Approach to Isolated Mediastinal Lymphadenopathy

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KEYWORDS

• Lymphadenopathy • Sarcoidosis • Lymphoma • Granuloma • Endobronchial ultrasound
• Enlarged lymph node • Isolated lymphadenopathy • Malignancy

KEY POINTS

- Isolated mediastinal lymphadenopathy may develop in patients with a variety of inflammatory, infectious, and malignant conditions.
- Consensus guidelines for evaluation and management of isolated mediastinal lymphadenopathy are not available, but various imaging modalities may provide useful information to direct additional testing.
- Biopsy is often necessary in the evaluation of isolated mediastinal lymphadenopathy, and endobronchial ultrasound-transbronchial needle aspiration is the preferred modality to confirm the etiology.

INTRODUCTION

Chest computed tomography (CT) is now readily available in most health care institutions and is increasingly being used for the assessment of a variety of thoracic complaints as well as for lung cancer and coronary artery screening evaluations. Not unexpectedly, the prevalence of incidental findings such as lung nodules and enlarged lymph nodes on chest CT scans is also increasing. After such incidental findings, health care providers are faced with the challenge of determining when additional workup is indicated and identifying the best modality for reaching a diagnosis. Therefore, proper evaluation and management of abnormal imaging findings is an important topic of discussion among health care providers. Guidelines for further investigation of incidentally identified lung nodules are well established. Thus, we have focused on a less frequently discussed topic: isolated mediastinal lymphadenopathy.

Mediastinal lymph nodes measuring at least 10 mm in the short axis diameter on chest imaging have historically been defined as enlarged and potentially worrisome.[1] Whereas accurately estimating the prevalence of mediastinal lymphadenopathy on all thoracic CT scans is difficult, researchers have estimated that it ranges from 1% to 6% in lung cancer and coronary artery disease screening CT scans.[2] More recently, Chalian and colleagues[3] found enlarged, noncalcified mediastinal lymph nodes on the chest CT scans of 1.6% of the 26,722 participants in the National Lung Screening Trial, and they identified isolated enlarged mediastinal lymph nodes without lung nodules in an even smaller proportion of patients. Despite the relatively low frequency of incidentally identified isolated mediastinal lymphadenopathy on chest CT scans, this is an important topic for discussion given the multiple potential etiologies and associated treatment consequences of this disease.

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Abbreviations	
CT	computed tomography
EBUS	endobronchial ultrasound
FDG-PET	PET with fluorodeoxyglucose
HL	Hodgkin lymphoma
LR	likelihood ratio
TBNA	transbronchial needle aspiration

Etiologies and Importance

Isolated mediastinal lymphadenopathy may develop secondary to a wide variety of both malignant and nonmalignant etiologies, most notably, granulomatous disorders such as sarcoidosis, tuberculosis, and certain fungal infections as well as in response to some medications, congestive heart failure and other chronic medical conditions, lymphoma, and metastatic cancers. Cancer is the most worrisome concern when lymphadenopathy is identified, although the prevalence rate for cancer in patients presenting with isolated mediastinal lymphadenopathy alone is quite low at an estimated 1.1%.[4] In patients with a preexisting pulmonary or nonpulmonary cancer, the prevalence is much higher at about 36% to 80% depending on the diagnostic method and patient population.[5,6] The most common cause of mediastinal lymphadenopathy varies depending on the patient's geographic location and may affect diagnostic algorithms. For example, granulomatous diseases are the most common causes in developing regions, whereas cancer is the most common cause in the United States.[7]

Given that many of these diagnoses are life-changing and often require targeted treatment, prompt, accurate diagnosis of the exact etiology of mediastinal lymphadenopathy is of the utmost importance. Also, avoiding unnecessary workup and procedures in patients with benign lymphadenopathy is just as crucial. A 2018 American College of Radiology white paper on the management of incidental mediastinal findings in thoracic CT suggests that no further workup is necessary for patients with incidentally identified mediastinal lymph nodes measuring less than 1.5 mm in the short axis in the absence of other specific symptoms and findings.[1] Whereas this guidance may prove helpful, it is based on a review of data from small studies in addition to expert opinion and thus requires further investigation prior to widespread adoption. Currently, no well-designed evidence-based guidelines are available for the evaluation and management of isolated mediastinal lymphadenopathy, which adds complexity to the management of these patients.

Given the importance of isolated mediastinal lymphadenopathy and the lack of consensus in the literature, we wrote this article to summarize relevant data on the most common etiologies of isolated mediastinal lymphadenopathy regarding patient presentation, imaging characteristics, and other workup findings to provide a reference for clinical practice.

Imaging Modalities for Evaluation

Chest X rays may reveal findings suggestive of mediastinal/hilar lymphadenopathy (Fig. 1), but a normal chest X ray does not rule out the possibility of this disease. Lymph node features on CT imaging can provide useful information, including the shape of the lymph node, the attenuation pattern, the presence of calcifications, or the presence of a fatty hilum. Nonmalignant lymph nodes tend to have homogeneous attenuation with smooth, well-defined borders and often a central fatty hilum. Also, except in patients with certain cancers, the presence of calcifications is usually a benign finding, seen most often with infections and sarcoidosis. Ill-defined borders of a lymph node, central necrosis, and heterogeneous attenuation raise suspicion for cancer (Fig. 2).[1]

PET with fluorodeoxyglucose (FDG-PET) may be helpful in the evaluation of isolated mediastinal lymphadenopathy, particularly in the absence of additional imaging abnormalities or clinical features suggesting a specific nonmalignant diagnosis. A standard uptake value of 2.5 or greater is often used as a cutoff suggestive of malignancy to prompt additional workup, although recognizing

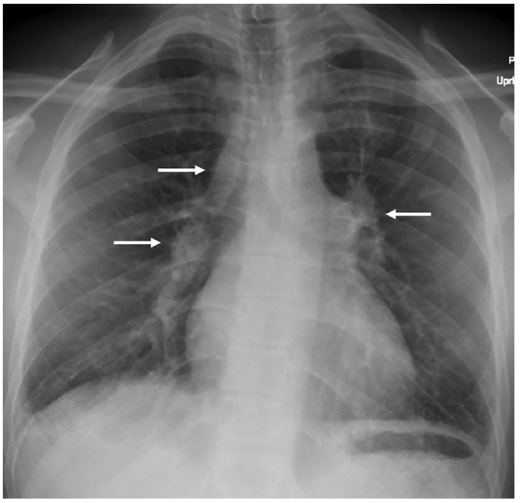

Fig. 1. Chest X ray suggestive of mediastinal and hilar lymphadenopathy (*arrows*) in a patient with sarcoidosis.

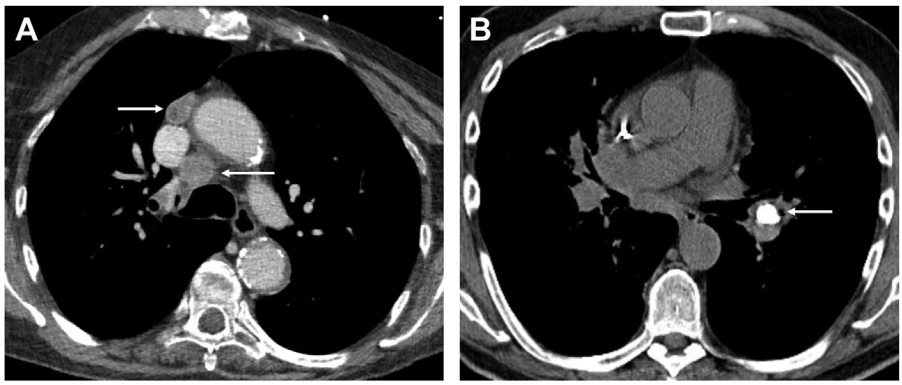

Fig. 2. (*A*) Chest CT scan revealing multiple enlarged mediastinal lymph nodes with heterogeneous enhancement, central necrosis, and irregular borders in a patient with metastatic lung cancer (*arrows*). (*B*) Chest CT scan revealing a densely calcified left hilar lymph node in a patient with advanced sarcoidosis (*arrow*).

that nonmalignant conditions such as sarcoidosis may also have elevated uptake is important.[7,8] Additionally, the size of the lesion in question on PET scans must be taken into consideration, as this can influence the standard uptake value.[8] In the setting of abnormal PET imaging, further evaluation with more invasive testing is often warranted.

Lately, diffusion-weighted magnetic resonance imaging has been used in the characterization of mediastinal lymph nodes, with an apparent diffusion coefficient being an independent predictor of malignancy. When researchers used an apparent diffusion coefficient of 1.0955×10^{-3} mm^2/s as a threshold value for differentiating malignant and benign nodes, they obtained the best results with a sensitivity rate of 94%, a specificity rate of 96%, and an area under the curve of 0.996.[9] Quantitative information from spectral CT is also being evaluated for its utility in differentiating malignant and nonmalignant lymph nodes, demonstrating promising results when used in conjunction with lymph node morphology.[10,11] Over time, imaging modalities may prove even more useful in the evaluation of undiagnosed, isolated mediastinal lymphadenopathy.

Techniques for Tissue Diagnosis

Various techniques are available for obtaining tissue and cytologic specimens in the evaluation of mediastinal lymphadenopathy. Less invasive options primarily include percutaneous needle biopsy, which may be helpful in the setting of isolated anterior mediastinal lymphadenopathy or a mass, and endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA). Conventional TBNA was historically used for the assessment of enlarged mediastinal lymph nodes but has been performed much less frequently because of the widespread availability and adoption of EBUS. More invasive surgical options primarily include conventional and video-assisted cervical mediastinoscopy, anterior mediastinoscopy (Chamberlain procedure), and video-assisted thoracoscopic surgery.[12]

EBUS allows for easy access to most thoracic lymph nodes via the tracheobronchial tree and has a more favorable safety profile than that of more invasive options, such as mediastinoscopy and video-assisted thoracoscopic surgery.[13] Just as with CT, EBUS-based evaluation can assist in differentiating between malignant and benign lymphadenopathy according to morphologic lymph node features, such as increasing short axis length, round shape, distinct margins, and heterogeneous echogenicity, each of which have varying sensitivity and specificity in the diagnosis of malignancy.[14] For example, well-defined nodal margins, the presence of a central hilar structure, and nodal conglomeration are predictive of benign lymphadenopathy, whereas features such as a round shape, indistinct margins, heterogeneous echogenicity, and coagulation necrosis sign are more indicative of malignancy (**Fig. 3**).[15,16] Even in the presence of abnormal lymph node ultrasound characteristics, sampling is often necessary, with multiple tools available to obtain tissue via EBUS guidance, including needles of various sizes, transbronchial forceps, and cryoprobes.[17] Surgical modalities are usually reserved for cases with a high suspicion of malignancy and negative or nondiagnostic results after EBUS sampling or if sampling of mediastinal station 5 or 6 is needed.[12,18]

Sarcoidosis

Sarcoidosis is a primary diagnostic consideration when isolated mediastinal or hilar lymphadenopathy is identified on chest CT. The specific worldwide incidence and prevalence of sarcoidosis are

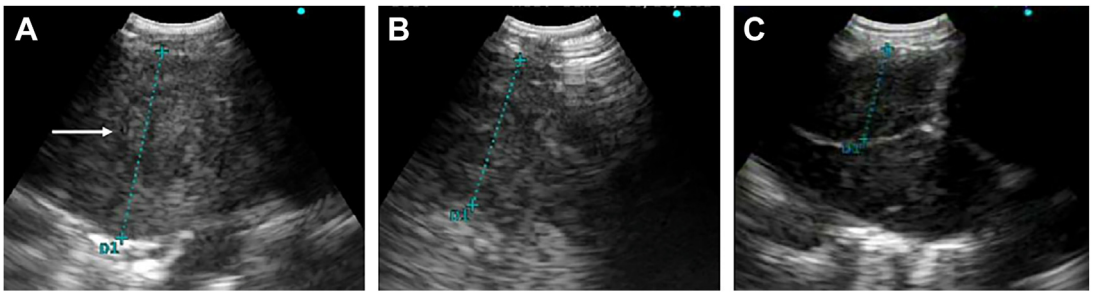

Fig. 3. EBUS images showing (*A*) central necrosis (*arrow*) and (*B*) a round, heterogeneous lymph node in a patient with cancer versus (*C*) a conglomeration of homogeneous appearing lymph nodes in a patient with sarcoidosis.

difficult to define owing to variations in methods and timelines for reporting, but the prevalence is known to vary significantly based on geography.[19] The prevalence of sarcoidosis in the United States alone is an estimated 60 per 100,000 adults, with women and African Americans most often affected,[20] although the prevalence likely varies significantly according to geography even within the United States.[21] Sarcoidosis is a multisystem disease of unknown etiology characterized by noncaseating granulomatous inflammation in affected tissues. The lungs and thoracic lymph nodes are most often involved, but almost any organ can be affected.[22] When symptoms are present, they are often nonspecific and primarily include a nonproductive cough, dyspnea, chest pain, fatigue, and fever.[23,24] A large proportion of patients with sarcoidosis are asymptomatic,[21,23,25,26] and suspicion is first raised for this diagnosis after enlarged hilar and/or mediastinal lymph nodes with or without parenchymal abnormalities are incidentally identified on chest imaging performed for other reasons.

Sarcoidosis is staged from 0 to IV according to the Scadding radiographic staging system as follows: 0, normal; I, bilateral hilar lymphadenopathy without pulmonary infiltrates; II, bilateral hilar lymphadenopathy with pulmonary infiltrates; III, pulmonary infiltrates without bilateral hilar lymphadenopathy; IV, extensive fibrosis with distortion or bullae.[27] When classic parenchymal abnormalities are present, the diagnosis of sarcoidosis can be more easily made in the proper clinical setting.[28] These findings are not always present, however, and in the setting of isolated mediastinal and/or hilar lymphadenopathy, further investigation is often pursued to rule out lymphoma or more ominous diagnoses.

CT lymph node characteristics in the setting of sarcoidosis are nonspecific, but bilateral lymphadenopathy is identified in more than 90% of patients and is the most common imaging abnormality (**Fig. 4**).[28] Less commonly, unilateral lymph node enlargement may be seen, and calcifications may develop, particularly late in the disease course.[28] In a previous review, Treglia and colleagues described that FDG-PET is not only useful in the setting of malignancy but may also play a role in the diagnosis and surveillance of sarcoidosis, as inflammatory cells have increased glucose metabolism.[29] They highlighted that available data support the use of FDG-PET/CT for staging, evaluation of disease activity, and monitoring of treatment response in patients with sarcoidosis (**Fig. 5**). FDG-PET/CT may also be useful in determining the optimal biopsy site for disease confirmation and to rule out other diseases, such as lymphoma.[29] FDG avidity in mediastinal and/or hilar lymph nodes is not specific for sarcoidosis, and when present, it most often prompts further evaluation with a biopsy. Spectral CT is a newer imaging modality that showed promise in early, small studies in differentiating sarcoidosis from Hodgkin lymphoma (HL) as described by Cao and colleagues[10] in 2022. Analysis of the receiver operating characteristic curves in that study demonstrated that a monochromatic CT value of 40 keV in the arterial phase and the slope of the spectral curve in the venous phase had the best sensitivity

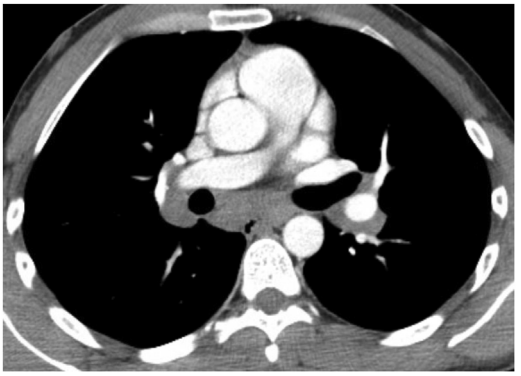

Fig. 4. Chest CT scan showing bilateral mediastinal and hilar lymphadenopathy in a patient with sarcoidosis.

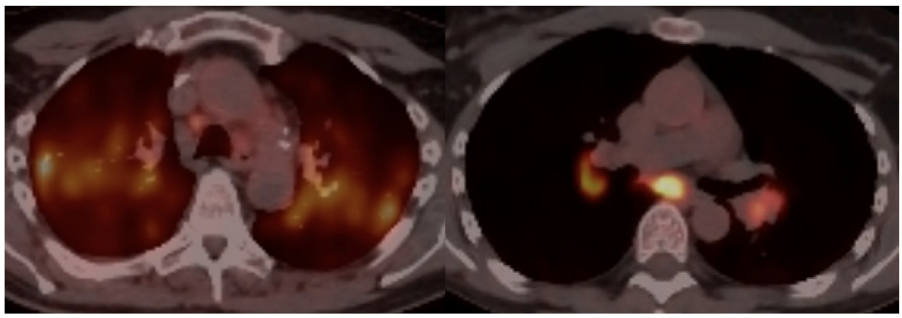

Fig. 5. Two PET/CT images of separate patients with sarcoidosis illustrating some of the abnormalities that can be seen with this disease.

(81%) and specificity (100%) in distinguishing between sarcoidosis and HL as the cause of mediastinal lymphadenopathy in a study population with biopsy-proven disease. However, larger studies are necessary before this imaging technique may be considered as a replacement for histopathological confirmation.[10] Serum biomarkers such as angiotensin-converting enzyme, soluble interleukin-2 receptor, and the bronchoalveolar lavage fluid CD4/CD8 ratio may assist in the diagnosis of sarcoidosis, but none of them are selective enough to be used independently.[28]

Whereas standard diagnostic criteria for sarcoidosis are lacking, diagnosis of it is likely when patients have a compatible clinical presentation, patients are found to have nonnecrotizing granulomas on biopsy, and alternative causes of granulomatous inflammation are reasonably excluded.[24] The American Thoracic Society Clinical Practice Guideline for the diagnosis and detection of sarcoidosis recommend avoidance of invasive lymph node sampling in patients for whom suspicion of sarcoidosis is sufficiently high, particularly those with Lofgren syndrome (fever, erythema nodosum, and bilateral hilar lymphadenopathy), lupus pernio, or Heerfordt syndrome (parotid or salivary gland enlargement, anterior uveitis, and facial nerve paralysis).[24] Data have demonstrated that most patients with isolated bilateral hilar lymphadenopathy will have confirmation of sarcoidosis by biopsy analysis,[24] but after multifactorial evaluation and patient discussion many patients undergo invasive sampling to rule out cancer or an indolent infection.

EBUS-TBNA, rather than mediastinoscopy, is recommended as the first-line sampling procedure in patients with suspected sarcoidosis that requires tissue evaluation.[24] This recommendation is based on the availability of technology and ease of sampling via EBUS and a more favorable complication profile than that of mediastinoscopy. No well-designed studies directly comparing the performance of EBUS with that of mediastinoscopy for the diagnosis of sarcoidosis are available, but EBUS-guided lymph node sampling had a reported diagnostic yield of 87% compared with 98% for mediastinoscopy in a review of 29 studies for the American Thoracic Society guidelines.[24]

A more recent retrospective study compared EBUS-TBNA specimens obtained using various-sized needles in the setting of undiagnosed mediastinal lymphadenopathy and demonstrated no significant differences in diagnostic yield or sensitivity for the diagnosis of sarcoidosis and other nonmalignant conditions.[30] Researchers have also evaluated the utility of forceps and cryoprobes for EBUS-guided biopsies but observed different results. For example, Lachkar and colleagues[31] retrospectively compared EBUS-TBNA specimens alone with EBUS-TBNA specimens plus EBUS intranodal forceps biopsy specimens and found that EBUS intranodal forceps biopsies allowed for a specific diagnosis in 17% more cases than did EBUS-TBNA alone. Furthermore, EBUS intranodal forceps biopsy was most helpful in diagnosing nonmalignant etiologies such as sarcoidosis as well as lymphoma as described later. Also, researchers have shown EBUS transbronchial lymph node cryobiopsy to be superior to EBUS-TBNA for diagnosing nonmalignant diseases such as sarcoidosis (89.9% vs 53.2%; P=.004).[32] The cryobiopsy procedure may improve the overall diagnostic yield even further when added to EBUS-TBNA during the evaluation of nonmalignant disease.[33] Histologic analysis of specimens in the setting of sarcoidosis most often reveals well-formed, nonnecrotizing granulomas with macrophage aggregates and multinucleated giant cells.[34] An important point to remember is that sarcoidosis is a diagnosis of exclusion. Therefore, other granulomatous processes such

as infection must be reliably excluded, particularly in the setting of necrotizing granulomas, which may develop in patients with sarcoidosis.[34]

Mediastinal Granulomatous Inflammation

Mediastinal granulomatous inflammation, often termed sarcoid-like reaction, may also develop in the setting of cancer patients, and can cause a clinical conundrum as to whether persistent or recurrent cancer is present. The exact etiology of this inflammation is currently unknown, but it may result directly from the cancer itself or associated treatments or occur as a reaction to a foreign body after mediastinal sampling.[35,36] The chemotherapeutic agents interferon-gamma and methotrexate are most commonly associated with mediastinal granulomatous inflammation in the setting of cancer.[37] Newer targeted therapies such as immune checkpoint inhibitors, antitumor necrosis factor-alpha antibodies, and other immunomodulators are also known to induce this reaction.[24,38] As described earlier, whereas imaging may suggest a benign diagnosis in certain instances, it is currently unable to completely distinguish between a sarcoid-like reaction and lymph node metastasis. Therefore, invasive sampling via EBUS-TBNA is warranted in this patient population. If recurrent or persistent disease is identified, the use of additional therapeutic agents can be pursued, but if mediastinal granulomatous inflammation is identified, patients can be followed longitudinally with imaging. Just as with sarcoidosis, ruling out infection is imperative, particularly if symptoms or parenchymal abnormalities are present. Authors postulated that patients with cancer and mediastinal granulomatous inflammation may have improved overall prognosis, but multiple studies have not proven this theory thus far.[36,39]

Silicosis is caused by inhalation of free silica particles and can lead to mediastinal and parenchymal abnormalities. In patients with silicosis, hilar lymph nodes are often enlarged and may contain calcifications in specific patterns, namely an eggshell or punctate distribution, which can assist in diagnosis. Also, as the name suggests, berylliosis occurs after exposure to beryllium compounds and may rarely lead to isolated lymph node enlargement. Both silicosis and berylliosis may cause the formation of noncaseating granulomas that can be identified in histologic specimens, but medical history, identification of additional imaging abnormalities, and ancillary testing are usually available to help differentiate these conditions from sarcoidosis.[40,41] Additionally, inflammatory bowel disease, other inhalational exposures, vasculitis, and autoimmune diseases may lead to granulomatous lung disease and should be considered in the differential diagnoses for particular patients suspected of having silicosis or berylliosis.[40] These conditions are not discussed in detail herein, as additional imaging abnormalities are usually present rather than isolated mediastinal lymphadenopathy.

Infection

Tuberculosis, nontuberculous *Mycobacterium* infections, and fungal infections may cause isolated mediastinal lymphadenopathy and should be considered in the proper clinical setting. Tuberculosis is an airborne disease caused by *Mycobacterium tuberculosis* that may cause cough, fever, night sweats, weight loss, and lymphadenopathy. The incidence and prevalence of tuberculosis have a wide geographic variation, but overall, an estimated total of 10.6 million people worldwide were infected with tuberculosis in 2022, with most cases occurring in regions of Southeast Asia, Africa, and the Western Pacific.[42] Lymphadenopathy is a primary feature of tuberculosis,[43] and isolated lymphadenopathy may be present even in the absence of classic symptoms. Therefore, maintaining a high level of suspicion for tuberculosis in immunocompromised patients or those residing in or returning from an endemic area is important.

Histoplasmosis is an infection caused by the soil-residing fungus *Histoplasma capsulatum*, which is endemic to various parts of the United States, most commonly the Ohio River and Mississippi River valleys. Many patients with histoplasmosis or other fungal infections (eg, coccidiomycosis, blastomycosis), particularly immunocompetent individuals, may be completely asymptomatic. When symptoms are present, they can vary from a self-limiting flu-like or pneumonia-like illness to severe, disseminated disease. Mediastinal lymphadenopathy is common in cases of acute infection and may rarely cause symptoms related to compression of other mediastinal structures.[7,40,43] Other fungal infections, such as those caused by *Coccidioides* species, also may cause mediastinal lymphadenopathy, and parenchymal abnormalities, including nodules, cavities, and pleural effusions, may be present in patients with either acute or chronic disease.[43]

Chest CT in the setting of infection, such as those described earlier, may reveal peripheral enhancement of lymph nodes with central necrosis (**Fig. 6**). Lymph nodes in patients affected by tuberculosis in particular may be significantly FDG-avid on PET images, making accurate differentiation of tuberculosis from malignant lymph node

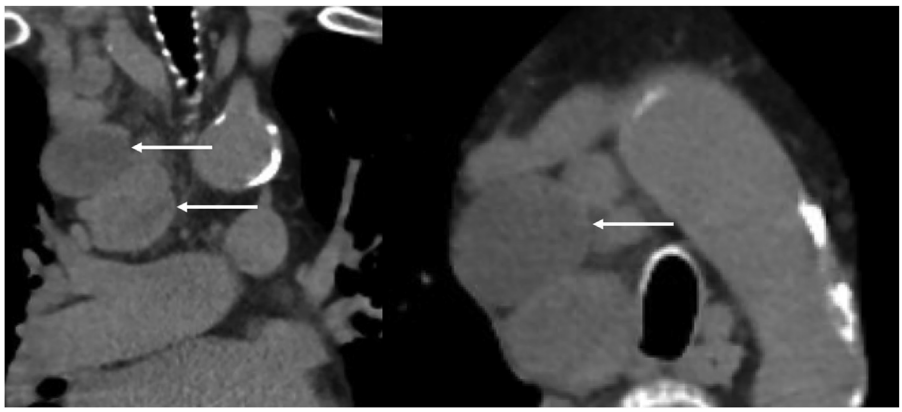

Fig. 6. Chest CT images showing significant mediastinal lymphadenopathy with extensive central necrosis (*arrows*).

involvement based on CT alone a challenge.[7,44] Lymphadenopathy that develops as a reaction to a fungal infection typically shrinks over time but rarely may cause fibrosis and calcifications, which can lead to alterations in surrounding mediastinal structures and, in its most extreme form, fibrosing mediastinitis.[7,43] Antigen and serologic testing for fungal infections and tuberculosis may provide support for a particular diagnosis, but culture and biopsy data are often necessary for a confident diagnosis and to direct appropriate treatment.[7]

Bronchoscopy is often pursued, and EBUS-TBNA of mediastinal lymph nodes in these patients typically reveals necrotizing granulomatous inflammation and, less commonly, frank purulence on aspiration or microbial organisms on smears.[7] Sending TBNA specimens for culture evaluation are often recommended to support a particular diagnosis.

Lymphoma

Patients with lymphoma typically present with nonspecific symptoms of weight loss, fatigue, and night sweats in conjunction with lymphadenopathy. Rarely, patients will present with isolated lymphadenopathy and no associated symptoms. HL, primary mediastinal B-cell lymphoma, and T-lymphoblastic lymphoma are the most common primary mediastinal lymphomas, which can present as isolated mediastinal adenopathy or masses.[45]

Primary mediastinal B-cell lymphoma arises from medullary B lymphocytes of the thymus and accounts for 2% to 3% of all non-HL cases.[46] Most cases typically present as a rapidly enlarging mediastinal mass that invades adjacent thoracic structures. These patients usually have a short clinical history and exhibit signs and symptoms related to local invasion or compression of airways and adjacent vasculature. As the disease progresses, extrathoracic organs become involved. HL presenting as isolated primary mediastinal disease is uncommon and has a distinct histology and biological behavior.[47] Precursor T-lymphoblastic lymphoma is the most common T-cell lymphoma, presenting as a mediastinal mass in young adults. Although not a malignant process, hyaline vascular Castleman disease is also presenting with lymphadenopathy, as this disorder commonly involves the mediastinum.[48]

Differentiation between malignant and benign hilar and mediastinal lymphadenopathy in lymphoma cases can be challenging. CT is the most frequently used imaging modality, and several studies demonstrated that homogeneous enhancement on contrast-enhanced multidetector CT scans is indicative of malignant lymphadenopathy in the context of lymphoma. In a study by Tang and colleagues,[49] they saw homogeneous enhancement in 83% of lymph nodes for both HL and non-HL patients but as per Tang's report only 8% in tuberculosis patients, who often exhibited peripheral enhancement. In addition, some specific CT features, such as the presence of irregular lymph node contours, are found more often in HL cases than non-HL whereas diffuse large B-cell lymphoma cases may have more regular contours.[50] CT can provide useful clues in differentiating malignant from benign lymphadenopathy in patients with lymphoma, although histopathological confirmation through biopsy analysis remains the gold standard for diagnosis. PET/CT scans are valuable tools in differentiating between malignant and benign hilar and mediastinal lymphadenopathy in the context of lymphoma. However, researchers have demonstrated that this imaging modality has a high rate of false positives, especially in cases

of sarcoid-like granulomatous inflammation.[51] This underscores the necessity of histologic verification for a definitive diagnosis of lymphoma.

Regardless of the imaging modality, a patient presenting with indeterminate lymphadenopathy suspicious for lymphoma will be referred for biopsy. For patients who present with isolated intrathoracic adenopathy that is suspicious for lymphoma or any other cancer, EBUS-TBNA is an attractive option given the risks of surgical and core needle sampling. The diagnostic utility of EBUS-TBNA in lung cancer diagnosis and staging, including biomarker analysis, is well established.[52,53]

Several studies suggested that EBUS-TBNA, along with appropriate immunohistochemical, flow cytometric, cytogenetic, and molecular studies, can definitively diagnose lymphoma. For example, Senturk and colleagues[54] reported a sensitivity rate of 86.7% and a diagnostic accuracy rate of 97% for EBUS-TBNA in diagnosing lymphoma in patients with mediastinal lymphadenopathy. Furthermore, Nason and colleagues[55] found that EBUS-TBNA had a sensitivity rate of 89% in lymphoma diagnosis when specimens were adequate for analysis. Grosu and colleagues[56] found that, in association with flow cytometry and immunohistochemical analysis, EBUS-TBNA had an overall sensitivity rate of 77%, specificity rate of 100%, and negative predictive value of 86% in the diagnosis and subtyping of de novo and recurrent lymphoma. EBUS-TBNA performed the best among patients with a final diagnosis of low-grade non-HL, with a 92% sensitivity rate. The sensitivity rate for HL was markedly lower.

Various needle sizes and/or aspiration techniques have been studied for obtaining larger specimens of lymph node tissue and improving the diagnostic yield of EBUS-TBNA, but these variables seem to have little effect.[16] On the contrary, cryobiopsy of a lymph node is a promising technique improving the diagnostic yield of lymphoma, although the data supporting this remain limited.[57,58] In addition, in a recent systematic review and meta-analysis investigating the diagnostic yield and complications of combined EBUS-guided intranodal forceps biopsy and EBUS-TBNA compared with EBUS-TBNA alone, the authors evaluated 6 observational studies with 443 patients undergoing 467 biopsies and concluded that the addition of the EBUS-guided biopsy procedure to EBUS-TBNA improved the overall diagnostic yield for lymphoma.[59] The complication rates for the combined approach were higher than those for EBUS-TBNA alone, but they were lower than those for transbronchial and surgical biopsies.[59]

If small EBUS biopsy specimens do not render a specific diagnosis, the gold standard for diagnosing lymphoma is surgical excision of a lymph node given that it provides a large, intact tissue specimen, which is often crucial for accurate subtyping of lymphoma. Specifically, for diagnosis of HL, the National Comprehensive Cancer Network guidelines recommend excisional biopsy but note that a core needle biopsy may be adequate in certain circumstances.[60] Similarly, the American Society for Clinical Pathology and the College of American Pathologists support excisional biopsy as the standard of care for lymphoma diagnosis but note that core biopsies can be used when excisional biopsy is not possible.[61]

Incorporating Likelihood Ratios in the Evaluation Algorithm for Isolated Mediastinal Lymphadenopathy

In each section in this article, we discuss the diagnostic accuracy of specific imaging and sampling techniques for individual diagnoses. One important concept when evaluating the literature for the diagnostic adequacy of a test is to fully understand the definitions. For example, diagnostic accuracy can be defined as how well a test discriminates between 2 conditions, and a reference standard is used to identify which of the 2 conditions is truly present.[62] When only 2 potential results are possible, sensitivity and specificity can be used to measure the discriminatory power of a diagnostic test.[62] An important point to understand is that sensitivity and specificity cannot be used when more than 2 distinct results are possible.

One example of a test that can have 3 or more possible results is EBUS-TBNA cytology in patients with isolated lymphadenopathy. One approach to resolving this problem is the use of likelihood ratios (LRs). These ratios provide insight into categories of results that include more than 2 possibilities (ie, results other than just the presence or absence of malignancy). Knowing the pretest probability of disease and the LR for a specific test allows for the use of Bayes' theorem to calculate the posttest probability of disease.[62] A high LR indicates increased odds of disease, a low LR indicates decreased odds of disease, and an LR of 1 indicates that a test result is noninformative.

Using lymphoma for illustrative purposes, when performing EBUS-TBNA for isolated mediastinal lymphadenopathy diagnosis in a patient with suspected lymphoma, the cytology may demonstrate one of the following results: lymphoma, granuloma, a disease other than cancer, or even a nondiagnostic result with either adequate or inadequate lymphocytes.[63] Using the LR highlights this

possibility and captures the differences among these groups of results. In patients with suspected lymphoma, the probability of actually having lymphoma decreases to a much greater degree if granulomas or a specific alternative diagnosis is found than if lymphocytes are found. A finding of inadequate lymphocytes is clearly very different from a finding of granulomas or lymphoma, as the former does not constitute a specific diagnosis other than lymphoma that may account for lymphadenopathy.[56] The clinical implications of test results depend not only on the LR but also on the pretest probability of disease.[56] When 3 or more categorical test results are possible, each with distinct clinical interpretations, as is often the case with interventional pulmonology studies, the use of LRs should be considered.

SUMMARY

Isolated mediastinal lymphadenopathy is a relatively uncommon finding on imaging but may present a diagnostic challenge given a lack of comprehensive guidelines on this topic. Details on chest CT or FDG-PET scans or images obtained using investigational modalities may provide information to support a benign versus malignant diagnosis, but a biopsy is often necessary for a specific diagnosis. Specifically, a biopsy is required in patients with a history of extrathoracic cancer, patients who have suspicious radiographic features such as PET-positive lymph nodes, and symptomatic patients with clinical signs of malignancy.[6] EBUS-TBNA is recommended as the first-line biopsy tool for isolated lymphadenopathy owing to its high diagnostic sensitivity rate of 89%.[5,64] A detailed patient history, serologic testing, and culture results may support a particular nonmalignant diagnosis when used in conjunction with EBUS-TBNA results to direct further treatment. The practice variability in the evaluation and management of mediastinal lymphadenopathy is wide,[65] and hopefully, robust clinical guidelines will be developed in the future to better direct care for this specific patient population.

CLINICS CARE POINTS

- The potential etiologies of isolated mediastinal lymphadenopathy vary widely and primarily include reactive lymph nodes, infection, inflammatory conditions, and cancer.
- Lymph node characteristics on computed tomography, ultrasound, and PET with fluorodeoxyglucose images may help differentiate benign and malignant lymph nodes.
- Biopsy is often required in the evaluation of isolated mediastinal lymphadenopathy, and endobronchial ultrasound-transbronchial needle aspiration is the preferred biopsy method.
- Sarcoidosis is a multisystem disease characterized by noncaseating granulomatous inflammation that is commonly associated with isolated mediastinal and/or hilar lymphadenopathy.
- Prior to making a diagnosis of sarcoidosis, an important step is to rule out other potential etiologies of granulomatous inflammation, namely, mycobacterial and fungal infections, medication effects, and cancer.
- Lymphoma should be considered in the setting of isolated mediastinal lymphadenopathy, and many patients will present with symptoms to assist in making this diagnosis.
- The use of likelihood ratios should be integrated into clinical practice in cases with 3 or more potential categorical test results with distinct clinical interpretations.

DISCLOSURE

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