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LETTERS TO THE EDITOR

Complications of endoscopic ultrasound-guided needle aspiration

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To the Editor,

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and esophageal ultrasound-guided fine needle aspiration (EUS-FNA) are minimally invasive techniques with established value in the diagnosis and staging of thoracic tumors as well as benign lung diseases. A linear ultrasound probe at the distal part of the endoscope enables puncture of mediastinal and hilar lesions, and the (left) adrenal gland under real-time guidance. Although mediastinoscopy has been considered the gold standard for mediastinal staging of lung cancer, the use of E(B)US-NA (EBUS-TBNA and/or EUS-FNA) has increased substantially in recent years. Studies have shown that despite a lower negative predictive value than mediastinoscopy it nonetheless has high diagnostic accuracy and it does not routinely require general anesthesia [1,2]. In addition, most authors report an excellent safety profile with E(B)US-NA [3–5]. Nonetheless, serious complications can occur and with the rapid diffusion into routine clinical practice, it is important that clinicians are aware of these. In this short report we describe six cases which were at some point managed in our institution in which significant complications were clinically attributed to E(B)US-NA. We then briefly review the relevant literature.

Case series

Case 1

A 51-year-old man had a chest x-ray suggestive of mediastinal lymphadenopathy and on computed tomography (CT) scan a solitary enlarged paratracheal

node was seen. EBUS identified a 3 cm hypoechoic node. Three passes were made using a 22 gauge (G) needle. Rapid on-site evaluation (ROSE) showed evidence of necrosis, which was subsequently confirmed on cytological examination. Specimen culture was negative. The patient was admitted to the hospital 18 days post-EBUS with severe chest pain, present for several days, pericardial effusion and fever. After an unsuccessful pericardiocentesis he was empirically treated with antibiotics. However, he deteriorated with cardiac tamponade and septic shock. A second pericardiocentesis obtained 550 ml purulent fluid. Gram positive cocci were seen but cultures were negative. The patient received intravenous antibiotics for six weeks and recovered. At three- and six-months follow-up the previously enlarged lymph node was still visible on CT scan but was regressing, and the patient was well with no confirmed pathology.

Case 2

A 71-year-old woman was found to have multilevel hilar and mediastinal lymphadenopathy on chest CT in addition to a small pericardial effusion and two small lung nodules. The lymph nodes were avid on FDG-PET. She underwent EBUS-TBNA of a subcarinal node (station 7). Two passes were made. Three days later she developed fever, chills and malaise. She was subsequently admitted to hospital and empirically treated with antibiotics. A chest CT identified a subcarinal abscess, slightly increased pericardial effusion and a new pleural effusion. Her condition deteriorated and thoracotomy was performed. The subcarinal pus, pericardial and pleural fluid were drained. Histopathologic examination was

non-diagnostic. Cultures revealed candida and bacteria. Prolonged antibiotics and ICU admission were needed, but she recovered. No explanation was found for the lymphadenopathy.

Case 3

A 27-year-old woman underwent EBUS-TBNA for an enlarged paratracheal lymph node. The procedure was poorly tolerated under conscious sedation, and abandoned after two passes due to agitation, excessive cough, and a short respiratory pause with no significant change in oxygen saturation. After removal of the scope the patient was very uncomfortable and unable to close her mouth. Bilateral temporomandibular joint dislocation was diagnosed. The joints were relocated by a surgeon. The patient subsequently reported that she had longstanding habitual temporomandibular joint dislocation. Culture of the aspirate specimen was positive for *Mycobacterium tuberculosis*.

Case 4

A 77-year-old woman with significant co-morbidities had a clinico-radiological diagnosis of stage IV non-small cell lung cancer (NSCLC). EUS was performed to confirm this. Scope insertion was difficult and an experienced pulmonologist and gastroenterologist were both unable to enter the esophagus. The procedure was converted to EBUS and a subcarinal lymph node was punctured with a regular 22 G needle. During recovery the patient developed chest pain. A chest x-ray and CT scan showed pneumomediastinum. Antibiotics were started and esophagoscopy revealed a perforation of the proximal cervical esophagus. This was treated conservatively. After initial improvement her condition deteriorated and she died. The subcarinal specimen was positive for adenocarcinoma.

Case 5

A 65-year-old woman underwent EUS examination for lung cancer nodal staging but the procedure was terminated due to inability to enter the esophagus by two experienced endoscopists. She subsequently developed subcutaneous emphysema and was admitted to the hospital with suspicion of proximal cervical esophageal perforation. She was treated with antibiotics and was hospitalized for two weeks. No esophagoscopy was performed. She recovered and started oral intake after two weeks. Although the perforation was not visualized, development of subcutaneous emphysema shortly after a difficult intubation at EUS is highly suggestive of proximal esophagus perforation.

Case 6

A 64-year-old woman received chemotherapy consisting of carboplatin and pemetrexed for NSCLC and developed an esophageal-mediastinal fistula at the subcarinal region after the first course. Several weeks before, for staging purposes EUS-FNA of a subcarinal lymph node had been performed. The clinical course and location of the fistula suggests a relation with EUS-FNA and this event was therefore considered a probable complication of EUS-FNA. A covered esophageal stent was placed over the fistula, complicated by several stent dislocations.

Summary of the literature

We conducted a comprehensive literature search using PubMed and individual references to identify complications of E(B)US for lung diseases. Studies and reports about the safety and complications of EUS for gastrointestinal diseases were excluded. Reports of minor complications, such as short oxygen desaturation, self-limiting bleeding from the puncture site and excessive cough as well as equipment-related problems were also excluded. The short report format of this paper precludes listing of all individual references, however Tables I (EBUS) and II (EUS) summarize the findings. A total of 185 complications from 39 publications were identified, including a small number of life threatening and fatal events.

Table I. Summary of significant complications of EBUS-TBNA.

Complications	Number of cases identified
Bleeding (including one death)	53
Infection (mediastinitis, abscess, pericarditis, cyst infection, sepsis, pneumonia, empyema, pleuritis, tumor infection)	39
Pneumothorax	15
Respiratory arrest, depression or failure	9
Hypoxia	6
Release of metal particles from needle, needle breakage	6
Atrial fibrillation or other cardiac arrhythmias	4
Lidocaine intoxication	4
Asthma attack and aggravation of airway obstruction	3
Cerebral infarction	2
Hypotension	2
Clinically significant airway injury	1
Endobronchial inflammatory polyp	1
Intramural hematoma of pulmonary artery and hematomapneumomediastinum	1
Tumor rupture	1
Hyperventilation syndrome	1
Rapid progression of interstitial pneumonia leading to death	1
All	149

Table II. Summary of significant complications of EUS-FNA.

Complications	Number of cases identified
Cervical esophageal perforation	20
Infections (mediastinitis, cyst infection)	11
Left adrenal hemorrhage	1
Needle tract tumor implantation	1
Severe chest pain	1
Mediastinal tuberculosis and esophageal-mediastinal fistula	1
Need for reversal of medications	1
All	36

Four studies related to this topic should be mentioned. Eapen et al. published data on prospectively enrolled patients undergoing EBUS-TBNA from the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education (AQuIRE) database [6]. Overall, complications occurred in 19/1317 patients (1.44%). In the subgroup of patients who also underwent transbronchial biopsy (TBBx) ($n = 187$) the rate was 3.21% compared with 1.15% in patients who did not (OR 2.85; 95% CI 1.07–7.59). The authors concluded TBBx was a risk factor for complications during EBUS-TBNA procedures. ROSE significantly reduced the use of TBBx.

Asano et al. published results of two postal questionnaire surveys (published in 2012 and 2013) involving all facilities certified by the Japan Society of Respiratory Endoscopy. In the first study deaths and complications associated with endoscopy (including but not limited to EBUS) were identified [7]. Complications occurred in 17/3689 EBUS-TBNA cases (0.46%) with infection being the most frequent. In the second study complications associated specifically with EBUS-TBNA were surveyed [8]. This identified complications in 90/7345 cases (1.23%; 95% CI 0.97–1.48%). Hemorrhage was the most frequent complication encountered ($n = 50$) followed by infection ($n = 14$).

Finally, in 2009 Varela-Lema et al. published the results of a systematic review, that included 20 publications ($n = 1782$ patients), to assess the effectiveness and safety of EBUS-TBNA [9]. Interestingly, the authors concluded that none of the studies reported serious complications. This highlights the importance of publication formats such as case reports and short communications in identifying some of the challenges of introducing new techniques into clinical practice.

The reports suggest that infectious complications might be more likely after aspiration of cystic or necrotic targets. Infectious complications have also been observed despite prophylactic antibiotics. Concerning proximal esophageal perforation one survey indicated a frequency of 0.03% during EUS and suggested that advanced patient age, prior

difficulty with upper endoscopic procedures, existence of large cervical osteophytes, and relative inexperience of the endosonographer might contribute [10].

Discussion

E(B)US-NA are now established minimally invasive diagnostic and staging tools. Their use is increasing and they are recommended as the initial staging investigation in a number of lung cancer guidelines. While they are generally very safe procedures there is a low risk of potentially serious, even fatal complications. As these techniques are rapidly diffusing into clinical practice it is possible that current estimates of serious complications are an underestimate and that they will increase. Case reports and case series were an important source of information in highlighting these complications. In a recent study determining the impact of trainee participation in interventional pulmonary practice it was suggested that trainee participation increased procedure time and amount of sedation used and resulted in a trend to increased complications [11]. This suggests a possible role for training aids such as simulators, however, whether these are effective in reducing complications, remains to be proven [12].

The cases presented in this report and identified in the literature have implications for informed consent and staff training. The largest number of significant complications was related to bleeding, infection, esophageal perforation and pneumothorax/respiratory dysfunction. Therefore, patients need to be informed of this, and advised to present urgently if they become unwell or develop specific symptoms including fever, chest pain, blood loss, subcutaneous air or breathing difficulties. Staff involved in performing E(B)US or looking after patients who have undergone these procedures need to be trained to identify the range of complications that can occur. Finally, to identify and to try to reduce complications, it is important that individual centers audit their own experience with E(B)US-NA.

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