

# EUS for unexplained mediastinal lesions

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## Introduction

Trans-esophageal endoscopic ultrasound (EUS) with fine needle aspiration (FNA) offers a unique ability to assess and biopsy posterior mediastinal lesions. This review will focus on EUS diagnosis of unexplained posterior mediastinal, lymph nodes, masses, and cysts. Table 1 shows the types of posterior mediastinal lesions which can be diagnosed with trans-esophageal EUS/FNA cytology.

## EUS evaluation of enlarged posterior mediastinal lymph nodes

### EUS appearance of normal benign posterior mediastinal lymph nodes

Benign mediastinal lymph nodes are commonly encountered during EUS for non-thoracic indications. These often have a triangular or crescent shape. An echogenic center may be visualized, representing the hilum of the lymph node.

### EUS appearance of malignant posterior mediastinal lymph nodes

EUS findings associated with malignancy include round shape, short-axis diameter greater than 5–10 mm, hypoechoic echotexture, and well-demarcated borders [1,2]. If all 4 features are present

in a lymph node, the chance of malignancy is 80–100% [2,3]. However, since all 4 features are only seen in 25% of malignant lymph nodes, tissue sampling is important to obtain diagnostic material [3].

## EUS/FNA and trucut biopsy of posterior mediastinal lymph nodes

Trans-esophageal EUS/FNA is performed using a linear array echoendoscope and usually a 22-gauge aspiration needle. If there is more than one lesion, the one which is most likely to be malignant (i.e. rounder, larger, more demarcated) is chosen as the target [4]. In the United States, the slides are often prepared and evaluated immediately to determine adequacy. If preliminary evaluation suggests lymphoma, then additional passes may be obtained for flow cytometry, and if suspicious for infection, then additional passes made for microbiologic studies. Final diagnosis is provided after the pathologist has evaluated all processed specimen slides, cellblock, and any additional material.

EUS-guided Trucut biopsy using a 19-gauge needle device has also been reported [5,6]. The potential advantage of core biopsies is preservation of tissue architecture. Some pathologists are more familiar with and prefer tissue sections. Some suggest histologic core with touch preparations, immediate cytologic evaluation, and then EUS/FNA for additional material [6]. However, touch preps may not demonstrate representative cells and crush artifact may be introduced to the core. Another disadvantage of core biopsy is technical difficulties with the current generation Trucut needle which limits its utility if tightly angulated. The Trucut needle may be useful in selected cases of mediastinal lymph nodes or masses for suspected smooth muscle tumors, sarcomas, and lymphomas, or when FNA cytology is non-diagnostic [7].

The overall accuracy rate for diagnosing posterior mediastinal malignancy with trans-esophageal EUS/FNA is approximately 93% [4]. The diagnostic accuracy of malignant posterior mediastinal lymph nodes increases with EUS/FNA cytology compared to EUS appearance alone. The risks of trans-esophageal EUS/FNA of mediastinal lymph nodes appears to be very small, but potentially includes mediastinitis, bleeding, stridor, or perforation [8–12].

## Differential diagnosis of enlarged posterior mediastinal lymph nodes

Enlarged mediastinal lymph nodes are usually defined by CT size  $\geq 1$  cm diameter. In the setting of a peripheral lung mass and mediastinal lymph nodes, the main concern is primary lung cancer with metastatic disease. The finding of unexplained numerous posterior mediastinal and hilar lymph nodes introduces a broader differential diagnosis: benign (sarcoid, histoplasmosis, tuberculosis, reactive) or malignant (especially lymphoma).

## Malignant posterior mediastinal lymph nodes

The rate of a malignant diagnosis in EUS/FNA of posterior mediastinal nodes in patients without a known diagnosis of cancer var-

Table 1 Posterior mediastinal lesions that can be diagnosed with EUS/FNA

Primary pulmonary cancer
Non-small cell lung cancer
Small Cell Lung Cancer
Metastatic cancer from extra-thoracic malignancy
Lymphoma
Reactive Lymph Nodes
Granulomatous Disease
Sarcoid
Histoplasmosis
Tuberculosis
Neurogenic Tumors
Duplication Cysts
Mediastinal Abscess/Mediastinitis

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ies depending on prior bronchoscopic evaluation and local referral patterns, but is approximately 50% [8,13]. The overall sensitivity, specificity, and accuracy for diagnosing malignancy in posterior mediastinal lymph nodes with EUS/FNA is greater than 90% [4,8,10].

### Metastatic disease to the posterior mediastinum

A variety of tumors metastasize to the posterior mediastinum, appearing as either a lymph node or mass. The most common metastatic lesion is primary lung cancer, of which 80% is non-small cell lung cancer (NSCLC) and the remaining 20% small cell carcinoma. Metastases from breast, colon, kidney, testis, larynx, pancreas, liver, and esophagus have been diagnosed by trans-esophageal EUS/FNA [14,11,15–17].

### Lymphoma

Material from EUS/FNA can be evaluated by cytology, immunohistochemistry, and flow cytometry, allowing diagnosis and workup of lymphoma in posterior mediastinal lymph nodes [18–21]. The sensitivity of diagnosing lymphoma can be increased (from 44% to 86%) by adding flow cytometry and immunocytochemistry [18]. Lymphoma can be rarely be associated with granulomas on lymph node FNA cytology, an important diagnostic caveat. Since additional studies require more material, a lymphoma diagnosis may necessitate additional needle passes. For some lymphomas, such as low grade follicular lesions, Trucut biopsies may provide helpful architectural details [5]. A few series have found that lymphoma was diagnosed with Trucut biopsies when cytology was non-diagnostic, although it is not clear whether immediate cytologic evaluation, flow cytometry, and/or immunostains were done in these cases [18,22].

### Benign posterior mediastinal lymph nodes

#### Reactive lymph nodes

Reactive lymph nodes are a usually the result of previous pulmonary infections or inhaled irritants. They have benign EUS features, and often have a draping or triangular appearance. Cytologically, they show a polymorphous population of lymphoid elements, sometimes with anthroctic pigment in macrophages.

#### Granulomatous lymph nodes

Granulomatous disease is diagnosed in EUS/FNA samples by its characteristic appearance of collections of palisaded histiocytes in a background of lymphocytes. The differential diagnosis includes sarcoid, histoplasmosis, tuberculosis, and coccidiomycosis. Necrosis or caseation in a lymph node can be seen with different etiologies and is not specific for tuberculosis. EUS/FNA material should be sent for fungal and mycobacterial stains and when infectious etiology is suspected.

#### Sarcoid

Sarcoid is a multisystem granulomatous disease of unknown etiology which commonly involves mediastinal lymph nodes. The EUS appearance of mediastinal sarcoid lymphadenopathy is generally several enlarged benign appearing lymph nodes. The final diagnosis requires clinical criteria and exclusion of other causes of granulomatous disease. There are no pathognomic laboratory or cytology findings. Elevated serum angiotensin converting en-

zyme levels support the diagnosis of sarcoid as does typically non necrotic granulomatous inflammation in mediastinal lymph nodes. EUS/FNA can obtain granulomatous material with high accuracy [23–25]. One retrospective study found the sensitivity and specificity of EUS/FNA for diagnosing granulomas in suspected sarcoid to be 89% and 96%, respectively [26]. Another EUS/FNA study demonstrated noncaseating granulomas in 41 of 50 patients (82%) with a final clinical diagnosis of sarcoidosis [25].

### Histoplasmosis

*Histoplasma capsulatum* infection is found worldwide. Within the United States, infection is most common in the midwestern states along the Ohio and Mississippi Rivers. The diagnosis is made by histopathology, serologic testing, and/or antigen testing. Histoplasmosis is usually suspected in patients from endemic areas with pulmonary symptoms or because of incidentally found posterior mediastinal adenopathy. The EUS appearance is several enlarged, benign appearing lymph nodes which may be matted together and calcified. EUS/FNA can identify granulomas in patients with suspected histoplasmosis [27,28].

### Tuberculosis

*Mycobacterium tuberculosis* can cause enlarged mediastinal lymph nodes or a nodal mass. EUS/FNA can obtain material for *M. tuberculosis* culture [13,24,29–31]. The addition of polymerase chain reaction testing for *mycobacterium tuberculosis* in EUS/FNA obtained samples may increase the diagnostic yield compared to cytology and culture in patients suspected to have tuberculosis.

### Mediastinal masses

The EUS distinction between a posterior mediastinal mass and lymph node can be difficult, because some lymph nodes are very large while some masses are very small. Additionally, numerous lymph nodes matted together can form a “mass”. Usually a mass is larger than an enlarged lymph node (i.e. several centimeters diameter), but there is no standardized terminology.

The differential diagnosis of a posterior mediastinal mass includes primary lung cancer extending into the posterior mediastinum, metastatic cancer (either primary lung or non-thoracic cancer), neurogenic tumor, cyst, and infection. Trans-esophageal EUS/FNA can easily sample large posterior mediastinal masses.

### Malignant posterior mediastinal masses

Just as with mediastinal lymph nodes, approximately 50% of mediastinal masses assessed by EUS/FNA are malignant [14,15,32,33]. Primary lung cancer masses abutting the esophagus are easily and safely biopsied with trans-esophageal EUS/FNA [34]. Mass-forming nodal metastases from lung, breast, colon, kidney, testicle, cervix, larynx, and esophagus have been diagnosed with trans-esophageal EUS/FNA [14,12,15,34]. EUS with trucut biopsy was able to diagnose a posterior mediastinal sarcoma which could not be diagnosed with EUS/FNA cytology [5].

## Neurogenic tumors

Primary neoplasms of the posterior mediastinum are rare. Approximately 75% are neurogenic, arising from peripheral nerves (schwannoma, neurilemoma, neurofibroma, nerve-sheath tumors), sympathetic ganglia (ganglioneuroma, ganglioneuroblastoma, neuroblastoma), or parasympathetic ganglia (paraganglioma). These are usually benign tumors, but approximately 10–20% may be malignant. Use of EUS/FNA cytology and Trucut biopsy have been reported to diagnosis mediastinal schwannomas [35,36].

## Benign posterior mediastinal masses

Benign mediastinal “masses” which can be diagnosed with EUS/FNA include cysts, histoplasmosis, sarcoidosis, leiomyoma, tuberculomas, and teratomas [14].

## Mediastinal cysts

Congenital foregut cysts are the most common benign mediastinal cysts, accounting for 10–15% of mediastinal masses. They probably arise as a result of aberrant development of the primitive foregut and are categorized on the basis of the embryonic origin into bronchogenic or neuroenteric (esophageal duplication cysts and neuroenteric cysts). Esophageal duplication cysts are adherent to the esophagus, while those away from the esophageal wall are suggestive of bronchogenic cysts. The pathologic evaluation of duplication cysts reveals them to be typically lined by columnar epithelia. Foregut cysts may show ciliated epithelium or detached cilia in the aspirated fluid.

Most patients with posterior mediastinal cysts are asymptomatic, and the cysts are discovered incidentally during other imaging studies. When symptoms occur, they can include chest pain, cough, dyspnea, and dysphagia. CT scan findings include well-defined, homogenous lesions ranging in size from 2–10 cm. They are non-enhancing with intravenous contrast. They can sometimes be mistaken for a mass based on CT findings. Surgical resection may be indicated in symptomatic patients. Because the malignant potential is considered to be extremely rare, incidentally found lesions can usually be followed clinically.

The EUS appearance of a mediastinal cyst is usually a round or tubular anechoic structure with acoustic enhancement [37–40]. It is often difficult to determine if the cyst is bronchogenic or esophageal in origin by EUS, and therefore the general term duplication cyst is often used to describe the lesion. Some cysts appear to be a mass lesion because of a more hypoechoic (rather than anechoic) echotexture and minimal acoustic enhancement. These mass-like cysts usually consist of a thick gelatinous cyst material [40–43].

Cysts have been aspirated with EUS/FNA, but usually only when the EUS is not highly compatible with a cyst, and instead appears to be a possible mass [37,40,42–45]. There have been reports of patients developing mediastinitis and/or cyst infection after undergoing EUS/FNA, including several with the use of trucut needle biopsy [41,36,42,45–47]. These patients required treatment with antibiotics, surgery, and/or endoscopic cyst drainage. Of note, most of these reported no antibiotic prophylaxis. A more

recent series which used antibiotics around of the time of the FNA reported no complications [43].

Since most posterior mediastinal cysts are benign and mediastinitis is a recognized complication, obvious posterior mediastinal duplication cysts should not be aspirated with EUS/FNA. If it is unclear whether the lesion is a cyst or a malignancy, then the safest next diagnostic test might be thoracic MRI or CT to confirm there is a cyst [42]. If EUS/FNA is performed on a lesion which turns out to be a cyst rather than a solid mass, then the cyst should be completely drained if possible, and prophylactic antibiotics should be administered, such as intravenous antibiotics during the procedure and oral antibiotics for the next 3–5 days after to minimize any risk of mediastinitis [43]. EUS-guided trucut needle biopsies should be avoided in suspected posterior mediastinal cysts because of the risk of mediastinitis.

## Mediastinal abscess/mediastinitis

EUS/FNA may have a role in the management of acute mediastinitis and abscess occurring after thoracic surgery or esophageal perforation. Fritscher-Ravens reported a series of 18 critically-ill patients with clinical mediastinitis (mostly after thoracic surgery) who underwent EUS/FNA [31]. The EUS appearance of the abscesses were 2–4 cm, inhomogeneous, well-demarcated hypoechoic areas. Some lesions had hyperechoic 2–3 mm spots with shadowing, which were felt to represent air. EUS/FNA revealed purulent material and bacterial organisms on microbiology culture. There were no apparent complications from performing EUS/FNA into the mediastinal abscesses. EUS/FNA has also been reported to diagnose candida mediastinitis [48]. There have been reports of mediastinal abscess/mediastinitis managed with EUS-guided drainage and/or placement of trans-esophageal pigtail stents [49,50].

## Conclusion

EUS is a very safe and effective means of visualizing and characterizing posterior mediastinal lesions. EUS/FNA allows accurate and safe biopsy of posterior mediastinal lesions. Because of the high rate of reported infectious complications, EUS/FNA of obvious mediastinal cysts should be avoided.

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