating granulomas in patients with suspected sarcoidosis. Endoscopic ultrasound-guided fine-needle aspiration qualifies as the next diagnostic procedure after a nondiagnostic bronchoscopy and may significantly reduce the number of mediastinoscopies.

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