

ENDOBONCHIAL ULTRASOUND – ONE YEAR OF EXPERIENCE IN CLINICAL PRACTICE

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Abstract

Background and aim. Endobronchial ultrasound (EBUS) is a recent minimally invasive, safe examination method for the mediastinum, with a good diagnostic precision.

This method makes possible real time examination with transbronchial fine needle aspiration, diagnostic transbronchial needle aspiration (TBNA) and staging of non-small pulmonary tumors, as well as diagnosis of mediastinal and hilar adenopathies of various causes.

Methods. We present the experience of the Bronchoscopy Department of the Pulmonology Clinic of Cluj-Napoca with EBUS-TBNA as a tool for the diagnosis and staging of tumors in contact with the bronchial wall and mediastinal and hilar adenopathies of unknown etiology. During the period August 2014 – January 2016 we examined 152 patients with no direct or indirect signs of lung tumor in traditional bronchoscopy. Rapid on site evaluation (ROSE) was available for all patients.

Results. Our study is a retrospective study of 152 EBUS-TBNA examinations. The average age of our patients was 54.43 years and 64% came from urban and 36% from rural background. EBUS-TBNA brought the final histological confirmation (tumors, sarcoidosis, lymphoma) in 82.8% of the cases. A tumor confirmation was obtained in 95% of the patients who were suspected of having tumor.

For a better understanding of the importance of this method in the daily clinical practice we present a case of peripheral pulmonary neoplasm with mediastinal and hilar adenopathies, where the contribution of EBUS-TBNA to a rapid diagnosis was essential.

Conclusion. By the introduction of this method in our country one year ago, we can diagnose patients with lung and mediastinal tumors, which cannot be diagnosed by traditional bronchoscopy. This brings a valuable contribution to the improvement of lung cancer staging and diagnostic.

Keywords: endobronchial ultrasound, fine-needle biopsy, lung adenocarcinoma, mediastinal neoplasms, pulmonary medicine

Background and aims

EBUS – Echobronchoscopy is a relatively recent examination method, introduced in clinical practice in 1992. It is a combination of echography and bronchoscopy, allowing the physician to directly examine the tumors and adenopathies situated next to the airways, both extrabronchial and extratracheal ones, inaccessible to traditional bronchoscopy. A real time, ultrasound guided sampling of cytology and histopathology specimens for diagnostic purposes is also possible with fine needle aspiration. There are 2 types of EBUS:

- Radial Probe EBUS (RP-EBUS) – for evaluation and bioptic sampling of peripheral tumors
- Convex Probe EBUS (CP-EBUS) – for evaluation and sampling of tumors and lymph node stations 2,3,4,7,10,11 outside of the bronchial tree but right next to the bronchial wall [1,2,3].

A doctor who wishes to perform EBUS should be familiar with mediastinal anatomy, the characteristics of ultrasound, and must have a good bronchoscopy and echography knowledge. The learning curve is usually longer than the one for traditional bronchoscopy.

Main indications of EBUS-TBNA:

- Diagnostic and staging of non-small cell lung cancer (NSCLC)
- Evaluation of mediastinal tumors (ex: lymphomas)
- Evaluation of mediastinal adenopathies of unknown etiology (sarcoidosis, lymph node metastasis of a known tumor) [1,2,3].

The contraindications of EBUS are similar to the contraindications of bronchoscopy and they include:

- Myocardial infarction
- Life threatening arrhythmias
- Poorly controlled heart insufficiency
- Severe hypoxia
- Uncooperative patient
- High risk for hemorrhage: current anticoagulation therapy, coagulopathies, thrombocytopenia, high urea and creatinine levels [4,5].

The examination can be performed in local anesthesia with 2% Xylocaine, under conscious sedation or under general anesthesia with laryngeal mask or endotracheal tube sized at least 8. The patient should be on an empty stomach for at least 6 hours. Examination is performed with the patient in supine position.

Methods

The introduction of EBUS TBNA has brought important changes to the staging and diagnostic strategy of lung cancer. Twenty years ago mediastinoscopy was the gold standard examination method for the mediastinum. The introduction of EBUS has changed this paradigm, EBUS being a minimally invasive method with a cost/efficiency value slightly superior to mediastinoscopy [1].

We present the experience of the Bronchoscopy

Department of the Pulmonology Clinic of Cluj-Napoca with EBUS-TBNA as a tool for the diagnosis and staging of tumors in contact with the bronchial wall and mediastinal and hilar adenopathies of unknown etiology.

During the period August 2014 – January 2016 we examined 152 patients with no direct or indirect signs of lung tumor at traditional bronchoscopy. The examinations were carried out with a FUJI Echoendoscope, under general anesthesia with laryngeal mask. There were no intra- or periprocedural complications or accidents reported. All patients underwent fine needle aspiration (TBNA) for diagnosis after rigorous evaluation, measuring and description of the visualized lymph node stations. At least 4 punctures per lymph node station were performed. The average examination time was 30 minutes.

EBUS preoperative staging for non-small tumors has been performed in 4 patients, starting with N3 contralateral to the tumor, followed by N2, N1.

Rapid on site evaluation (ROSE) was available for all patients. An experienced cytopathologist was part of the team and she was present in the operation room where she performed the Quick-Diff rapid coloration and the cytological examination. The real-time examination provided us a direct feedback on the quality of the sampled tissue, it confirmed that the tissue was indeed taken from a lymph node (>30% lymphocytes from nucleated cells) or from the tumor, and identified within 1-3 minutes the existence of tumoral cells or infirmed the supposition of a malignant disease.

These results were confronted with the results of the histopathological examination with immunohistochemical staining, performed by a laboratory of reference.

Results

The distribution of the patients according to their presumed diagnostic was as follows: adenopathies of unknown etiology: 25 patients; suspect of lung tumor: 81 patients; sarcoidosis: 28 patients; suspect of lymphoma: 2 patients; lung or bone metastasis of unknown origin: 6 patients; unknown adenopathies with a documented tumor (breast, prostate, cervical, renal) in personal history: 10 patients.

The average age of our patients was 54.43 years and 64% came from urban and 36% from rural background.

The results of the onsite examination ROSE showed a positive diagnostic rate of 59.2% from the total number of the patients from our study, for 62 patients the results were negative, and for 90 patients we could make up a diagnosis on the spot. Regarding the diagnostic yield of tumors: in 97 patients suspected of having primary lung tumor or other tumors we could confirm the existence of tumoral cells on site with microscopic examination ROSE in the case of 79 patients, representing 81% of the patients.

EBUS-TBNA brought the final histological confirmation (tumors, sarcoidosis, limfoma) in 82.8% of the cases.

A tumor confirmation was obtained in 61.8% of the total number of patients and in 95% in the case of the patients who were suspected of having tumor.

The histological profile of the cases was the following: adenocarcinoma: 29 patients; small cell lung cancer: 19

patients; squamous cell carcinoma 8 patients; non-small cell carcinoma: 18 patients; metastatic carcinoma: 5 patients (1 metastases from prostate carcinoma, 2 metastases from renal carcinoma, 1 metastasis of melanoma and 1 metastasis of colonic carcinoma).

Background of the patients

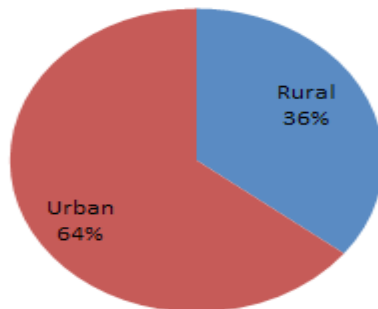


Chart 1: Background of the patients.

Diagnostic confirmation rate for tumors with ROSE (in 97 patients with a presumptive TU diagnostic)

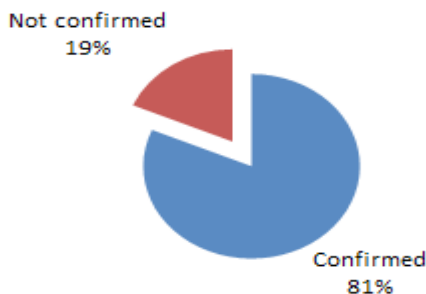


Chart 2: Diagnostic confirmation rate for tumors with ROSE.

EBUS diagnostic confirmation rate with histopathological examination

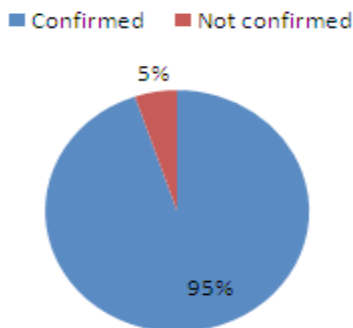


Chart 3: EBUS diagnostic confirmation rate with histopathological examination.

Clinical case

We present one of our clinical cases to illustrate a clinical and imaging pattern of EBUS indication and to emphasize the importance of this method for the diagnosis in pulmonology.

A 38 year old female, non-smoker, with no personal or familiar medical history, with professional exposure to toxic substances (worker in a factory of car cables) is admitted for intense precordial pain of a sudden onset, without radiation.

Clinical examination is non-specific. Laboratory tests show slightly elevated troponine and CPK levels. Electrocardiogram showed sinus rhythm, a heart rate of 90 b/min, intermediate QRS, inferior-lateral T waves. Echocardiography shows no pathological changes.

A differential diagnosis between pulmonary embolism and an acute coronary event emerged.

Myocardial infarction was excluded by a normal coronarography while Angio-Computed Tomography (Angio-CT) excluded lung embolism (no evidence of pulmonary emboli). However, the Angio-CT showed a 2

cm suspicious nodule in the right lower lobe (RLL), lower from the bronchial bifurcation towards the basal segments, small bilateral pleural effusions, mainly in the right side, and multiple adenopathies: right interbronchial, subcarinal, Baret space, right paratracheal, with dimensions varying up to 2.5 cm.

At this moment our diagnosis is: lung tumor of the RLL, T1bN2Mx.

We performed a traditional bronchoscopy which evidenced the following: no modifications of the trachea, slightly enlarged tracheal bifurcation, hypervascularization of the main bronchus. Indirect signs of a tumor.

For further diagnostic procedures, we can choose from: mediastinoscopy, open lung biopsy, EBUS-TBNA. We pick the less invasive procedure available that can bring a rapid result: EBUS with on-site cytodiagnostic.

The EBUS examination showed enlarged mediastinal and hilar lymph nodes, their size varying between 1-3 cm. Fine needle aspiration of the lymph nodes was performed with EBUS TBNA.

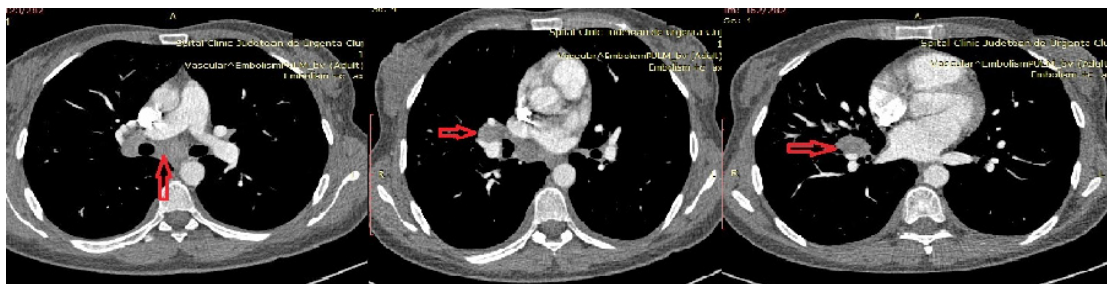


Figure 1. CT Image : adenopathy in stations 10R,7; peripheral tumor.

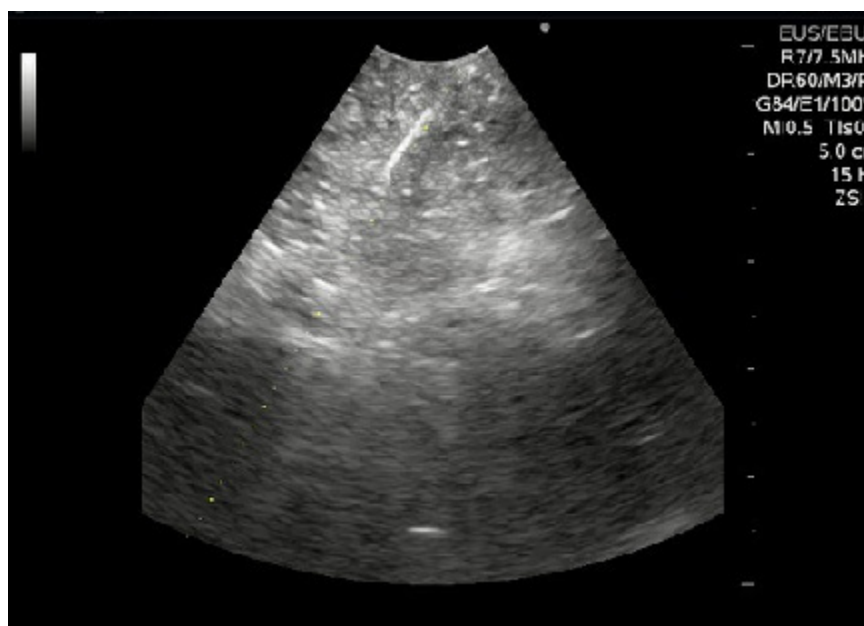


Figure 2a. EBUS images: we can see the needle into lymph node station 10R.

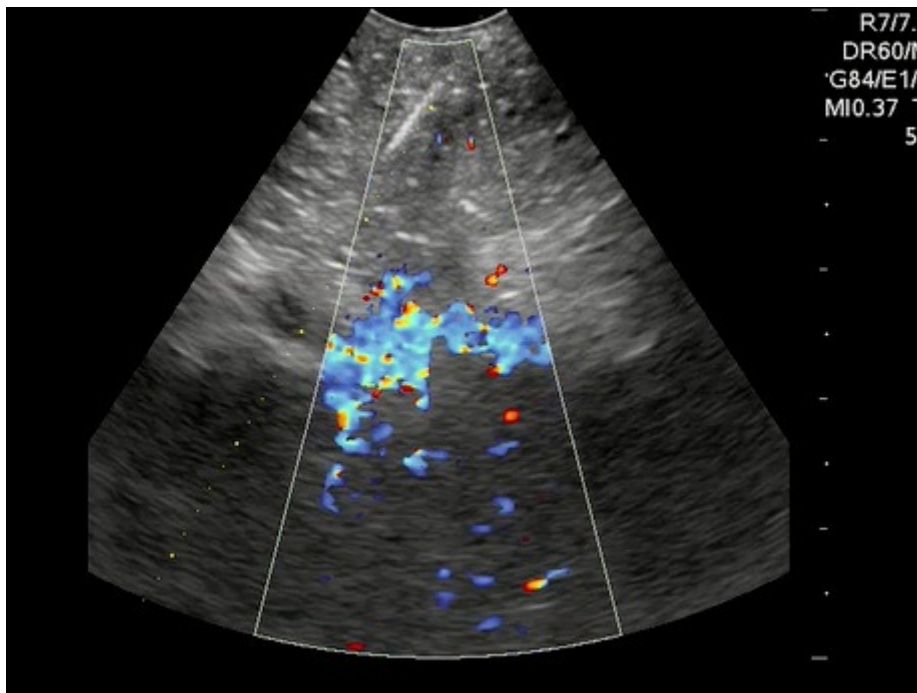


Figure 2b. EBUS images: we can see the needle into lymph node station 7 with Doppler image.

The on-site cytological examination brought the following: “Lymph node stations 7, 11R: moderate cellularity, mainly made up of tumor cells, frequent red blood cells, rare eosinophils and polymorphonuclear cells. The tumor cells are medium sized, mononucleated, with excentric nucleus, one macronucleoli/nucleus, cytoplasmatic vacuoles. Their distribution is isolated or in plaques with a morular aspect. The cytoplasm of the tumor cells was PAS positive. The conclusions of the cytological examination was of non-small cell carcinoma (adenocarcinoma).

The final histopathological examination with

immunohistochemical staining concluded that the final diagnosis was TTF-1 positive adenocarcinoma of the lung.

The next steps in order to offer our patient a proper staging and pre-therapeutic evaluation would have been a head and abdominal computed tomography (for evaluation of possible brain/liver/abdominal metastasis), followed by referral to medical oncologist for chemotherapy, but an unfortunate complication occurred: bilateral infrapopliteal deep venous thrombosis diagnosed clinically and by echo- Doppler. We started anticoagulation therapy with Rivaroxaban. Further evolution was unfavourable.

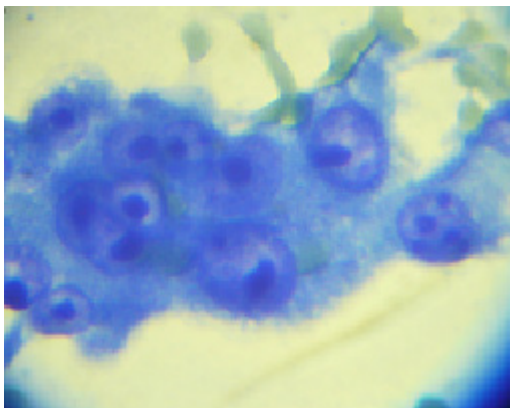


Figure 3. Microscopic image in Diff-Quick stain, objective 100x10.

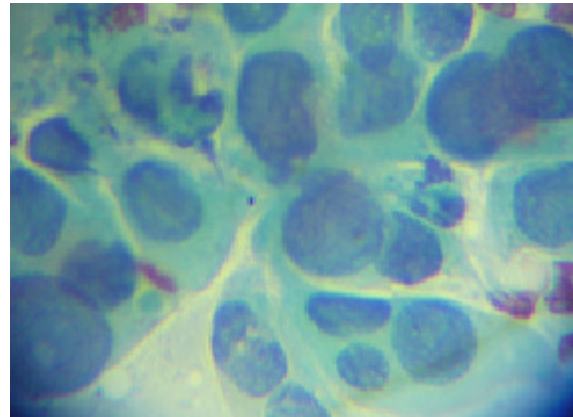


Figure 4. Microscopic image in Diff-Quick stain, objective 40x10.

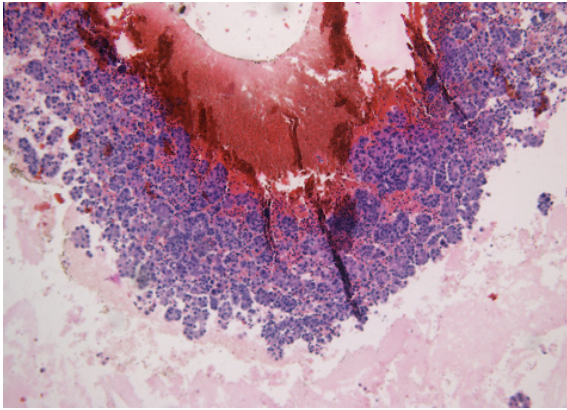


Figure 5. Histopathological image, Citoblock, objective 10x.

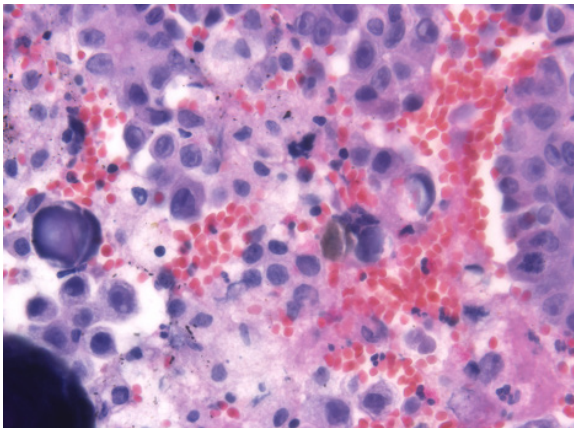


Figure 6. Histopathological image, Citoblock, objective 40x.

Discussion

Lung cancer comes first among cancer-related death worldwide. A proper diagnosis and staging of lung cancer is very important, as it is the key to treatment. Computer tomography and PET-CT continue to play a key role in the diagnosis and staging of lung cancer. In order to achieve histological confirmation, which allows a modern cancer therapy, tumor tissue is needed. Twenty years ago tissue samples from tumors localized in the mediastinum was obtained by mediastinoscopy or open lung biopsy with thoracotomy. The introduction of the minimally invasive method EBUS has changed the diagnostic and staging methodology of lung cancer [3]. The cost/efficiency rate is high, when compared with surgical procedures [6,7].

The sensitivity of CT, PET-CT and EBUS-TBNA for lung cancer diagnosis and staging is 76.9%, 80% and 92.3% respectively according to a study by Yasufuku et al. The specificity of the methods was 55.3%, 70.1% and 100%, and the diagnostic accuracy 60.8%, 72.5% and 98% [8].

In our study the sensitivity of the method and

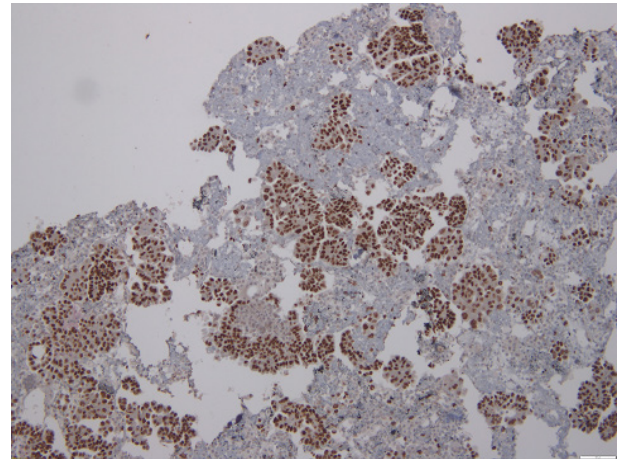


Figure 7. Immunohistochemical staining, intense positive nuclear TTF1.

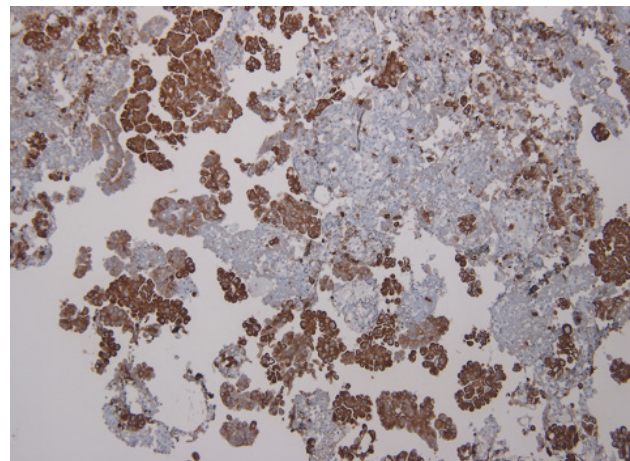


Figure 8. Immunohistochemical staining, positive CK7.

diagnostic accuracy in lung cancer was 95 % confirmation from the total number of cancer suspicions.

There were no significant intra- or post-procedural complications reported in our study.

The ACCP's ACQuIRE registry has begun collecting and analyzing data on 1317 patients undergoing EBUS at 6 hospitals (all or nearly all were academic centers training fellows). EBUS proved to be quite safe, indeed, with the following reported complications occurring within 24 hours: risk of pneumothorax with EBUS alone: 0.2%, or 1 in 500. In comparison the risk of pneumothorax after transbronchial biopsy was of: 2.7%, or 1 in 37. The study reported seven pneumothorax complications of which 4 required tube thoracostomy and the others resolved without intervention. The risk of bleeding requiring intervention was reported at 0.2%, or 1 in 439 and one patient succumbed from bleeding (1 in 1317 or 0.08%).

The overall 24-hour complication rate was 1.4%, but it was <1% if transbronchial biopsy was not performed [9].

Lung cancer is fairly uncommon in patients aged <45. About 10-15% of lung cancers occur in non-smokers of which 2/3 are women [10].

In case of young patients, lung cancer has a few particular characteristics: it appears in a large percent in women, the predominant histological type being adenocarcinoma, it is usually diagnosed in advanced stages and survival rate is similar to the one in case of older patients [11].

The particular features of our case were the young age, lack of smoking history, atypical clinical presentation and the presence of a lung nodule accessible only by EBUS, mediastinoscopy or thoracotomy, but not by traditional bronchoscopy. The evolution of the case was extremely rapid and unfavorable.

There are still some unanswered questions left. For example: Was it a lung embolism, although it was refuted by Angio-CT? The ulterior onset of a deep venous thrombosis, most probably in the context of a paraneoplastic syndrome suggests a possible lung embolism not seen on CT, which can explain the initial symptoms (sudden onset of severe chest pain).

The M (metastasis) status is also not perfectly clear: The CT-based stage showed Mx – but the bilateral pleural effusion of possible malignant origin could have classified it as M1, stage IV.

The influence of environmental factors: the patient was a factory worker, possibly exposed to: chrome, rubber, nickel, cadmium, carbon electrodes. According to the Journal of Thoracic Disease, the exposure to chrome, nickel, cadmium and rubber derivatives has been proved to have carcinogenic effects in humans, and the carbon electrodes are possible to be carcinogens [12].

A review of the literature shows that patients with lung adenocarcinoma have a 20x increased risk to have thrombophlebitis/deep venous thrombosis [13]. Our patient presented a deep venous thrombosis and possible lung embolism.

Young patients with adenocarcinoma of the lung are frequently diagnosed in advanced stages, stadium IV [14]. According to Journal of Thoracic Disease, regarding adenocarcinoma patients, the average time passed from first contact with a doctor until consultation by a respiratory specialist is of 27 days, and 23 more days are generally required to complete the investigations and have a final diagnosis. That makes a total of 50 days [11, 12]. In our case, the unusual presentation form, the quick investigations and the availability of EBUS-TBNA allowed a very quick diagnosis. The total time from the first manifestation of the tumor (with severe chest pain) lead to emergency admission to hospital and start of the diagnostic pathways, leading to a definitive diagnosis of lung adenocarcinoma in just 12 days.

The 3rd edition of the ACCP (American College Of Chest Physicians) guidelines regarding lung cancer

recommends the minimally invasive technique EBUS as a gold standard for the diagnosis and staging of lung cancer with involvement of the N2, N3 lymph node stations, before mediastinoscopy, thoracotomy or other more invasive techniques [15]. In our case, EBUS was the only minimally invasive diagnostic method available.

Regarding the cost-effectiveness of EBUS compared with mediastinoscopy, Gargoum et al. concluded that an EBUS based diagnostic pathway results in cost effective patient management compared with traditional mediastinoscopy even in the first year of service [16]. In a 2009 study from the UK, Medford et al. also found that EBUS can save health community costs, pointing out the need for new, more precise coding procedures for EBUS to reflect the true value and difficulty of the procedure [17]. Our team has experienced the same problem: lack of proper procedure code for EBUS-TBNA, the available codes were those of standard bronchoscopy with biopsy or lymph node puncture.

Conclusions

Endobronchial ultrasound examination combined with fine needle aspiration EBUS-TBNA is a minimally invasive diagnostic and staging examination tool of the mediastinum. It is also well tolerated by patients, which is a major advantage, and grants EBUS a top position among the diagnostic and staging methods of lung cancer.

By combining the EBUS technique with ROSE (rapid on site cytological examination) we can obtain a cytological confirmation on the examination site, during the examination. A histopathological confirmation with immunohistochemical staining can be later done on the EBUS specimens. It is a valuable and cost efficient tool for the mediastinum and exo-bronchial tumors in contact with the bronchial wall.

By examination of the mediastinal and hilar lymph node stations, EBUS TBNA is a quick staging tool for lung cancer, avoiding thoracotomies and mediastinoscopies, which are more invasive and with more risk for the patient.

By the introduction of this method in our country one year ago, we can diagnose patients with lung and mediastinal tumors, which cannot be diagnosed by traditional bronchoscopy. This brings a valuable contribution to the improvement of lung cancer staging and diagnostic.

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