

Severe Complications of Ultrasound Guided Transbronchial Needle Aspiration – A Case Series and Review of the Literature

Schwergradige Komplikationen nach EBUS-TBNA – Fallserie und Literaturübersicht

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Abstract

Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has become essential for the workup of patients with lung cancer and other pulmonary diseases. The emphasis of currently available literature is related to the diagnostic yield of EBUS-TBNA which was found to be high. Complications seem to be rare but such data are scant. We report three cases of complications including mediastinitis, pneumothorax and bleeding and provide a review on the existing literature.

Introduction

Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has become standard in the diagnostic workup of patients with suspected lung cancer, particularly in mediastinal lymph node staging [1,2]. The sensitivity of EBUS-TBNA for the detection of mediastinal metastasis has been shown to range between 80 and 96%, the specificity to reach almost 100% [1–7]. Moreover, EBUS-TBNA has the lowest rate of complications (below 1% in all of the above mentioned studies evaluating complications) among all invasive methods such as mediastinoscopy, thoracoscopy and CT- or ultrasound-guided transcutaneous biopsy. Nevertheless, several possible complications deserve the attention of clinicians.

Case reports

For all patients presented below informed consent was obtained.

Zusammenfassung

Die endobronchiale ultraschallgesteuerte transbronchiale Feinnadelaspiration (EBUS-TBNA) ist essenziell in der diagnostischen Aufarbeitung von Patienten mit Lungenkarzinom und anderen Lungenerkrankungen. Der Schwerpunkt der vorhandenen Literatur zur EBUS-TBNA liegt in der Beurteilung ihrer diagnostischen Wertigkeit, welche als hoch eingeschätzt wird. Die Komplikationsraten erscheinen niedrig, jedoch ist die diesbezügliche Datenbasis schmal. Wir berichten über jeweils einen Fall von Mediastinitis, Pneumothorax und Blutung nach EBUS-TBNA und geben einen Überblick über die aktuelle Literatur.

Case 1 – Mediastinitis

A 61-year-old woman with a history of non-small-cell lung cancer three years before was admitted with several enlarged mediastinal lymph nodes in CT. The primary therapy three years before had been combined radio-chemotherapy. Until time of readmission, the patient had been in full remission.

EBUS-TBNA from lymph node stations 4 right and 7 was performed. The procedure was carried without complication. Cytology showed a necrotizing lymphadenopathy. Histology did not reveal malignancy.

On day 4 after TBNA, the patient was readmitted because of fever up to 39°C, chills, fatigue, dyspnea and headache. The blood tests showed a high level of c-reactive protein (26 mg/dl, normal range <0.5 mg/dl) and otherwise no abnormalities. An empiric antibiotic treatment (piperacillin/ tazobactam) was initiated.

Bronchoscopy and CT revealed a new cavitation (maximum diameter 1.6 cm), edematous alterations below the tracheal bifurcation and pneumomediastinum (● Fig. 1). In a second bronchoscopy on day 5 after admission, a bronchomediastin-

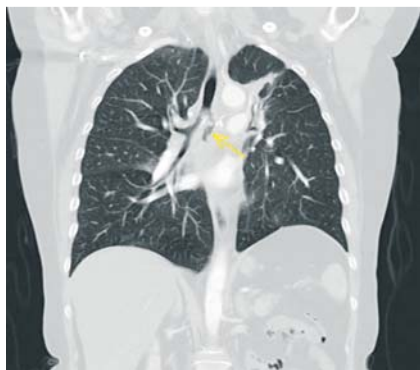


Fig. 1 CT of the chest on day 4 after EBUS-TBNA showing pneumomediastinum and mediastinitis.

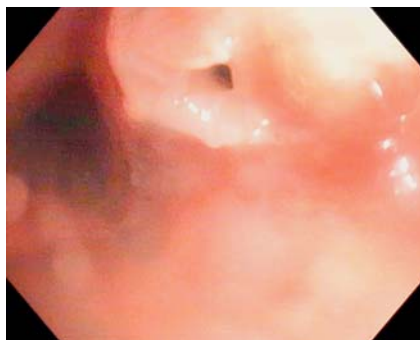


Fig. 2 Bronchoscopy on day 5 after EBUS-TBNA with fistula from left main bronchus.

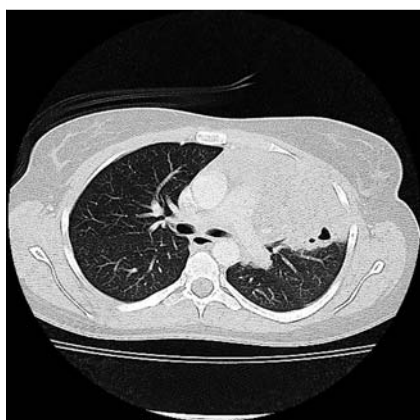


Fig. 3 Chest-CT with consolidation of the left upper lobe.

al fistula of the left main bronchus was detected (● Fig. 2). After installation of contrast media, the size of the cavity appeared to be small. A single lavage with gentamicin was performed. Microbiological examination did not reveal any pathogens. The patient received an i.v. antibiotic therapy (meropenem). As she remained stable no further surgical intervention was done. After two weeks of antibiotic treatment the patient recovered clinically and bronchoscopy as well as CT showed improvement. The patient was discharged on day 15 after admission with oral moxifloxacin for further 14 days. No relapse occurred.

Case 2 – Pneumothorax

A 28-year-old woman presented in the emergency unit with chest pain together with productive cough including small spots of blood since 2–3 weeks. There was no comorbidity, and the only medication was an antidepressive agent prescribed in a low dosage. The laboratory findings showed elevated leukocytes (24.000/ μ l), c-reactive peptide (8.2mg/dl, normal range <0.5 mg/dl), lactate dehydrogenase (401 U/l, normal >250 U/l) and were otherwise unremarkable.

In chest-CT, a consolidation of 10×10 cm in the left upper lobe (● Fig. 3) was detected. Five days after admission bronchoscopy was performed. The intraluminal findings were unremarkable. EBUS-TBNA was performed from the subcarinal and interlobar lymph nodes on the left and paratracheal lymph node on the right side. Furthermore, a bronchoalveolar lavage from the left upper lobe was done and seven transbronchial biopsies (TBB) from the side of consolidation were taken. During the procedure and directly afterwards, no complications occurred. A chest radiograph about three hours after intervention excluded pneumothorax.

Approximately 36 hours after bronchoscopy, the patient complained about increasing chest pain, particularly on the right side. Chest radiograph now revealed a pneumothorax on the right side – contralateral to the side of TBB – with a width of 5 cm and shift of the mediastinum to the opposite side. Emergency chest tube insertion was done. After five days, the chest tube was removed without complications and the pneumothorax was treated successfully.

The histological findings from TBNA, TBB and bronchoalveolar lavage (BAL) did not show malignancy. In a subsequent CT-guided puncture of the mass, Hodgkin's lymphoma was diagnosed.

In summary, the 28-year-old female patient suffered pneumothorax after EBUS-TBNA of a single right-sided lymph node, while on the left side, where TBB and further EBUS-TBNA was performed, no complications occurred. The pneumothorax was successfully treated by insertion of a chest tube.

Case 3 – Bleeding

A 47-year-old woman with complaints of dyspnea and chest pain presented in our outpatient department. The patient had a history of systemic lupus erythematosus, anti-phospholipid-syndrome and factor V Leiden thrombophilia and was therefore treated with phenprocoumon.

Chest-CT revealed a solitary pulmonary nodule with a maximum size of 1.7 cm in the right upper lobe and an enlarged hilar lymph node in station 10 on the right side. EBUS-TBNA of the lymph node was done. Phenprocoumon had been stopped a week before and instead low-molecular heparin (enoxaparin) started in weight-adapted doses. The evening before, as well as on the day of puncture, enoxaparin was paused. PTT was 30 sec and INR 0.96 (both in normal range). After TBNA of the 1.8 cm sized lymph node, a moderate bleeding was seen which stopped spontaneously after a few minutes. No further complications occurred, enoxaparin was restarted on the day after EBUS-TBNA and the patient was discharged two days later without complaint.

Seven days after bronchoscopy, the patient was readmitted with severe hemoptysis. An emergency bronchoscopy revealed a blood clot in the right upper lobe carina, precisely where TBNA had been performed (● Fig. 4). After reduction of the dose of enoxaparin, the patient remained stable with only minor and self-limiting hemoptysis. Histological examination confirmed the diagnosis of a primary adenocarcinoma of the lung and extended resection of the right upper lobe including the site of bleeding was performed.



Fig. 4 Blood clot at the right upper carina at site of EBUS-TBNA seven days after the puncture.

Discussion

We report three rare complications of EBUS-TBNA of mediastinal lymph nodes, including mediastinitis, pneumothorax and bleeding.

Complications in literature

There are two large studies from 2013 which examine the incidence of complications after EBUS-TBNA – one from Japan [8] and one from the USA [9]. The latter was a prospective trial with 1317 patients undergoing EBUS-TBNA, some of them (in 12.4% of cases) an endobronchial and transbronchial (10.3%) biopsy additionally. The overall complication rate was 1.44%. The second study, conducted by the Japanese Society for Respiratory Endoscopy [8], was a retrospective questionnaire-based multicenter study including about 7300 patients with EBUS-TBNA of a mediastinal lesion or (in less than 4%) of the lung. The total rate of complications was 1.23%.

Another retrospective and questionnaire-based survey of endosonography-related complications was recently published. It provides a nationwide survey in the Netherlands and predominantly includes patients undergoing endosonographic guided fine needle aspiration (EUS-FNA) (14075 cases) as well as patients with EBUS-TBNA (2675 cases). It found a rate of severe adverse effects of only 0.11% for EBUS-TBNA and 0.16% for EUS-FNA, including seven fatalities. [10]

Considering infectious complications, an overview of all case reports published to date is given in **Table 1**. Beside mediastinitis [11–13], mediastinal or lung abscess [14–18], pericardial and pleural empyema [15, 19–23], and prolonged fever [19] were described. The Japanese study reports 14 cases (0.19%) of infection (seven times mediastinitis, four times pneumonia, three times other infections) and the Dutch survey 21 cases (17 with mediastinal infection, three with pneumonia, one with pleural empyema) [10]. In the prospective US study, no infections were found because the follow-up period was limited to 24 hours.

Concerning pneumothorax, our patient is only the second case report published [24]. In the mentioned large studies, seven (two of them in patients without simultaneous TBB) [9], two [8] and one case [10] of pneumothorax, respectively, were reported. Reports of bleeding complications are limited to three cases of hemomediastium [25–27]. The retrospective study from Japan describes a relatively high rate of bleedings (0.68%/50 cases, one of these massive) [8] while the American as well as the Dutch study [9, 10] mention only three bleeding adverse events out of more than 1300 and 16000 patients, respectively.

Further complications reported in the studies are cardio-respiratory complications like hypoxia/respiratory failure, hypotension and cardiac arrhythmias and single cases of pneumomediastinum as well as subcutaneous emphysema – all of them being rare (below 0.3%).

Risk Factors

The only risk factor identified by the authors of the American multi-center trial [9] was simultaneous TBB of the lung with 3.2% of complications in TBB versus 1.2% in lone EBUS-TBNA ($p=0.04$). For pneumothorax this tendency was even more marked, with 2.7% versus 0.2% ($p=0,001$). Risk factors for an escalation in the level of care were a patient in- versus outpatient status, general anesthesia versus sedation and an age above 70. At least the latter was not confirmed by a more recent British single-center study [28].

The second multicenter study from Japan [8] discusses a higher rate of complications among inexperienced versus experienced examiners that was not significant considering the overall complication rate and became significant if only bleedings were considered. Though these findings could not be supported by the data from the above-mentioned American trial because of low incidence, Stather et al. found a non-significant trend for lower complication rate in experienced examiners as well [29]. The size or location of the punctured lymphatic nodes could not be identified as risk factors. Also, there was no significant inter-center difference found in neither of the studies.

The retrospective Dutch survey observed reduced performance status and comorbidities in all fatalities. Although there was no systematic examination of risk factors, patients with necrotic lymph nodes and granulomatous disease were detected as being at risk [10].

There is another trial from Japan from 2013, including only 109 patients [30]. It didn't find an age-related difference in multiple endpoints/complications when using 70 years and above 70 years as cut-off.

Evidently, there is not enough evidence yet to identify all potential risk factors for complications after EBUS-TBNA. Considering the presented case series from our center and the published cases listed above, further risk factors for complications after EBUS-TBNA might exist and other features might be relevant. These might include:

1. *Full needle extension* as a risk factor for infectious complications was mentioned and discussed by Haas and Gochi [12, 19]. Another risk factor for any complication might be the *needle diameter*. Concerning diagnostic yield there seems to be no significant difference between 21 and 22 gauges needles [31]. Differences in complications are not explicitly examined in the literature.
2. *Microbiological contamination* of the puncture needle by the microbiologic flora of the naso-pharynx, worsened through repeated passages of the needle through the working channel, has been discussed as a possible factor for infection [15, 19]. In addition, there are reports of positive blood cultures with bacteria from the naso-pharyngeal flora after TBNA without occurrence of clinical symptoms [20, 32].
3. *Histological findings*: In the vast majority of published cases of mediastinitis, the later finding was a malignancy (compare **Table 1**). In the existing systematic studies quoted above, there was no differentiation between histological diagnosis and complication rate. In our case of pneumothorax and in one case of fatal mediastinitis [11], the histological finding was

Table 1 Overview of published cases of severe infectious complications after endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

Author/Institution/Country	Journal/ Year	Type of complication, patients characteristics, histology of the punctured structure
Epstein et al., Boston Univers. School of Medicine, USA [20]	Am Rev Respir Dis, 1992	Pericarditis/pericardial tamponade after EBUS-TBNA. 63 years, male.
Haas, Jefferson Medical College, Philadelphia, USA [19]	Eur Respir J, 2009	2 cases: 1.: Moderate fevers 1–3 days after EBUS and diagnosis of pericardial empyema. Germs: Actinomyces odontolyticus and Streptococcus mutans. Full recovery after pericardiocentesis and antibiotic treatment. 50 years, male, adeno-carcinoma of unknown origin. 2.: Fever after 2 days, infection of the tumour bed. Full recovery after long-term antibiotics. 58 years, female, SCC of the lung.
Huang et al., National Taiwan Univers. Hospital [15]	Eur J Cardiothorac Surg, 2010	Malaise and dyspnea a few days after EBUS; after 10 days: pleural empyema, mediastinitis and lung abscess. Germs: Streptococcus viridians. Complete recovery after surgical and antibiotic therapy. 68 years, male, metastasis of known hepatic cancer.
Moffatt-Bruce et al., Ohio State Univers., USA [16]	J Cardiothorac Surgery, 2010	Fever/dyspnoea 10 days after EBUS, diagnosis of paratracheal abscess and sepsis on day 14. Germs: Alpha-Streptococcus and diptheroids. After surgical and antibiotic treatment slow but full recovery. 89 years, female, no malignancy found.
Parker et al., New York Univers., USA [17]	Ann Thorac Surg, 2010	19 days after EBUS-TBNA: fever, malaise, dyspnea and productive cough. Mediastinal abscess and septic shock 10 days later. Germs: Klebsiella pneumoniae and gram-positive cocci. Discharged home after surgery and antibiotic treatment. 48 years, male, small mediastinal mass.
Kurimoto et al., Japan [13]	Nihon Kokyuki Gakkai Zasshi, 2011	13 days after EBUS elevated inflammation parameters and cough. Diagnosis of mediastinitis. Full recovery after antibiotic therapy. 67 years, male, necrotic lymphnode.
Leong et al., Univers. of Queensland, Australia [14]	J Bronchology Interv Pulmonol, 2013	Mediastinal abscess 5 days after EBUS-TBNA. 64 years, female.
Motas et al., Bucharest, Rumania [11]	Interact Cardiovasc Thorac Surg, 2013	Purulent mediastinitis and bronchomediastinal fistula 6 days after EBUS-TBNA and mediastinoscopy. Patient died. 62 years, female, Hodgkin Lymphoma.
Gochi et al., Kyoto Univers., Japan [12]	Interact Cardiovasc Thorac Surg, 2013	Fever after 1 day, mediastinitis on day 7. Complete recovery under antibiotics. 59 years, male, SCLC (pneumectomy due to SCC of the lung 8 years before).
Tachjian et al., Canada [21]	Canad J Cardiol, 2014	Hypotension/unresponsiveness 2 weeks after EBUS-TBNA, diagnosis of pericardial empyema. Germs: Streptococcus milleri, Prevotella, Veillonella and Peptostreptococcus. Full recovery after surgery and antibiotics. 28 years, female, sarcoidosis.
Lee et al., Seoul University Hospital, Korea [22]	Eur J Cardiothorac Surg, 2015	2 cases of bacterial pericarditis. One recovery under antibiotics, one fatality.
Mc Govern et al. [18], University of Calgary, Canada	J Bronchology Interv Pulmonol, 2015	Mediastinal abscess 3 weeks after EBUS-TBNA. 42 years, male, sarcoidosis.
Gamrekeli et al. [23], Völklingen Heart Centre, Germany	Ann Thorac Surg, 2015	Fever, chest pain, dyspnea, cough 2 weeks after EBUS-FNA. Purulent pericarditis and infection of the punctured cyst. Germs: beta-hemolytic streptococci. Full recovery after surgery and antibiotics. 36 years, female, bronchogenic cyst.

References see text document. SCLC=small-cell-lung-cancer, SCC=squamous cell carcinoma.

Hodgkin's lymphoma. Considering bleeding, data are limited. In one case report of mediastinal hematoma [27], as well as in the case presented above, the later finding was non-small-cell lung cancer. Other reports do not provide histological details.

4. *Type of tissue punctured*: necrotic or liquid formations might increase the risk of complications (also discussed in literature [10, 13, 23]) as well as an alternated tissue due to a state after radiotherapy, surgery or chemotherapy, as it was the case in our patient with mediastinitis (with cytology also revealing necrotic tissue in that case).
5. *Anticoagulation*: The general recommendation is to perform EBUS-TBNA without anticoagulation. It has to be paused and PTT has to be at least less than 50 seconds. A single anti-plate-

let agent as acetylsalicylic acid and maybe clopidogrel can be accepted. In our case of bleeding, anticoagulation was stopped and coagulation parameters were normal prior to bronchoscopy.

Conflict of Interest



The author declares that no conflicts of interest exist for this publication.

Conclusion

The real incidence of complications after EBUS-TBNA might be higher than outlined in the studies discussed above (1.23 and 1.44% or even below 0.2% respectively) as in these studies either the follow-up period was very short and did not include infectious complications [9]. Also, questionnaires were retrospective and relied on the memory of examiners [8, 10]. There have been only three systematic examinations of EBUS-TBNA-complications at all, only one of them being performed in Europe. Considering the relatively high amount of published reports of infectious complications after EBUS-TBNA (12 in the last six years) these might be more relevant than generally assumed, particularly as they might be missed because of late occurrence of symptoms.

Even if the incidence of complications after TBNA was only around 1%, the number of examinations is increasing and disease burden is considerable since the complications might be severe and even fatal outcomes are reported. Further multicenter studies are needed to identify risk factors and, in a next step, to decrease the risk of EBUS-TBNA.

Currently, careful performance of EBUS-TBNA and TBB and an awareness of rare complications is mandatory. Consideration of late pneumothorax and bleeding is important. In patients with fever, dyspnea or malaise after bronchoscopy, infectious complications such as mediastinitis must be considered.

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