Mediastinal Mysteries: What can be solved with EBUS?

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Disclosures

- None
Objectives

- Introduce you to the technique of Endobronchial Ultrasound
- Learn the utility of EBUS in the diagnosis of mediastinal pathology such as in sarcoidosis and malignancy.
- Review the updated lung cancer staging guidelines.
First case...

- 53 year old AAF presents with lower respiratory track infection (productive cough, fevers). Exam is otherwise normal. Following failure of antibiotics a CXR is obtained...
CXR
Clinical course…

- Patient given another antibiotic and sent for a chest CT to further evaluate the hilar adenopathy. The patient had a family history of lung cancer but she had never smoked. No other PMHx. No medications.
CT
CT
Clinical course…

- Pt seen by Pulmonary and sent for a PET scan, ACE level, and histoplasmosis titers.
PET-CT
Lab data…

- ACE level = 38 (range 2-52 units/L)
- Histoplasmosis Comp Fixation negative
- Histoplasmosis Immunodiffusion negative
- Histoplasmosis Urine Antigen negative
Histoplasma capsulatum antigen (Ag) can be detected in up to 75 percent of cases of acute pulmonary histoplasmosis and is found more commonly in patients with severe clinical manifestations. Detection of high titers of complement fixing antibodies to the yeast or mycelia antigen precedes detection of M or H bands by immunodiffusion in most patients. However, antibodies rarely appear before the fourth week of infection and often do not reach maximal titers until the second or third month of infection.

*Courtesy of Joseph Wheat, MD.*
What next?

- 53 yr old AAF presented with cough and fever and found to have bilateral hilar adenopathy (PET active), a normal ACE, negative histo titers, and a normal physical exam.
A Mediastinal Mystery…

- PET scan does not differentiate sarcoid or histoplasmosis from malignancy.
- ACE is elevated in 75% of untreated sarcoidosis.
- Lung cancer vs. Lymphoma vs. Sarcoidosis vs. Fungal vs. Metastatic disease vs. other…
- Refer to GI versus Pulmonary versus Thoracic Surgery?
Next step…

What is the safest way to achieve the diagnosis and potentially stage the patient with one sedation?

- Mediastinoscopy
- Trans-bronchial biopsy with blind TBNA
- Endoscopic Bronchial Ultrasound (EBUS) with TBNA (EBUS-TBNA)
- Endoscopic Esophageal Ultrasound (EUS) with FNA
Mediastinoscopy
Mediastinoscopy

- Limited access to many lymph node stations (ex subcarinal station 7)
- Requires general anesthesia
- 2% morbidity and 0.08% mortality risk
- $\$ > TBNA

Traditional “blind” TBNA
Problems...

"Pull out, Betty! Pull out! ... You've hit an artery!"
Other problems with blind TBNA
What is EBUS?

- Endoscopic Bronchial Ultrasound
  - Direct visualization
  - Improved angulation
EBUS transducer and needle
Transbronchial Needle Aspiration (TBNA)

EBUS: Seeing is believing…
Doppler
# Linear EBUS-TBNA for mediastinal lymph nodes

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<td>493 (98)</td>
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Krasnik M et al. Thorax 2003  
Yasafuku K et al. Chest 2004 and Lung Cancer 2005  
Vilman P et al. Endoscopy 2005  
Rintoul RC et al. Eur Respir J 2005  
Herth FJF et al. Thorax 2006
Mediastinoscopy versus EBUS

- Prospective crossover trial EBUS-TBNA versus cervical mediastinoscopy
- Diagnosis of lung cancer
- EBUS w/ diagnostic yield 91% versus 78%
- Superior sens and spec and NPV

What about EUS?
What about EUS?

**Advantages**
- Larger 19 gague needle (21 gague for EBUS)
- Esophageal bleeding better?
- Can reach L-adrenal, para-aortic, liver

**Disadvantages**
- Access to fewer nodal stations (esp on R)
- No airway control (OSA patients etc…)
- Negative biopsies need confirmation
Station #5 better with EUS
Complimentary?
EUS + EBUS vs. Mediastinoscopy

Mountain CF et al. Chest 1997;111:1718-1723
Rintoul R et al. Endoscopy 2006; 38:S110-S113
139 pts w/ NSCLC
- 229 nodes via EUS-FNA
- 390 nodes via EBUS-FNA

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Back to our case…

- Which nodes should we go after?
What nodes to go after???
EUS (green)  

EBUS (red)  

Journal of Thoracic Oncology • Volume 4, Number 12, December 2009
EBUS performed

- Can look for endobronchial involvement
- Can send Bal for CD4:CD8 (high in sarcoid)
- Can access all enlarged nodal stations
- With rapid on-site cytology (ROSE) can get diagnosis before patient goes home!
Sarcoidosis – dx via FNA
The Role Of EBUS-TBNA For The Diagnosis Of Sarcoidosis - Comparisons With Other Bronchoscopic Diagnostic Modalities

- Compared: EBUS-TBNA, Trans-bronchial biopsy (TBB) and Bronchoalveolar lavage (BAL)

- 38 patients with suspected Sarcoidosis

- BAL was followed by TBB and finally EBUS-TBNA in that order in the same procedure

- Respir Med. 2009 Aug 11. [Epub ahead of print]
The Role Of EBUS-TBNA For The Diagnosis Of Sarcoidosis - Comparisons With Other Bronchosscopic Diagnostic Modalities

- Diagnostic accuracy was significantly better by EBUS-TBNA (91.4%, p<0.001) compared to the other two modalities

- 31 stage I patients and 4 stage II patients

- EBUS-TBNA can be added as a diagnostic modalities

- Respir Med. 2009 Aug 11. [Epub ahead of print]
A Randomized Controlled Trial Of Standard Vs EBUS-TBNA In Patients With Suspected Sarcoidosis

A Randomized Controlled Trial Of Standard Vs EBUS-TBNA In Patients With Suspected Sarcoidosis

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Mystery #2

- A 60 yr-old white male presents to ED with cough and chest pain. No fevers or weight loss. He has a 35 pack year smoking history. No other significant PMH. Works for City of Indianapolis. A chest x-ray and subsequent CT are performed....
CXR
Differential?

- Cancer
- TB
- Fungal (aspergillous, blastomycosis, histoplasmosis)
- Sarcoidosis (stage II w/ cavitations)
- Wegener's Granulomatosis
- Bacterial abscess w/ LN activation
  - Anaerobes
  - Nocardia
Very next step?

1. TB isolation for rule-out
2. Consult Pulmonary (EBUS-FNA)
3. CT guided FNA
4. Quantiferon Gold testing
5. PET Scan
Very next step?

1. TB isolation for rule-out
2. Consult Pulmonary (EBUS-FNA)
3. CT guided FNA
4. Quantiferon Gold testing
5. PET Scan
Clinical course…

- Following 3 negative sputum’s for AFB’s, a negative PPD, and negative serologies a bronchoscopy is performed….
ROSE “Rapid On-Site Cytology”
Stage?

- No endobronchial invasion
- Size 6x5 cm (mediastinal node)
- Size 3x2 cm (cavitary lesion)
T

- **T1a** = in lung <2cm
- **T1b** = in lung 2-3cm
- **T2** = 3-7cm or endobronchial >2cm from carina or visceral pleura or atelectasis
  - <5cm T2a
  - >5cm T2b
- **T3** = >7cm or has grown into: parietal pleura, diaph, phrenic, pericardiaum, total atel, or >1 tumor same lobe
- **T4** = Invades: mediastinum, the heart, a major blood vessel, trachea/carina, esophagus, spine, recurrent pharyngeal nerve, or >1 lobe same lung
N

- N0 - none
- N1 - ipsilateral
- N2 – ipsilateral mediastinum (subcarinal)
- N3 – contralateral nodes or above clavicle
- **Dx IIIa T2 N2 M0**

- **Set up for a PET-CT to further stage....**

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PET

- PET-CT finds *left supraclavicular node*

- Does this re-classify our patient? (was stage IIIa)
What is IIIb?

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Prognosis

Detterbeck F C et al. 
Chest 2009;136:260-271
What did we learn?

- Could we have diagnosed/staged with supra-clavicular biopsy initially?
- Benefit of checking PET-CT prior to endoscopy.
- New question: Does this extend to patients with limited/early stage disease?...
Conclusion: Preoperative staging with PET-CT and cranial imaging identifies more patients with mediastinal and extrathoracic disease than conventional staging, thereby sparing more patients from stage-inappropriate surgery, but the strategy also incorrectly upstaged disease in more patients.
Preoperative Staging of Lung Cancer with Combined PET–CT

Barbara Fischer, Ph.D., Ulrik Lassen, Ph.D., Jann Mortensen, Dr.Med.Sci., Søren Larsen, Ph.D., Annika Loft, Ph.D., Anne Bertelsen, M.D., Jesper Ravn, M.D.,

CONCLUSIONS

The use of PET–CT for preoperative staging of NSCLC reduced both the total number of thoracotomies and the number of futile thoracotomies but did not affect overall mortality. (ClinicalTrials.gov number, NCT00867412.)
Another mystery…

61 yr old WM is found to have a 2.1cm L-lung lesion along with subcarinal and left hilar adenopathy on a CT performed in the ED for chest pain last week. Patient has a history of mild COPD (100+ pk/yr smoking history), OSA, and was diagnosed with “costocondritis” s/p kayaking on Eagle Creek.
CT

Node
What next?

- Given need to stage and diagnose a PET-CT is performed...
Subcarinal (7)
Left hilar (station 10)
Who ya gonna call?

- PET-CT confirms activity in stations 7 (subcarinal) and L-hilar (10)

- Where do you want to biopsy?

- What are the risks of the procedure?
  - Pt w/ COPD and OSA
- **T1a** = in lung <2cm
- **T1b** = in lung 2-3cm
- **T2** = 3-7cm or endobronchial >2cm from carina or visceral pleura or atelectasis
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N

- N0 - none
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- N3 – contralateral nodes or above clavicle
Solved…

- EBUS-FNA diagnosed non-small cell cancer

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PET-CT

- In this case the PET-CT “discovered” the subcarinal node and correctly upstaged the patient following an EBUS assisted subcarinal biopsy positive for non-small cell lung cancer.
NSCLC Treatment....

- To oversimplify, for stage Ia and Ib, the treatment is surgery.
- For stage IIa and IIb, the treatment is surgery.
- For stage IIIA, the treatment is surgery for some, neoadjuvant therapy followed by surgery for some, and chemotherapy/radiation therapy for some.
- For stage IIIB, except for some T4N0M0, the treatment is chemotherapy and XRT, preferably concurrently, if possible.
- For stage IV, the treatment is “best supportive care” or chemotherapy.

Subcarinal nodes really change things!
The future of staging…..?
The future of staging.....?

- Oncogene mutations
History

- 52 yr-old WF non-smoker dx w/ breast cancer in 2002. She had a 4mm invasive ductal carcinoma on L (given neo-adj chem) than at time of b/l mastectomies found to have R invasive ductal carcinoma as well.

- R is HER-2 positive, ER, PR negative
- L is HER-2, ER, PR, negative
6 years later…

- She develops mediastinal adenopathy (presumed recurrence), RML lesion, and 2 liver lesions
- Develops pleural effusion → tapped and found to be primary adeno lung cancer!
- Per new staging guidelines a pleural effusion is a **T4 lesion stage IV**.
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Lung cancer

- Fluid from effusion was TTF-1 positive
  - Thyroid transcription factor 1
  - Lung adeno-ca and small cell-ca marker

Coupled with cyto a diagnosis of primary lung adenocarcinoma is made.
Need more tissue?

- Patient is referred for EBUS to obtain FNA hilar lesion for more cells after dx made. WHY?
Oncogenes

- Gain of function gene mutations leading to cellular hyperproliferation
- HER2
- EML4-ALK
- K-ras
- EFGR
EML4-ALK mutation

- Anaplastic lymphoma kinase gene
- Echinoderm microtubule-associated protein-like 4 gene
- Inversion of chromosome #2 juxtaposes each
EML4-ALK mutation

- FISH is gold standard for dx
- Never or light smokers, younger, adenos
- Highly sensitive to ALK-targeted inhibitors
- Crizotinib (TKI) in phase III trial
Summary

- Reviewed the utility of EBUS for the diagnosis of mediastinal pathology.
- Reviewed the updated lung cancer staging guidelines.
- Introduced the concept of oncogene mutation directed chemotherapy for lung cancer treatment.
A final mystery...
Questions?