Improved negative predictive value of EBUS-TBNA in isolated mediastinal / hilar lymphadenopathy:

Improved negative predictive value of EBUS-TBNA in isolated mediastinal / hilar lymphadenopathy: Why and what it means for patients?

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Introduction

The traditional differential diagnosis of isolated mediastinal and hilar lymphadenopathy includes benign granulomatous disorders e.g. sarcoidosis and tuberculosis and malignant conditions such as lymphoma and carcinoma. Each of these diagnoses requires pathological confirmation to ensure appropriate treatment. Lymphadenopathy in which such causes have been excluded has been termed "reactive lymphadenopathy", and is considered benign.

In a prospective trial of 77 patients with isolated mediastinal lymphadenopathy EBUS-TBNA prevented mediastinoscopy in 87% of patients and demonstrated a sensitivity of 92%[1]. EBUS-TBNA is therefore recommended as a first line investigation in such patients. However the negative predictive value was 40% suggesting in cases of negative EBUS-TBNA further sampling, such as mediastinoscopy, is required. Of note, only 4 patients in this study were ultimately diagnosed with 'reactive lymphadenopathy'.

There is increasing evidence that common chronic diseases, both respiratory and non-respiratory, are associated with mediastinal and hilar lymphadenopathy. This includes: emphysema and chronic bronchitis, interstitial lung disease, bronchiectasis, pulmonary hypertension, heart failure and rheumatoid arthritis[2-10]. Lymphadenopathy in this scenario would fall under the term "reactive lymph nodes" following pathological sampling. Could this lead to a higher prevalence of reactive lymphadenopathy in the isolated lymphadenopathy population and do these patients require further surgical biopsy following a negative EBUS-TBNA?

Objectives

The primary objective of this study was to determine the prevalence of reactive lymphadenopathy in patients undergoing EBUS-TBNA for isolated lymphadenopathy at a tertiary centre. Secondary aims were to determine the presence of respiratory and non-respiratory disease that may explain the lymphadenopathy in this group and to investigate for potential clinical and radiological characteristics that could identify which patients may need further invasive sampling and which may undergo surveillance in cases of negative EBUS-TBNA.

Materials and Methods

The study was a prospective observational cohort of all patients undergoing EBUS-TBNA for investigation of isolated mediastinal and/or hilar lymphadenopathy, between March 2010 and November 2012, at the Bronchoscopy Unit of the University Hospital of South Manchester, UK.

Patients were included if they had enlarged hilar or mediastinal lymph nodes (≥10mm in short axis diameter) without evidence of an intra-pulmonary mass and no evidence of extra-thoracic malignancy. The final diagnosis for each patient was based on EBUS-TBNA results, any subsequent pathological sampling and clinical-radiological follow-up, which was undertaken for a period of six months after the procedure.

Diagnoses were classified as one of: sarcoidosis, tuberculosis, lymphoma, carcinoma or reactive lymphadenopathy. A lymph node was only classified as reactive if the EBUS-TBNA, any subsequent pathological sampling and 6 months of clinical-radiological follow up failed to demonstrate any evidence of the other diagnoses.

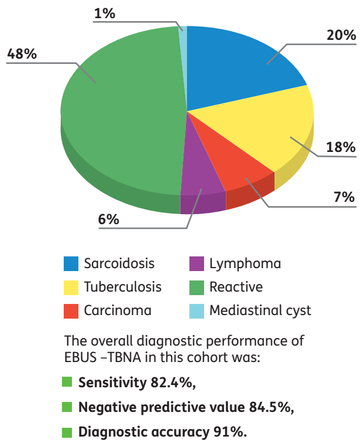
Results

A total of 100 patients underwent EBUS-TBNA for isolated mediastinal / hilar lymphadenopathy during the study period (Table 1) and the final diagnosis is demonstrated in Figure 1.

Table 1: Patients' Characteristics (n=100)

Patient characteristics	n=100
Age (mean ± SD)	58.7 ±15.6
Gender (male)	63
Ethnicity:	
Caucasian	70
Asian	24
African	6
Symptoms:	
Cough	64
Dyspnoea	52
Weight loss	27
Fever or night sweats	18
Chest pain	9
Asymptomatic	14

Figure 1: Final Diagnosis (n=100)



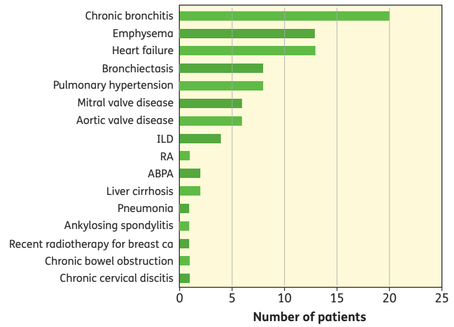
The overall diagnostic performance of EBUS –TBNA in this cohort was:

- **Sensitivity 82.4%,**
- **Negative predictive value 84.5%,**
- **Diagnostic accuracy 91%.**

Reactive lymphadenopathy

Reactive lymphadenopathy was the most common cause of isolated lymphadenopathy. There was a higher prevalence of co-morbidities compared to the other diagnosis groups (Table 2). There was only 1 patient in which no co-morbidity was present to account for the lymphadenopathy. Figure 2 demonstrates the co-morbidities present in those patients with reactive lymphadenopathy.

Figure 2: Co-morbidities



Granulomatous disorders

Sarcoidosis accounted for 20% of the final diagnoses.
The sensitivity of EBUS-TBNA was 80% (16/20 correctly diagnosed). Patients with sarcoidosis had a higher total number of enlarged lymph node stations compared with the other diagnoses and mediastinal lymphadenopathy always occurred with hilar lymphadenopathy and the lymphadenopathy was almost always symmetrical (table 2). In 45% (9/20) of patients there were lung parenchymal abnormalities suggestive of sarcoidosis (nodularity with upper zone predominance). One patient had associated erythema nodosum.

Tuberculosis accounted for 18% of the final diagnoses.
EBUS-TBNA correctly diagnosed 17/18 patients (sensitivity 94.4%). All patients diagnosed with tuberculosis in this cohort were of non-Caucasian ethnicity (table 2). In addition, patients frequently had isolated mediastinal lymphadenopathy without hilar lymphadenopathy (67% of cases). The lymphadenopathy was frequently asymmetrical. Five patients had known TB contact and 1 patient had cavitating upper lobe consolidation in association with the lymphadenopathy.

Table 2: Patient characteristics stratified into diagnosis groups

	Sarcoidosis n=20	Tuberculosis n=18	Lymphoma n=6	Carcinoma n=7	Reactive LN n=48
Age (mean ± SD)	50.6 ± 13.8	41.2 ± 13.3	66.3 ± 13.2	70.9 ± 5.3	68.0 ± 11.1
Ethnicity:					
Caucasian	15 (75%)	0	6 (100%)	7 (100%)	41 (85%)
Asian	3 (15%)	16 (89%)	0	0	5 (11%)
African	2 (10%)	2 (11%)	0	0	2 (4%)
Co-morbidities:					
Emphysema	2 (10%)	0	0	3 (43%)	13 (27%)
Ch bronchitis	1 (5%)	1 (5%)	0	0	20 (42%)
ILD	0	0	0	1 (14%)	4 (8%)
Bronchiectasis	0	0	1 (17%)	1 (14%)	8 (17%)
Pul HTN	0	0	0	0	8 (17%)
HF	0	0	0	0	13 (27%)
MVD	0	0	0	0	6 (12%)
AVD	0	0	0	0	6 (12%)
CTD	0	0	0	1 (14%)	1 (2%)
LN Stations:					
0-2	0	14 (78%)	1 (17%)	2 (29%)	20 (42%)
3-4	5 (25%)	3 (17%)	3 (50%)	4 (57%)	24 (50%)
≥5	15 (75%)	1 (5%)	2 (33%)	1 (14%)	4 (8%)
Isolated M	0	12 (67%)	2 (33%)	4 (57%)	16 (33%)
Isolated H	0	2 (11%)	1 (17%)	0	4 (8%)
Symmetrical M	15 (75%)	1 (5%)	2 (33%)	3 (43%)	10 (21%)
Symmetrical H	18 (90%)	2 (11%)	2 (33%)	0	10 (21%)

Key: Isolated M = isolated mediastinal lymphadenopathy, without hilar lymphadenopathy
Isolated H = isolated hilar lymphadenopathy, without mediastinal lymphadenopathy
Symmetrical M = symmetrical (bilateral) mediastinal lymphadenopathy
Symmetrical H = symmetrical (bilateral) hilar lymphadenopathy

Malignant diagnoses

Lymphoma accounted for 6% of the diagnoses.
EBUS-TBNA correctly diagnosed 2/6 patients (sensitivity 33.3%). 67% (4/6) of patients had extra-thoracic lymphadenopathy (sites included: abdominal 3, axillary 2, neck 1, inguinal 1). One patient had previously undergone a liver transplant was therefore heavily immunosuppressed.

Carcinoma accounted for 7% of diagnoses
(small cell lung cancer 4, squamous cell carcinoma 1, non-small cell lung cancer "not otherwise specified" 1, mesothelioma 1), all were correctly diagnosed with EBUS-TBNA (n=7/7; sensitivity 100%). Two patients (29%) had anterior mediastinal lymphadenopathy.

Table 3: Sensitivities for EBUS-TBNA in this study

	Sensitivity
Sarcoidosis (n=20)	80%
Tuberculosis (n=18)	94.4%
Lymphoma (n=6)	33.3%
Carcinoma (n=7)	100%
Overall	82.4%

False negative EBUS-TBNA

There were 9 false negative EBUS-TBNA (sarcoidosis 4, lymphoma 4, tuberculosis 1). In each case there was a high pre-test probability of a diagnosis other than reactive lymphadenopathy, based on pre-procedure radiology and clinical history.

Conclusions

In patients undergoing EBUS-TBNA at our centre for isolated mediastinal and /or hilar lymphadenopathy, nearly half had reactive lymphadenopathy rather than one of the traditional diagnoses in this setting (sarcoidosis, tuberculosis, lymphoma, carcinoma).

The most common chronic diseases that could be responsible for this reactive lymphadenopathy are emphysema, chronic bronchitis and heart failure.

Clinical and radiological features that suggest a high probability of a diagnosis other than reactive lymphadenopathy and indicate the need for further sampling in cases of negative EBUS-TBNA include:

- ≥5 lymph stations enlarged with symmetrical mediastinal and hilar lymphadenopathy (suggestive of sarcoidosis),
- lung parenchymal abnormalities (upper lobe cavitating consolidation in tuberculosis and upper zone nodularity in sarcoidosis),
- non-Caucasian ethnicity (suggestive of tuberculosis),
- anterior mediastinal lymphadenopathy (suggestive of lymphoma or carcinoma),
- extra-thoracic lymphadenopathy (suggestive of sarcoidosis or lymphoma),
- splenomegaly (suggestive of sarcoidosis or lymphoma),
- absence of diseases associated with lymphadenopathy.

With the increasing use of CT, an ageing population and an increasing prevalence of chronic diseases the detection of isolated hilar and mediastinal lymphadenopathy is increasing and reactive lymphadenopathy is representing a higher proportion of these cases.

The negative predictive value of EBUS-TBNA may be significantly higher than previously reported due to this subgroup of patients. This may allow a period of surveillance rather than requiring further invasive sampling with mediastinoscopy in carefully selected patients.

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