Case Series

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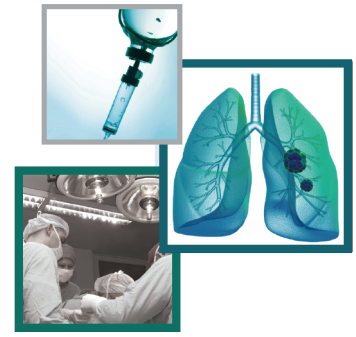
Lung Cancer Management



Lymphadenopathy and granulomas: benignancy of malignancy and differential diagnosis with endobronchial ultrasound-transbronchial needle biopsy 19G needle fine-needle aspiration biopsy

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Practice points

- Differential diagnosis is important among entities with similar clinical findings.
- Convex-endobronchial ultrasound transbronchial needle biopsy is essential for central lesions.
- Convex-endobronchial ultrasound sample is enough as a quantity to have efficient diagnosis.
- PET-computed tomography is also essential in several cases as a first diagnostic tool.

Endobronchial ultrasound (EBUS) is a very useful tool for the diagnosis of lymphadenopathy of the mediastinum. Nowadays, EBUS can substitute video-assisted thoracic surgery when a 19G needle is used. Several studies have provided data for efficient diagnosis not only for lung cancer, but for also sarcoidosis, tuberculosis and lymphoma. We present five cases of EBUS-transbronchial needle biopsy 19G needle used for the diagnosis of mediastinum lymphadenopathy. We present not only the pathological diagnosis, but also the steps for the differential clinical and pathological differential diagnosis for sarcoidosis, tuberculosis, cancer metastasis, respiratory infection and lymphoma.

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Keywords: EBUS • lymphoma • sarcoidodis • tuberculosis

Current technology allows us to approach different lesions within the thorax. We can use computed tomography (CT)-guided biopsies to approach lesions within the lung parenchyma or other thoracic lesions or even large lymph nodes. Moreover, we can use ultrasound probes – both linear and convex – in order to make superficial biopsies. Endoscopic methods during the past decade have been upgraded and new techniques such as the endobronchial ultrasound (EBUS) have enabled not only lung cancer diagnosis and staging, but also diagnosis of mediastinum lymphadenopathy [1,2]. The EBUS endoscope can use 22, 21 and 19G needles [3,4]. Cell blocks are being made

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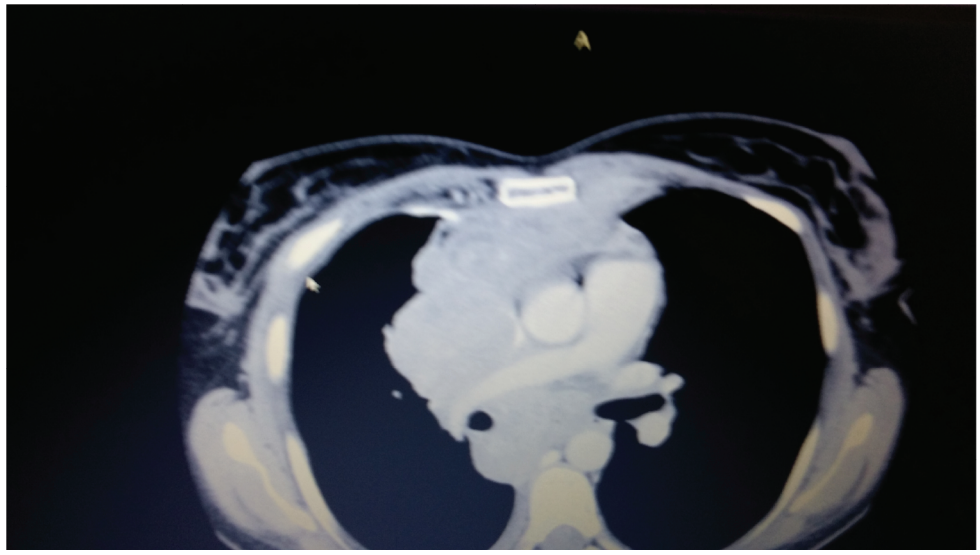

Figure 1. Lymph node mediastinum enlargement.

from the biopsy samples and can provide us with the diagnosis for several diseases such as: sarcoidosis, tuberculosis (TB), lung cancer, lymphoma and metastasis from other cancer types to the thorax lymph nodes [5]. It has been observed that 22 and 21G needles are not the best option for the diagnosis of lymphoma or even sometimes for sarcoidosis. This is due to the small tissue sample in comparison with the larger thoracic surgery sample, but also due to the nature of lymphoma and infiltration of the lymph nodes with sarcoidosis granulomas [6,7]. Furthermore, granulomas are a nonspecific finding in tissue samples and a clinical interpretation is needed [8,9]. During the last decade with the use of 19G needle and PET-CT, we were able to increase our pathologist experience with this type of fine-needle aspiration biopsy sample and diagnostic efficiency for lymphoma [10]. EBUS-transbronchial needle biopsy (TBNAB) can be easily performed with sedation and jet ventilation [11]. EBUS-TBNA has very few complications related to any endoscopy such as: mild adenitis, pneumothorax and mild hemoptysis [12]. We present four cases where medical history correlates with undiagnosed mediastinum lymphadenopathy.

Case 1

A 35-year-old woman had an x-ray 2 days after she gave birth due to shortness of breath. A CT scan of the thorax followed with intravenous contrast (Figure 1). Parenchymal involvement other than small atelectasis in different parts and very small pleura effusions due to atelectasis were observed. An EBUS-TBNAB with 19G needle was performed in order to make a differential diagnosis between lymphoma and sarcoidosis. We used a PENTAX EB-1970UK EBUS endoscope with a EUB-7000 HV ultrasound source and a Pentax 1000 camera light source (Figure 2) . We used for the biopsy a 19G needle which we can use through the EBUS EB-1970UK working channel. The angiotensin converting enzyme (ACE) was 28, which for our laboratory is within normal range. The pathology report was positive for sarcoidosis and the patient received bolus cortisone at a dosage of 1000 mg for 3 days and afterward 30 mg of methylprednisolone for a month. We performed additional blood tests for systematic collagen disease and the results were and still are negative. Indeed, nowadays she is on follow-up without any enlarged mediastinum lymph nodes (Figure 3).

Case 2

A 60-year-old woman was referred to her general practitioner for cough and fever. She was diagnosed with real time (RT)-PCR with COVID-19. The CT of the thorax was performed with intravenous contrast and mildly enlarged lymph nodes were observed (Figures 4 & 5). Owing to the patient's history, EBUS was proposed and performed to the patient after 20 days when the RT-PCR was negative. Lymph node biopsies from 4R and lymph node seven were negative for neoplasm; however, they contained necrotic debris. Biopsy with forceps from the bronchial epithelium was taken and again there was necrotic debris (Figure 6).

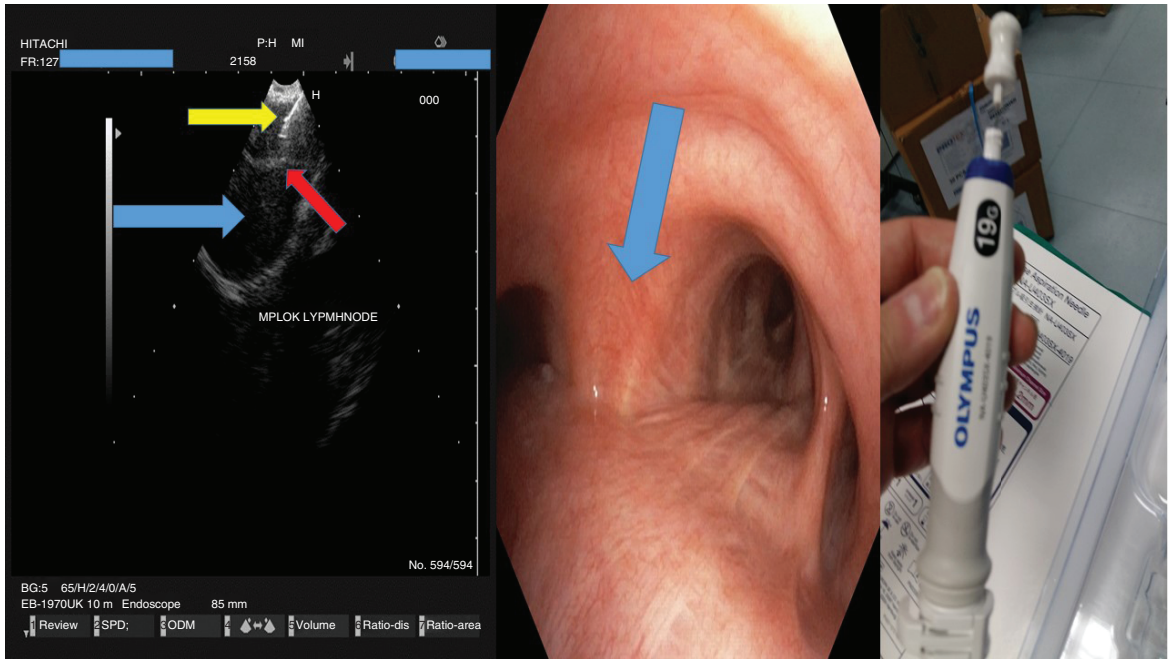

Figure 2. Clinical practice. Left: the blue arrow indicates the lymph node block, the yellow arrow indicates the 19G needle and the red arrow indicates a normal lymph node wall that surrounds a lymph node. Middle: we can observe an enlarged main carina. Right: a 19G Olympus needle.

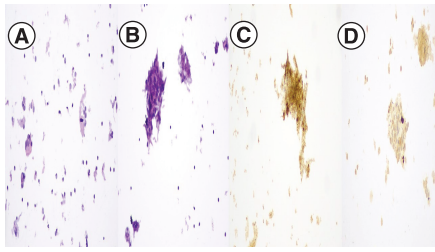

Figure 3. Clinical practice. (A & B) Hematoxylin and eosin: aggregates of epithelial-like histiocytes. **(C)** CD68: the majority of epithelial-like histiocytes were CD68 positive. **(D)** Ceratin cocktail: the histiocytic population was negative against pankeratin immunostain.

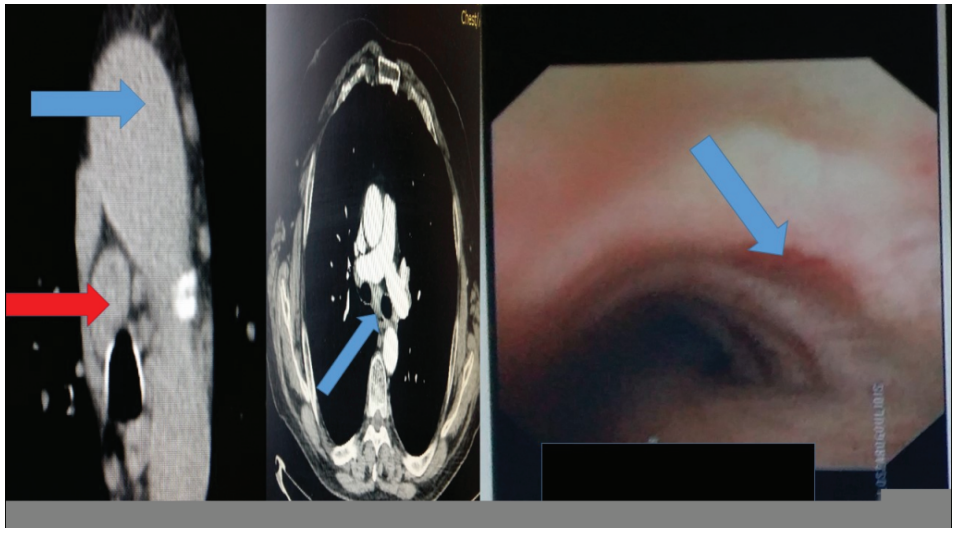

Figure 4. Clinical practice. Left: the blue arrow indicates the aorta arch and the red arrow indicates the 4R lymph node station. Middle: the blue arrow indicates the lymph node number 7. Right: the blue arrow indicates the puncture site of the OLYMPUS 19G needle where station 4R is stationed.

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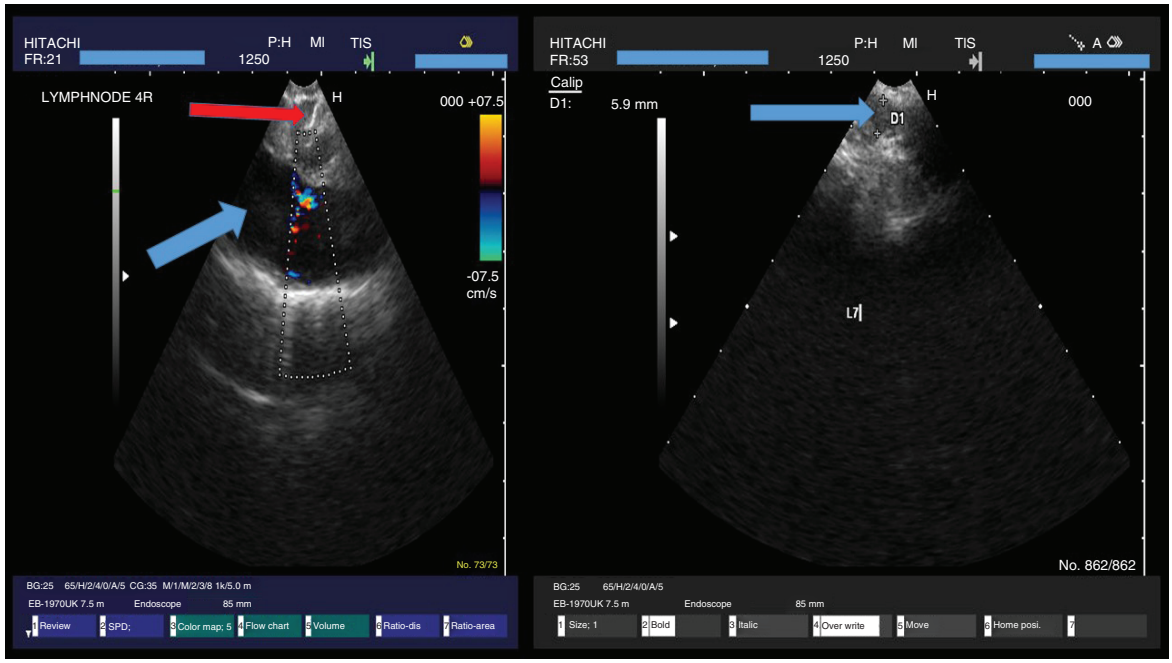

Figure 5. Clinical practice. Left: the blue arrow indicates the blood flow within the aorta and the red arrow indicates the needle within lymph node station number 4R. Right: station number 7 subcarinal, 5.9 mm in maximum diameter.

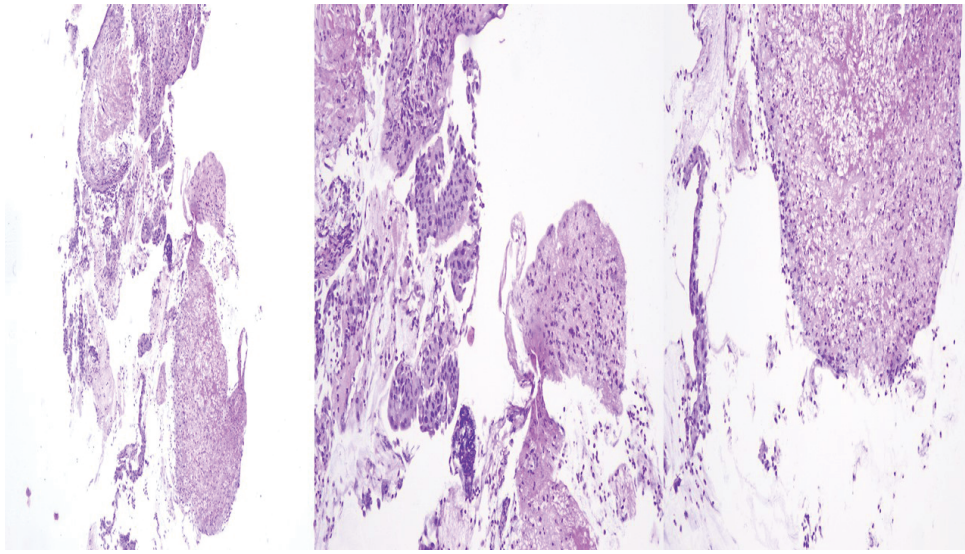

Figure 6. H&E: acute ulcerative bronchitis with necrotic debris.

Case 3

A 16-year-old female patient was presented with severe cough as an outpatient in our pulmonary patient care. She did not have any fever; however, she reported one instance of mild hemoptysis. A CT of the thorax revealed an extensive lymphadenopathy. EBUS-TBNAB 19G needle was performed along with sputum cultures for TB as the patient was an immigrant, living for the past 10 months in an immigration camp (Figure 7). There was also an endobronchial mass of granulomas (Figure 8). The subject was positive for TB. Her sputum cultures, the first result of which was available within 3 days and then her culture after 40 days, were positive for TB. We also performed PCR using the RealAccurate Quadruplex Mycobacteria PCR Kit *in vitro* diagnostic medical device directive (CE/IVD) (Pathofinder, Maastricht, The Netherlands). The PCR diagnosed DNA of *Mycobacterium*

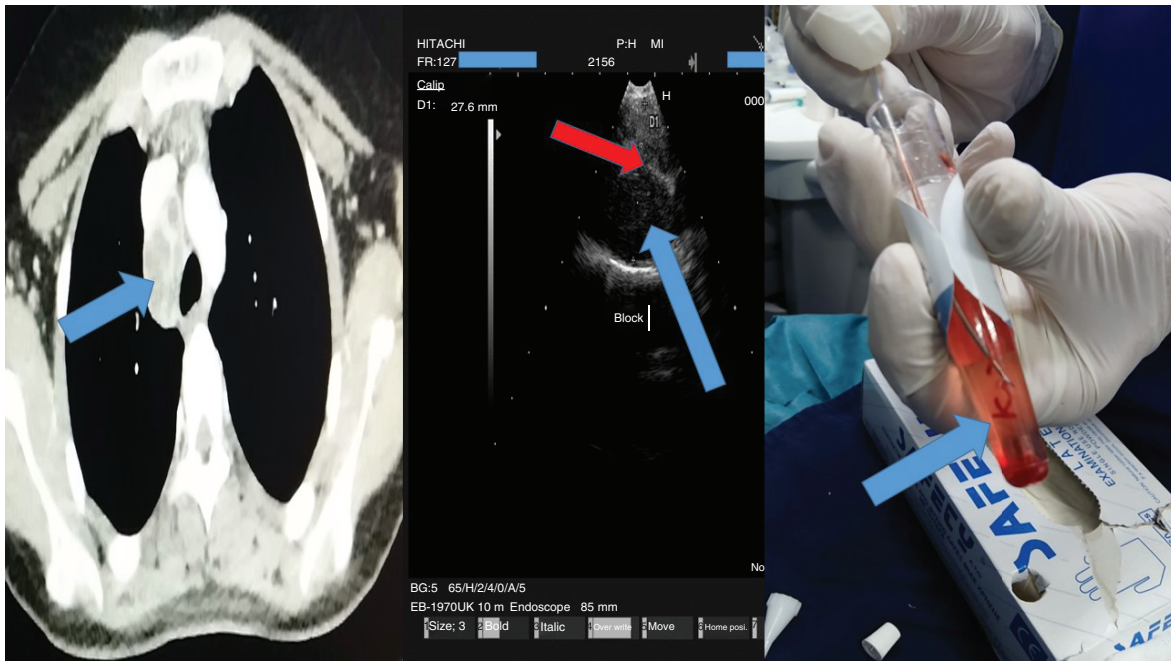

Figure 7. Clinical practice. Left: the blue arrow indicates the station 4R. Middle: the blue arrow indicates the enlarged lymph node and the red arrow indicates a normal lymph node border. Right: the blue arrow indicates the tissue sample.

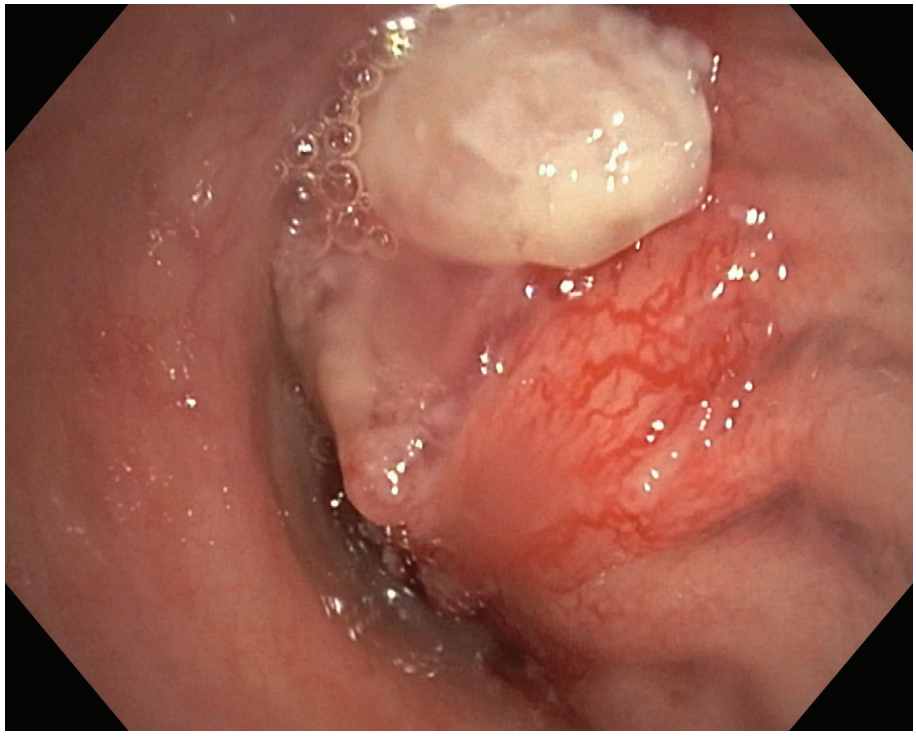

Figure 8. The female patient had an endobronchial mass with necrosis on the surface.

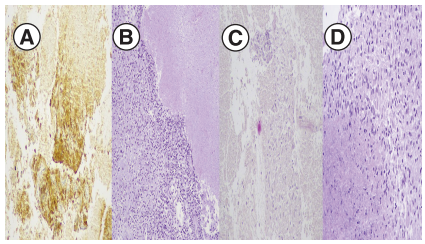

Figure 9. Clinical practice. (A & B) Hematoxylin and eosin: aggregates of epitheliomatous histiocytes and granulomatous caseating areas (×100). **(C)** CD68 stain highlighted the histiocytic population. Cytokeratin stain was negative (×100). **(D)** Ziel Nielsen histochemical stain revealed the presence of mycobacterium (magenta color) (×200).

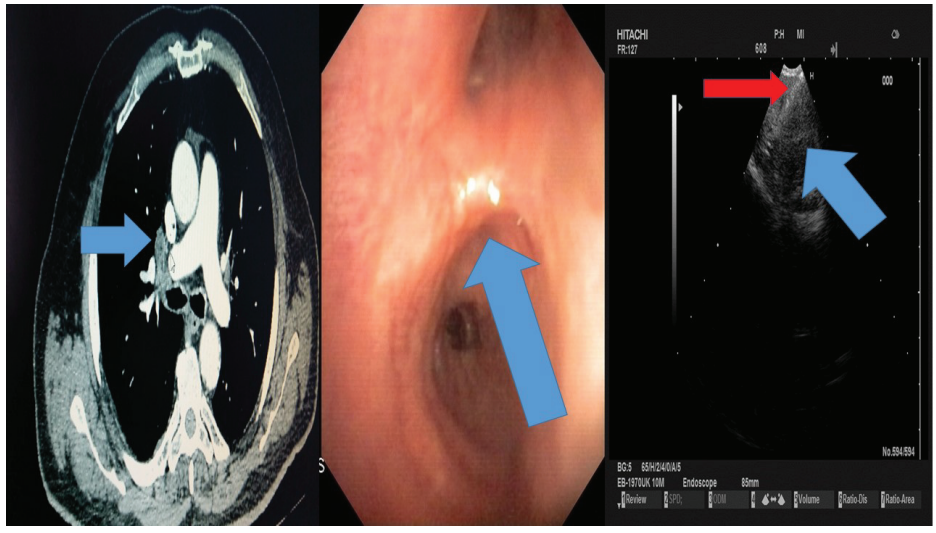

Figure 10. Clinical practice. Left: the blue arrow indicates the enlarged lymph node 10R. Middle: bronchoscopic image, there is no endobronchial lesion. Right: the blue arrow indicates the enlarged lymph node and the red arrow indicates the needle inside the lymph node.

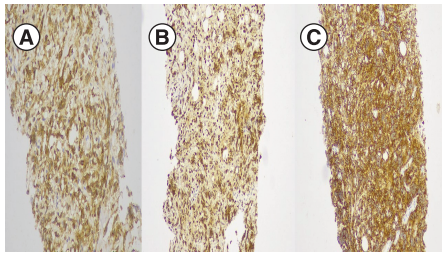

Figure 11. Clinical practice. The majority of neoplastic cells were positive against: **(A)** BCL2; **(B)** BCL6; **(C)** CD10.
BCL: B-cell lymphoma.

bovis, Mycobacterium africanum, Mycobacterium microti, Mycobacterium caprae, Mycobacterium canett (Figure 9). No microbiological study was performed from our EBUS-TBNA specimen.

Case 4

A 60-year-old non smoker man came to our outpatient cabinet for sleep apnea evaluation. Upon clinical workup a CT of the thorax with intravenous contrast revealed an enlarged lymphnode number 7 (Figure 10). EBUS-TBNAB 19G revealed lymphoma (non-Hodgkin) (Figures 11 & 12).

Case 5

A 60-year-old woman was admitted to our outpatient ward for lymph node biopsy after consultation with her oncologist (Figure 13). She was diagnosed with breast cancer 10 years prior and had surgery with mastectomy in both breasts. Lymphnode biopsy revealed disease relapse (Figures 14 & 15).

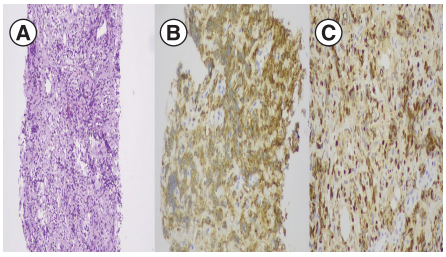

Figure 12. Clinical practice. (A) Hematoxylin and eosin: small to medium sized neoplastic cells with scant cytoplasm and basophilic nuclei invading the lung parenchyma diffusely. **(B)** The majority of neoplastic cells were positive against CD79a, c-MYC and MUM1 immunostains were negative. **(C)** Ki67: more than 67% of neoplastic cells were Ki67 positive (×200).

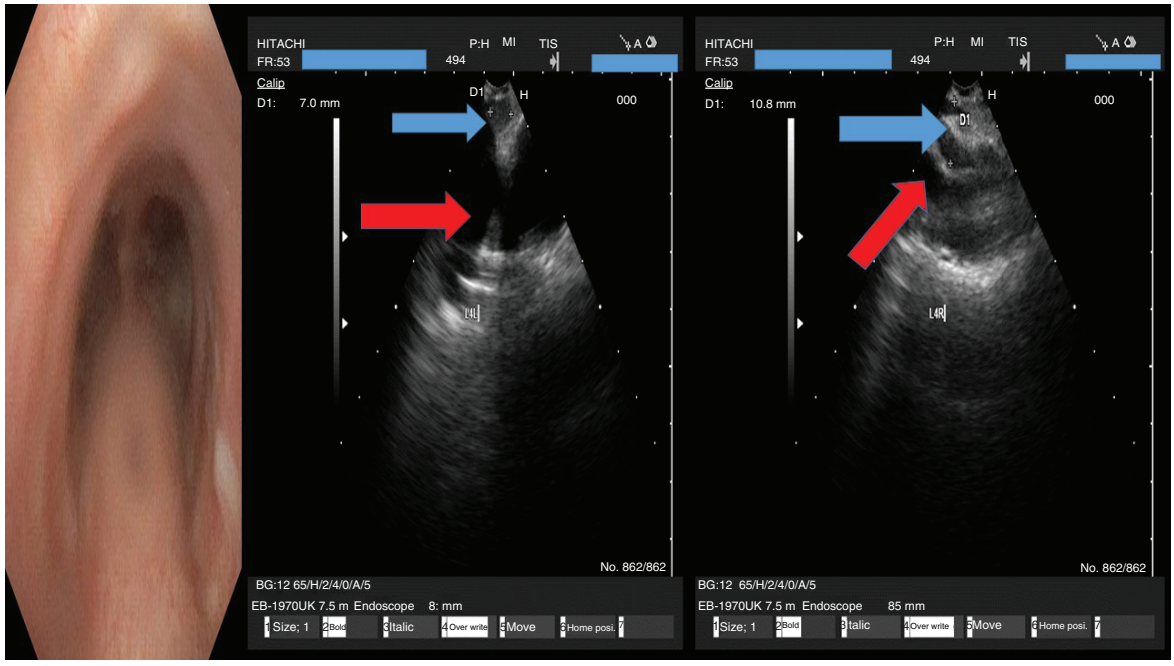

Figure 13. Clinical practice. Left: Endobronchial view of the trachea and main carina, without any pathological findings of lung cancer. Middle: the blue arrow indicates the lymph node number 4 L with 7 mm in diameter and red arrow indicates the aortic arch. Right: the blue arrow indicates lymph node number 4R and red arrow indicates the superior vena cava.

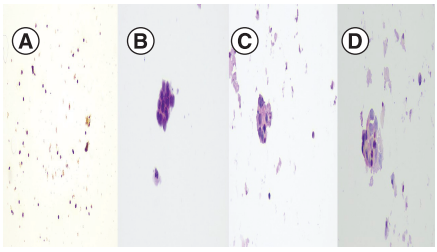

Figure 14. Clinical practice. (A) CK-COCK: most of the examined cells were positive in pancytokeratin immunostain. **(B–D)** Hematoxylin and eosin: a limited number of malignant neoplastic cells with swollen nuclei, unequal in size and abnormal chromatin distribution, arranged mostly in small aggregates.

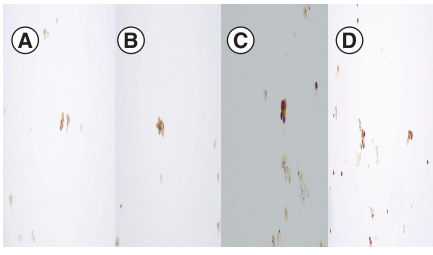

Figure 15. Clinical practice. (A & B) Endoplasmic reticulum: a small number of neoplastic cells showed weak nuclear positivity in endoplasmic reticulum immunostain. **(C & D)** GATA-3: most of the examined cells were positive in GATA-3 immunostain.

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Discussion

CT scans should be routinely used in the case of cough and other clinical symptoms such as hemoptysis. CT scans of the thorax are easy and fast to perform and are currently used as a screening tool for early lung cancer diagnosis in chronic obstructive pulmonary disease patients. A careful medical history of each patient is necessary in order to have a complete diagnostic work up for each patient. In the case of suspicion for NSCLC we should perform at the same time not only diagnosis, but also staging with convex-EBUS-TBNA [13]. In the event of suspicion for other types of cancer then the possibility of sarcoidosis should be included by taking several biopsies from all lymph node stations [14,15]. Blood tests should be performed simultaneously when investigating collagen disease. The issue of the EBUS sample has nowadays been resolved with the use of larger needles like the 19G needle [16]. This means the sample size is larger and cell blocks have enough tissue sample to diagnose lymphoma, sarcoidosis and other types of cancer (metastatic) [16]. The sample size of the 19G needle means more tissue and less cytology [17,18]. The issue remains for cases with high suspicion of lymphoma (Hodgkin and less for non-Hodgkin) and false negative results; however, the same issue remains for other cases of false negative results when we have necrotic samples. This can happen for NSCLC or other metastasis. In this case rebiopsy is the solution with thoracoscopy [17]. In the case of suspected TB, PCR is a rapid solution for the sputum sample where with a positive result we can immediately start therapy. In the case of TB we can have endobronchial lesions which have granulomas and the pathology report alone cannot distinguish sarcoidosis versus TB versus silicosis [8,19]. Other laboratory findings such as ACE or the bronchoalveolar lavage can assist us in the diagnostic workup of sarcoidosis; however, they assist as surrogate markers [20]. Moreover; there are cases where we have enlarged mesothoracic lymph nodes and also lesions within the lung parenchyma or even pleura effusion; these findings can be all manifestations of sarcoidosis or other collagen disease [21–23]. There is also the case of skin and subcutaneous manifestation of sarcoidosis [24,25]. Current technology allows us to perform biopsies of the mesothoracic lymph nodes efficiently and safely. PET-CT can assist in order to identify which lesions will provide us with the best sample since the PET-CT indicates 'cell activity' and we minimize the false negative results [26]. We expect the PET-CT exam to be a surrogate diagnostic and restaging tool for sarcoidosis. The 19G EBUS needle provides us with larger tissue samples in order to identify lymphoma and granulomas [7]. The EBUS biopsy can identify sarcoid reaction after immunotherapy drugs [27]. Sarcoidosis can even manifest after TB infection as a result of the immune system hyper activity [9]. The EBUS should be included along with other clinical marker and laboratory test in order to diagnose enlarged lymph nodes of the mediastinum without any other findings.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patients for the inclusion of their medical and treatment history within this case report.

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