Spectrum of CT Findings in Thoracic Extranodal Non-Hodgkin Lymphoma

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Abbreviations: DLBCL = diffuse large B-cell lymphoma, EBV = Epstein-Barr virus, ECG = electrocardiography, EMZL = extranodal marginal zone lymphoma, FDG = fluorodeoxyglucose, HIV = human immunodeficiency virus, NHL = non-Hodgkin lymphoma, PAL = pyothorax-associated lymphoma, PEL = primary effusion lymphoma, PPL = primary pulmonary lymphoma, PTLD = posttransplant lymphoproliferative disorder, SPL = secondary pulmonary lymphoma

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SA-CME LEARNING OBJECTIVES
After completing this journal-based SA-CME activity, participants will be able to:
- Discuss the impact of diagnosing extranodal involvement on staging and management in different clinical scenarios for patients with known or suspected NHL.
- List the various manifestations of pulmonary NHL and describe clinical and patient characteristics that should increase suspicion for this diagnosis when a compatible lung abnormality is encountered at CT.
- Recognize the common manifestations and distinguishing imaging features of NHL involving other extranodal structures in the chest and confidently direct further workup for suspicious findings where appropriate.

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Non-Hodgkin lymphoma (NHL) frequently manifests in extranodal structures in the chest, often in the form of secondary involvement but occasionally as primary disease. Because staging and treatment are affected by the presence of extranodal disease at imaging, radiologists’ interpretation and management of suspicious findings are critical to patient care. Unfortunately, owing to considerable imaging overlap with other diseases, primary extranodal lymphoma is difficult to diagnose with imaging alone. Radiologists should have a heightened degree of suspicion in patients at risk (including patients with immune compromise, autoimmune diseases, or a history of stem cell or solid organ transplant) or with particular imaging appearances (including the vertebral wraparound sign, nonresolving consolidation, an infiltrative soft-tissue mass, and lesions demonstrating vascular encasement without invasion). For patients with known NHL, positron emission tomography/computed tomography (PET/CT) using fluorine 18 ($^{18}$F)–labeled fluorodeoxyglucose (FDG) is now preferred for routine staging in most cases. CT remains heavily used, and identification of subtle extranodal involvement with CT can be improved with use of intravenous contrast material and careful review of multiplanar images. Pericardial effusion, pleural soft tissue (even when mild), mass-like consolidation, pleural effusion, and new lytic bone lesions are particularly suggestive of secondary involvement in a patient with known NHL. Magnetic resonance imaging is a helpful problem-solving tool when equivocal findings would change staging and treatment. This comprehensive review illustrates the spectrum of CT manifestations of extranodal NHL in the chest, including the pleura, lung, airways, heart, pericardium, esophagus, chest wall, and breast.

Introduction

While radiologists are familiar with lymphoma manifesting as nodal disease, extranodal lymphoma can present a diagnostic challenge due to considerable imaging overlap with other malignant and benign processes. This can lead to diagnostic delays and errors, particularly when the extranodal disease represents primary lymphoma rather than secondary involvement.

The definition of primary extranodal lymphoma is controversial (1). Strict criteria include lymphomas confined to an extranodal site and its contiguous lymph node group (2,3). However, because extranodal lymphomas often spread more widely, most authors apply more liberal criteria and include cases with regional or even distant nodal involvement when the extranodal disease is thought to be dominant (2,3). Generally, secondary involvement is far more common than primary lymphoma in a given tissue (2,4).

Non-Hodgkin lymphomas (NHLs) account for 90% of all lymphomas, while Hodgkin disease comprises the remaining 10%
(2,4,5). Almost all primary extranodal lymphomas are NHL (2,3). Depending on the diagnostic criteria applied, a surprising 25%–40% of all NHLs are primarily extranodal (1,3). Diffuse large B-cell lymphoma (DLBCL) is the most common NHL subtype, representing 25%–30% of all lymphomas (6). DLBCL tends to be aggressive and often involves extranodal sites (2,4). Extranodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) is another subtype that commonly affects the lung (2,3).

Although lymphoma fits into the differential diagnosis of many thoracic imaging findings, it is a particularly important consideration in certain populations. Individuals with autoimmune diseases or severe immune compromise are generally at greater risk for lymphoma. Radiologists should have a heightened suspicion for lymphoma when evaluating unexplained thoracic abnormalities in these patients. Because secondary pulmonary involvement is common, a high index of suspicion is required in any patient with a new lung abnormality and known NHL.

Differentiating primary NHL from other cardiac neoplasia can be difficult, but the propensity of lymphoma to infiltrate along the epicardial surfaces and particularly its tendency to encase vessels without invasion should raise greater suspicion for this diagnosis.

Spinal involvement in lymphoma may appear as a draping paraspinal soft-tissue mass associated with extensive involvement of a vertebral body but with limited cortical bone destruction or height loss.

Even in the setting of suspected or known disseminated NHL, the high population prevalence of breast carcinoma must be taken into account when a suspicious breast lesion is encountered. Biopsy should still be performed when diagnosis and treatment of a potential breast cancer could affect life expectancy or when staging and management of the lymphoma would be affected by identification of breast involvement.

NHL and Hodgkin disease are both staged according to the Ann Arbor system with Cotswald modifications (Table 1) (6,8,11). Radiology plays an important role in management of NHL because staging and treatment are primarily determined by the anatomic distribution of disease as demonstrated at imaging (14).

Computed tomography (CT) is the cross-sectional imaging modality of choice for initial detection in most patients with thoracic NHL and is the focus of this review. Positron emission tomography (PET)/CT using fluorine 18 (18F)–labeled fluorodeoxyglucose (FDG) has proven to be an indispensable problem-solving tool and is now preferred for routine staging and follow-up in most NHL subtypes, particularly those known to exhibit strong 18F-FDG avidity (7,8,13,15). Overall, PET/CT changes staging in up to 30% of cases (15). Ultrasonography (US) and magnetic resonance (MR) imaging are excellent modalities for targeted problem solving and can complement CT and PET in select cases (3).

**Pleura**

**Primary**

Primary pleural lymphoma is rare, and almost all cases are represented by one of two distinct NHL subtypes: primary effusion lymphoma (PEL) or pyothorax-associated lymphoma (PAL) (2,16).

Although lymphoma is commonly included in the differential diagnosis of a pleural mass, isolated solid pleural lesions are generally unlikely to represent lymphoma unless there is evidence of the disease elsewhere or if there is a history of chronic pyothorax (2).

**Primary Effusion Lymphoma.**—PEL or body cavity lymphoma is a rare human herpesvirus 8–positive DLBCL (16–18). Most patients have advanced AIDS and often Kaposi sarcoma (18,19). PEL can occur in the pleural, pericardial, or peritoneal spaces (2,17). The clinical course is aggressive with a poor prognosis (16,17).

PEL manifests as an isolated effusion with no clinical or imaging evidence of solid disease. The effusion is typically unilateral and homogeneous with near-water attenuation. It does not have distinguishing features at CT. Radiologists should consider PEL when an effusion is identified in severely immunocompromised patients, particularly those with AIDS (16,18).

**Pyothorax-associated Lymphoma.**—PAL is a rare Epstein-Barr virus (EBV)–positive DLBCL that occurs exclusively in patients with chronic inflammatory pyothorax, usually secondary to
Table 1: Modified Ann Arbor Staging System for NHL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
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<tbody>
<tr>
<td>I</td>
<td>Involvement of single lymph node region or lymphatic organ (eg, spleen, thymus, Waldeyer ring)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions on same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions/structures on both sides of diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Involvement of extranodal site(s) beyond that designated E</td>
</tr>
<tr>
<td>E (for stages I–III)</td>
<td>Involvement of single extranodal site contiguous or proximal to known nodal site</td>
</tr>
<tr>
<td>A/B</td>
<td>Absence (A) or presence (B) of fever, drenching sweats, or loss of &gt;10% of body weight within past 6 months</td>
</tr>
</tbody>
</table>

Sources.—References 11 and 13.

Figure 1. Benign transudative effusion in a 78-year-old woman with DLBCL and increasing dyspnea. Axial CT scan (soft-tissue window) shows a large left pleural effusion. There are associated enlarged mediastinal nodes (*), the effusion has homogeneous low attenuation, and there is no pleural nodularity or thickening. A benign cause of effusion such as venous or lymphatic compression should be considered if all these characteristics are present. Pleural fluid cytology was negative for malignant cells, and the effusion resolved completely as the adenopathy responded to systemic therapy. The constellation of imaging and clinical characteristics points to a benign hydrostatic cause, and pleural biopsy was not pursued. Note the enlarged left internal mammary node (arrow).

iatrogenic pneumothorax for treatment of tuberculosis (2,16,19). Historically, most patients have been Japanese males (2). The prognosis is poor (17).

PAL manifests as a solid pleural mass that may extend directly into the lung and can be associated with pleural effusion (2). It may be difficult to determine the site of origin at CT, but a history or imaging findings of chronic pyothorax should prompt consideration of the diagnosis in the setting of a pleural mass.

Secondary

The vast majority of pleural NHL is secondary and is usually seen in concert with other thoracic involvement (5) and in aggressive subtypes (18,20). It may arise through hematogenous or lymphatic dissemination or by direct extension from pulmonary or nodal disease. The clinical presentation is nonspecific and may reflect pleural irritation (chest pain or cough) or compression of adjacent lung (dyspnea) (20).

Effusion is the most common manifestation of pleural NHL and occurs at some point in up to 20% of patients with NHL (16). In fact, approximately 10% of all cytology-positive malignant effusions are due to NHL (16,18). Fluid is usually serous or serosanguineous.

Direct involvement of the pleural space with dissemination of malignant cells is the most common cause of effusion in NHL (18,21). Alternatively, extrinsic lymphatic or venous compression by enlarged mediastinal or hilar nodes may cause a benign transudative effusion (Fig 1), but this is less likely in NHL than in Hodgkin disease (18,21).

Both compression and invasion of the thoracic duct may cause chylothorax (5,21,22). Malignancy is the most common cause of nontraumatic chylothorax, and lymphoma accounts for 70%–75% of cases (22). While fat-attenuation pleural fluid at CT is specific for chylothorax, most chylothorax has near-water attenuation and cannot be distinguished from serous fluid with CT. Malignant cells are frequently identified in chylous samples in patients with NHL (18).

Solid pleural disease is less common than effusion alone but occurs with some frequency in disseminated NHL and can even manifest without associated pleural effusion (5,20) (Figs 2, 3). It manifests at CT as soft-tissue–attenuation nodules (Fig 2a), masses (Fig 3), or broad thickening of the pleural membranes (Fig 2b) (7,12,21). Solid pleural lesions are frequently overlooked at CT, whether due to small size (Figs 2a, 3) or poor detectability in the context of pleural effusion (5).
Figures 2, 3. (2) Secondary pleural involvement in a 57-year-old man with small lymphocytic lymphoma. (a) Axial CT scan (soft-tissue window) when the patient was asymptomatic shows subtle left-sided soft-tissue–attenuation nodular pleural thickening (arrows). Pleural involvement should be strongly suspected with this appearance in the setting of known lymphoma elsewhere, regardless of effusion. Recognizing the importance of this subtle finding allows the radiologist to identify higher-stage disease. (b) Axial CT scan 2 months later when the patient developed chest pain shows marked disease progression with diffuse pleural thickening (arrow), a new effusion, and mediastinal adenopathy (*). (3) Secondary DLBCL in a 74-year-old woman with a persistent small pleural effusion (not shown). (a) Axial CT scan (soft-tissue window) shows subtle plaque-like thickening of the anterolateral right pleura (large arrow). Apparent cortical irregularity of the overlying rib was confirmed to be artifactual, related to volume averaging. Small internal mammary nodes are visible (arrowheads), which may be abnormal despite their small size. A small right axillary node is not abnormal at CT (small arrow). (b) Axial 18F-FDG PET/CT scan shows intense radiopharmaceutical uptake in the pleural lesion despite its small size (large arrow), making it highly suspicious for malignancy. Intense uptake is also seen in the internal mammary (arrowheads) and right axillary (small arrow) nodes, consistent with malignant involvement despite their inconspicuous appearance at CT. Similar uptake in several small right paratracheal nodes (not captured on the section in a due to differences in respiratory phase) indicates their involvement. Results of pleurocentesis were negative, but the diagnosis of DLBCL was established with thoracoscopic biopsy.

Differential Considerations and Diagnostic Strategies

 Imaging features of pleural lymphoma largely overlap with those of other malignant and benign pleural diseases (Tables 2, 3). Among malignant effusions, lymphoma is second only to metastatic adenocarcinoma (usually from the lung, breast, and ovary) in frequency. Lymphoma should be considered in the differential diagnosis of a pleural effusion without an identified benign cause, particularly if there are findings suggestive of lymphoma elsewhere or risk factors such as severe immune compromise (18).

 In patients with known extrapleural NHL, a simple-appearing effusion at CT associated with bulky mediastinal adenopathy (Fig 1) should prompt consideration of a benign hydrostatic cause, but fluid sampling is still warranted if diagnosis of malignant pleural involvement would affect management (21). In patients with lymphoma, other potentially relevant benign causes of pleural effusion include autoimmune diseases, opportunistic pneumonia, and radiation therapy (16,18). In patients with chronic pyothorax, the appearance of a new or enlarging region of mass-like thickening should raise suspicion for PAL.

Because the lung enhances earlier than the pleura, routine CT protocols for evaluation of the lung may not opacify the pleura optimally. The conspicuity of solid pleural disease associated with effusion can be improved by increasing the postcontrast delay to 45 seconds in problem-solving scenarios (23). If concurrent portal venous phase CT of the abdomen is available, pleural masses in the inferior thorax may be better defined. Subtle early pleural nodularity without effusion is also easily missed at CT (Fig 2). Coronal reconstructions are helpful to detect lesions along the diaphragmatic pleura. Pleural lesions in lymphoma do not possess CT features that allow reliable distinction from
other causes of malignancy, but a history of NHL is highly suggestive of the diagnosis (24).

\(^{18}\)F-FDG PET/CT readily allows differentiation of solid pleural disease from effusion in \(^{18}\)F-FDG–avid lymphomas, and solid lesions should be strongly suspected with a focal abnormality at PET, even if there is no mass distinguishable from pleural fluid at CT. PET can also increase diagnostic certainty when equivocal findings are demonstrated in a patient with known NHL (Fig 3). False positives occur rarely in the setting of prior talc pleurodesis or benign inflammatory disease.

Thoracentesis with pleural fluid cytology is the first-line diagnostic tool but unreliable for excluding involvement. Thoracoscopic biopsy may be indicated if less invasive sampling is not definitive.

### Lung

**Clinical Features and CT Findings**

**Primary.**—Primary pulmonary lymphoma (PPL) represents only 0.5% of primary lung neoplasms (25) and 3%–4% of primary extranodal NHL (17). It is more common in immunocompromised patients (26,27).

EMZL of mucosa-associated lymphoid tissue (MALT) arises from the native pulmonary lymphoid tissue aggregates and represents the majority of PPL (3,17,26–28). Patients with pulmonary EMZL occasionally present with cough, fever, or weight loss but are most often asymptomatic, with the disease detected incidentally at imaging (3,17,25). While the prognosis is favorable...
(84%–94% 5-year survival) (17,25), relapse is common and a small proportion of cases eventually transform into more aggressive DLBCL (2,17). Up to 29% of cases of pulmonary EMZL are associated with autoimmune disorders including Sjögren syndrome, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and Hashimoto thyroiditis (2,27). It is also more common in smokers (2). Imaging manifestations are variable and include single or multiple ill-defined nodules, consolidation, ground-glass opacity, or interstitial thickening (Fig 4) (3,5,25). In consolidative forms, bronchial dilatation is a common feature, although the mechanism is poorly understood (25). Notably, pleural effusion is usually absent (17,25,27).

DLBCL is the second most common type of PPL and, unlike EMZL, is usually symptomatic with cough, dyspnea, fever, or weight loss. DLBCL is also usually more extensive at diagnosis and has a poorer prognosis (27). Patients with human immunodeficiency virus (HIV) infection are at increased risk of aggressive EBV-positive DLBCL (17). DLBCL manifests variably at imaging but more commonly manifests as single or multiple nodules, consolidation, ground-glass opacity, or interstitial thickening (Fig 4) (3,5,25). In consolidative forms, bronchial dilatation is a common feature, although the mechanism is poorly understood (25). Notably, pleural effusion is usually absent (17,25,27).

PTLD may occur in patients with solid organ or stem cell transplants (9,10). Following lung transplant, its incidence is 2.5%–8% (17). PTLD constitutes a wide spectrum of disease from benign proliferations to aggressive NHL (17). Imaging manifestations of monoclonal forms of PTLD within the NHL spectrum are similar to those of DLBCL, including solid nodules or masses, consolidation, ground-glass opacity, and interstitial disease (5,10). Solid masses in PTLD tend not to cavitate (5).

Secondary.—In contrast to PPL, secondary pulmonary lymphoma (SPL) is quite common. Although its occurrence rate is higher in Hodgkin disease (38%) than in NHL (24%), NHL is a far more common disease and thus represents 80%–90% of all SPL cases (2,17,25). Only half of patients with SPL have evidence of other thoracic involvement at presentation (25). SPL may arise through direct extension of nodal or other thoracic disease or by hematogenous or lymphatic dissemination (8,17,28). Because secondary pulmonary involvement is common, a high index of suspicion is required in any patient with a new lung abnormality and known NHL (5,17). The clinical behavior of SPL depends strongly on the primary subtype, with more aggressive forms being more extensive at presentation and rapidly progressive. Conversely, low-grade SPL may not show any significant progression over periods of months (26).

Imaging manifestations of SPL are similar to those of PPL. Nodules, masses (Fig 7), and mass-like consolidation are common and may cavitate, particularly in aggressive NHL (30). Consolida-
Figure 5. Primary pulmonary DLBCL in a 26-year-old woman who presented to the emergency department with chest pain. Chest radiographs (not shown) demonstrated consolidation in the right lung, and the patient was treated for pneumonia. (a) Axial CT scan (soft-tissue window) after 1 month of antibiotic treatment with no symptomatic improvement shows lobar consolidation with central cavitation. Indistinctness of the mediastinal pleural margin (arrow) suggests possible mediastinal invasion, but this could be explained by inflammatory stranding. Extension to the internal mammary vessels (arrowhead) is also unusual for pneumonia. (b) Axial CT scan (soft-tissue window) after 2 months of further treatment of presumed necrotizing pneumonia shows progressive lung consolidation and cavitation. There is now irregular pleural thickening (arrow) and loculated effusion, highly suspicious for direct involvement. There is also evidence of contiguous spread to the chest wall, indicated by a bulky soft-tissue mass involving the serratus anterior muscle (arrowhead).

Figure 6. Primary pulmonary lymphoplasmacytic lymphoma in a 57-year-old woman with fever, cough, and dyspnea. Axial CT scan (soft-tissue window) shows extensive consolidation in the right lung with air bronchograms and preserved vascular markings (CT angiogram sign). While this is a typical appearance of consolidative lymphoma, bacterial pneumonia would be a much more common consideration. A small pleural effusion (arrow) and mediastinal adenopathy (arrowhead) are concerning but can be seen in both pneumonia and primary or secondary lymphoma. The patient had initially presented with consolidation 5 months earlier, which continued to progress despite multiple courses of antibiotics. This lack of improvement raised concern for lymphoma. The diagnosis was established with CT-guided core biopsy.

Differential Considerations and Diagnostic Strategies

Primary.—PPL should be considered in the differential diagnosis of nonresolving airspace consolidation or ground-glass opacity. Unexpected persistence or progression of consolidation despite appropriate antibiotic therapy in patients thought to have pneumonia should increase suspicion for PPL. The differential diagnosis also includes lepidic-predominant lung adenocarcinoma, organizing pneumonia, and lipoid pneumonia (Tables 4, 5). While postobstructive consolidation secondary to bronchogenic carcinoma can manifest as nonresolving consolidation, this is typically associated with bronchial obstruction and impaction rather than the air bronchograms frequently seen in PPL (Figs 4, 6) (28).

Visualization of enhancing vessels within consolidated lung parenchyma (the CT angiogram sign) is a feature of pulmonary lymphoma (Fig 6) but is nonspecific and also common in mucinous adenocarcinoma and postobstructive consolidation (31). Although pneumonia may produce mediastinal or hilar nodal enlargement, internal mammary nodal enlargement is rare in benign causes of chronic consolidation and is usually
Figure 7. Secondary pulmonary involvement in a 40-year-old woman with a history of follicular lymphoma and new fatigue and night sweats. Axial CT scan (soft-tissue window) shows a circumscribed homogeneous soft-tissue mass in the left lower lobe containing an air bronchogram and traversing pulmonary arteries (arrows). These features favor lymphoma, although they are not pathognomonic. CT-guided biopsy showed DLBCL (transformed lymphoma). Note the similar smaller nodule in the right middle lobe (arrowhead), also consistent with lymphoma in this setting.

Figure 8. Secondary pulmonary involvement in a 70-year-old woman with small lymphocytic lymphoma and gradual onset of cough and dyspnea. (a) Axial CT scan (lung window, 5-mm section thickness) shows bilateral perilymphatic nodularity, most prominent in the right upper lobe (large arrows). There is more subtle involvement of the left upper lobe (small arrows). Small intraluminal nodules are also demonstrated in the left main and upper lobe bronchi (arrowheads). (b) Axial high-resolution CT scan (lung window, 1.25-mm section thickness) 2 years later shows marked progression of perilymphatic and central peribronchovascular nodules. Central endobronchial nodularity has also progressed (arrows). Although the patient was known to have NHL, a surgical wedge biopsy was performed to confirm SPL and exclude sarcoidosis, which could appear identical at CT.

Figure 9. Secondary pulmonary involvement in an 87-year-old man with a history of cutaneous T-cell lymphoma and new fatigue, cough, and dyspnea. Axial CT scan (lung window) shows marked nodular peribronchovascular thickening and consolidation in some areas demonstrating surrounding ground-glass opacity. Clusters of nodules in both lungs (arrows) closely parallel the bronchovascular structures. These findings are consistent with pulmonary involvement in a patient with known NHL.

Secondary to either breast cancer or lymphoma (4,14,32,33). The presence of internal mammary nodal enlargement associated with nonresolving consolidation is highly suggestive of lymphoma. The utility of 18F-FDG PET/CT is limited in the setting of nonresolving consolidation, as both benign and malignant causes may exhibit similar 18F-FDG activity.

PPL in the form of solitary or multiple solid lesions may be indistinguishable from bronchogenic carcinoma, metastases, or sarcoidosis at imaging. However, it should be high in the differential diagnosis when there are compatible
imaging findings in a patient with immune compromise or other risk factors. PPL manifesting as interstitial thickening at CT may appear smooth or nodular. It can be identical to lymphangitic carcinomatosis or pulmonary sarcoidosis at CT and should be included in the differential diagnosis (25,28). 

\[^{18}F\text{-FDG PET/CT does not allow conclusive differentiation between these various causes of interstitial thickening. PTLD should be considered for any unexplained pulmonary finding in a patient with a history of transplant (10). Presumed transient abnormalities should be followed up to ensure resolution.}

Biopsy is ultimately required for diagnosis in essentially all cases of PPL. For solid lesions, percutaneous CT-guided or bronchoscopic biopsy may be sufficient. For consolidation, ground-glass opacity, and interstitial disease, thoracoscopic or open surgical biopsy may be required to yield adequate tissue for complete diagnosis (2).

**Secondary.**—Secondary pulmonary involvement should be considered in the setting of a new lung abnormality in a patient with known NHL (5,17).

The radiologist should first evaluate for alternate benign causes including postobstructive opacity (look for bulky obstructive mediastinal or hilar adenopathy), pulmonary infection (consider the degree of immune compromise and the nature and acuity of symptoms), and treatment-related pneumonitis (consider the history of chemotherapy or radiation therapy) (5,7,12). Direct pulmonary extension of nodal NHL should also be differentiated from noncontiguous involvement where possible, as the latter typically has greater implications for staging and management (5).

If there is persistent clinical and radiographic uncertainty, short-term CT follow-up can be performed. If this shows persistence of consolidation, ground-glass opacity, or interstitial thickening, the concern for lymphoma is increased. Even in the setting of known extrapulmonary NHL, biopsy may be required for confirmation of lung involvement. \[^{18}F\text{-FDG PET may be helpful if there is a marked difference in metabolic activity between nodal and pulmonary disease, which suggests differing causes, although this may not be entirely reliable.}

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**Table 4: Differential Diagnosis for CT Findings of Pulmonary NHL**

<table>
<thead>
<tr>
<th>NHL Manifestation</th>
<th>Alternative Explanation</th>
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<tbody>
<tr>
<td>Nodules or masses</td>
<td>Bronchogenic cancer</td>
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<td>Metastases</td>
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<td></td>
<td>Fungal or mycobacterial infection</td>
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<td>Nonresolving ground-glass opacity</td>
<td>Numerous causes of inflammation or infection</td>
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<td>Interstitial pneumonias</td>
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<td>Mucinous adenocarcinoma</td>
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<td>Interstitial pulmonary edema</td>
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<td>Sarcoïdosis</td>
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<td>Lymphangitic carcinomatosis</td>
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**Table 5: Distinguishing Imaging Features and Problem-solving Strategies for CT Findings of Pulmonary NHL**

- Maintain high suspicion in patients with risk factors for NHL, particularly those failing to respond to treatment of presumed pneumonia
- For masses and consolidation: homogeneous attenuation, air bronchograms, and preserved vascular markings are typical of NHL but not specific
- Routinely consider NHL in the differential diagnosis of perilymphatic nodularity
- Pulmonary abnormalities associated with abnormal internal mammary nodes suggest lymphoma in the absence of breast cancer
- Consider short-interval CT follow-up if infection or inflammation is suspected
- \[^{18}F\text{-FDG PET does not allow conclusive differentiation of SPL from benign processes, but demonstration of similar activity in lung to that at known sites of NHL increases suspicion}

Biopsy is ultimately required for essentially all cases of PPL.
Figure 10. Secondary tracheal involvement in a 64-year-old woman with disseminated DLBCL who presented with progressive dyspnea. (a) Axial CT scan (lung window) at the level of the trachea shows a lobulated endotracheal mass causing greater than 50% luminal narrowing (arrow). (b) Axial CT scan (lung window) at the level of the left main bronchus shows diffuse nodular bronchial thickening (arrows). Note the complete consolidation of the right lung without air bronchograms (*), due to right main bronchial obstruction by lymphomatous involvement. There is also significant narrowing of the right main pulmonary artery (arrowhead) due to hilar and subcarinal lymph node enlargement.

Enlarging solid nodules and masses usually cause less confusion as they less often represent benign processes (Fig 7). While no specific CT features exist, a reasonably confident diagnosis can sometimes be made without biopsy, particularly in the setting of disseminated NHL. Demonstration of similar metabolic activity as at other sites of NHL at 18F-FDG PET is also supportive.

Airways

Clinical Features
Primary tracheobronchial lymphoma is considered a form of PPL (17,28) and is rare, representing less than 1% of primary extranodal NHL. Similar to other PPL, secondary involvement is more frequent (34–36). Most cases are EMZL of mucosa-associated lymphoid tissue (MALT) (2,34). The clinical presentation is often related to airway obstruction and may include cough, wheeze, and stridor depending on the degree of luminal narrowing. In contrast to tracheal carcinoma, hemoptysis is uncommon (34,36).

CT Findings
Both primary and secondary tracheobronchial disease most commonly manifest as a soft-tissue nodular or polypoid mass (Fig 10a). Diffuse polypoid or broad-based lesions are seen in a minority of cases (Figs 8, 10b) (2,37,38). Post-obstructive atelectasis or consolidation may be present where there is significant airway narrowing (Fig 10b).

Differential Considerations and Diagnostic Strategies
More common airway lesions, particularly primary epithelial tumors, may be indistinguishable from primary NHL at imaging (Tables 6, 7) (34,39). As with other unusual sites of primary malignancy, a history of disseminated NHL is highly suggestive of lymphomatous involvement in the presence of tracheobronchial nodularity or thickening.

Airway masses and thickening can usually be identified at CT with careful review. Thin reconstructions in the plane closest to the orthogonal of the bronchus provide optimal assessment, as small lesions may otherwise be obscured by volume averaging. This also allows accurate measurement of the residual lumen. Differentiation from mucus is not always possible, although solid-appearing soft-tissue foci are more suspicious.

18F-FDG PET/CT may help distinguish benign from malignant airway lesions in some NHL subtypes, but sensitivity depends on both the size and 18F-FDG avidity of the lesion. Because the tracheobronchial tree is more frequently affected by low-grade NHL and lesions tend to be small at presentation, the sensitivity of PET may be limited. Regardless, when a suspicious lesion is demonstrated at CT, bronchoscopy with biopsy is typically indicated for further assessment.

Heart and Pericardium

Clinical Features
Clinical involvement of the heart and pericardium is relatively uncommon and occurs mainly in the setting of disseminated disease. Patients
with PTLD and EBV-associated lymphomas are at higher risk than others (40). For both primary and secondary disease, DLBCL is the most common subtype (2,40).

Primary cardiac lymphoma represents only 1%–2% of primary cardiac tumors and comprises only 0.5% of cases of primary extranodal lymphoma (2,40). Immunocompromised individuals, particularly those with HIV infection or organ transplant, account for approximately 50% of cases (2).

Although cardiac involvement is relatively common (present in up to 20% of patients with disseminated NHL), it is frequently subclinical and unrecognized (41). Lymphoma may spread to the heart and pericardium via direct extension from mediastinal disease, infiltration of lymphatics along coronary arteries and the epicardium, or hematogenous seeding (40,42). Involvement of the heart and pericardium often occurs together but may occur in either structure in isolation. Cardiac and pericardial involvement are typically late manifestations of NHL (median onset, 20 months after initial diagnosis) and may not manifest clinically until the involvement is advanced (42,43).

The clinical presentation is usually nonspecific and includes chest pain, dyspnea, and congestive heart failure. Cardiac arrhythmias and conduction blocks are also relatively common, with tamponade, valvular disease, outflow obstruction, and myocardial ischemia also described in the literature (41,42). Sudden cardiac death is occasionally the presenting manifestation (40,42).

Both primary and secondary cardiac lymphoma have historically been associated with poor prognosis, likely due in part to late clinical manifestation (2,40,41). More recent cases have shown better outcomes due to improvements in diagnosis and treatment (2). Identification of advanced cardiac or pericardial lymphoma may be considered an oncologic emergency due to its propensity for rapid progression and cardiac morbidity (40).

**Imaging Findings**

Imaging findings are similar in primary and secondary cardiac NHL. CT typically shows a bulky, poorly defined, infiltrative epicardial or myocardial mass, isoattenuating or slightly hypoattenuating to myocardium (Figs 11, 12). Solid masses are often associated with a pericardial effusion (Fig 11c) (2,40,41). At MR imaging, T1 hypointensity and T2 isointensity or hyperintensity are typical, although there is variation (Fig 11b, 11c) (40). Contrast enhancement may be homogeneous or heterogeneous with either modality.

The right atrium is the most frequently involved chamber, although approximately 75% of cases involve more than one chamber (41). Soft-tissue infiltration along the epicardial surfaces and the atrioventricular groove with encasement of coronary arteries and the aortic root are common features that should raise suspicion for cardiac NHL (Figs 11, 12) (40). Masses may also extend outside the heart to the superior or inferior vena cava, leading to obstruction or thrombosis (40).

Isolated pericardial involvement may manifest as pericardial thickening or nodules, pericardial effusion, or both (Fig 13). Large effusions may cause tamponade, while extensive pericardial involvement may be constrictive (44). PEL may manifest as an isolated effusion, although this

<table>
<thead>
<tr>
<th>NHL Manifestation</th>
<th>Alternative Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal airway mass</td>
<td>Primary carcinoma</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine tumor</td>
</tr>
<tr>
<td></td>
<td>Benign neoplasm (hamartoma, leiomyoma, papilloma)</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
</tr>
<tr>
<td></td>
<td>Foreign debris or mucus</td>
</tr>
<tr>
<td>Diffuse airway nodularity or thickening</td>
<td>Papillomatosis</td>
</tr>
<tr>
<td></td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Metastases</td>
</tr>
</tbody>
</table>

**Table 7: Distinguishing Imaging Features and Problem-solving Strategies for CT Findings of Tracheobronchial NHL**

CT features do not allow reliable distinction of NHL from other airway neoplasms
Prone CT acquisition or short-term follow-up can be considered if endobronchial debris is suspected
Bronchoscopy is indicated for most airway lesions and permits biopsy of suspicious abnormalities
Figure 11. Primary cardiac DLBCL in an immunosuppressed 66-year-old man with a history of rheumatoid arthritis who presented with chest pain and third-degree heart block. (a) Axial CT scan (electrocardiographically [ECG]-gated cardiac protocol, soft-tissue window) shows an infiltrative soft-tissue mass (*) involving the right atrium, interatrial septum, and atrioventricular groove (small arrow). There is also extension through the left atrium and around the aortic root (large arrow). The right coronary artery (arrowhead) is encased but patent. (b, c) MR imaging shows the mass (*) to be nearly isointense to myocardium on a T1-weighted image (repetition time msec/echo time msec = 1791/22) (b) and hyperintense on a T2-weighted image (1791/87) (c). A moderate pericardial effusion had developed by the time of MR imaging (arrows in c). Despite its homogeneity, it is almost certainly malignant in this context. The mass was hypoenhancing to normal myocardium (not shown). All of the CT and MR imaging characteristics are typical of cardiac lymphoma. Open surgical biopsy confirmed DLBCL with malignant effusion (note the postsurgical changes in the right anterior chest wall in a). The patient had a complete response to urgent chemotherapy with resolution of the mass and arrhythmia.

Differential Considerations and Diagnostic Strategies

Differentiating primary NHL from other cardiac neoplasia can be difficult, but the propensity of lymphoma to infiltrate along the epicardial surfaces and particularly its tendency to encase vessels without invasion should raise greater suspicion for this diagnosis (Tables 8, 9) (40,41,45,46). For secondary involvement, a history of disseminated NHL is highly suggestive of the diagnosis, given the rarity of both primary and secondary cardiac tumors otherwise. Several reports suggest improved survival with early diagnosis and treatment of cardiac involvement, supporting an aggressive diagnostic approach (42).

Cardiac lesions with overlapping imaging features include metastatic carcinoma (particularly lung), metastatic melanoma, and primary angiosarcoma (40,47). Compared with lymphoma, angiosarcomas tend to show greater enhancement and central necrosis and are more likely to invade vascular and valvular structures (40). Like lymphoma, right-sided involvement of the heart is most common (40).

Pericardial effusion and smooth thickening may be inflammatory or treatment related but should nonetheless be regarded as suspicious.
Figure 13. Pericardial DLBCL in an immunosuppressed 66-year-old woman with a history of rheumatoid arthritis. The patient initially presented with a neck mass, proven to be DLBCL of the parotid gland at core biopsy. She soon developed severe dyspnea and clinical cardiac tamponade. (a) Axial CT scan at the level of the aortic root (non–ECG gated, soft-tissue window) shows a large pericardial effusion with a questionable area of higher attenuation anteriorly (arrow). Pericardiocentesis was negative for malignancy, and rheumatoid-related pericarditis was considered in the differential diagnosis. (b) Axial 18F-FDG PET/CT scan 2 weeks later shows focal intense pericardial uptake in the region of high attenuation on the CT scan (arrow) as well as in two larger lesions (*), which were not clearly defined at CT. These abnormalities are consistent with pericardial NHL. The pericardiocentesis results were falsely negative. Subsequent mediastinoscopic biopsy of one of the solid lesions confirmed DLBCL. It is uncertain whether this was primary or secondary pericardial NHL because the patient presented with simultaneous involvement of two extranodal sites.

Echocardiography provides a low-cost noninvasive initial assessment when solid myocardial or pericardial tissue is suspected clinically or at CT (40), although sensitivity is limited (41). 18F-FDG PET/CT can easily demonstrate solid masses in most cases, given the high 18F-FDG avidity of most cardiac lymphomas (Figs 12b, 13b). Although physiologic myocardial 18F-FDG activity can be intense and heterogeneous, it is usually greatest in the left ventricle, while NHL...
usually involves the right heart. Anatomic detail is still limited by motion blurring, and further evaluation is usually warranted. ECG-gated CT or MR imaging can mitigate motion artifact, with MR imaging being the preferred modality due to superior soft-tissue definition (Fig 11b, 11c) (40,41,47).

Pericardiocentesis should be pursued in the setting of effusion to confirm malignant involvement if management will be affected (41), although it may not be diagnostic in one-third of cases (40). In the absence of effusion, solid lesions may be evaluated with mediastinoscopic or thoracoscopic biopsy, or even less invasively with transesophageal echocardiographic or transvenous endomyocardial biopsy (2,41).

### Esophagus

**Clinical Features**

While the gastrointestinal tract is the most common site of primary extranodal NHL, the esophagus is the least common segment to be involved: esophageal lymphoma accounts for only 0.2% of all primary extranodal disease and 1% of esophageal tumors (2,48–50). Secondary involvement of the esophagus is more common, occurring in 1.5% of NHL cases (2). DLBCL is the most likely subtype to involve the esophagus (2,7).

The most common mechanism is direct spread from mediastinal nodal or gastric disease (the stomach being the most common gastrointestinal site of NHL), but hematogenous and lymphatic spread also occur (2,49,50). Middle-aged or older adults are most commonly affected (2). The clinical presentation is nonspecific and includes dysphagia, chest pain, and weight loss (2).

### CT Findings

Manifestations of primary and secondary NHL are similar and include polyloid or circumferential masses, broad submucosal lesions, diffuse thickening, and ulceration (Fig 14) (2,50–52). A varicoid appearance may be seen with diffuse submucosal infiltration (52). The distal esophagus is the most common region involved because of direct spread from the stomach (52). When esophageal disease is contiguous with airways, fistulization can occur and may be evident at CT (Fig 14b) (52–54).

### Table 8: Differential Diagnosis for CT Findings of Pericardial and Cardiac NHL

<table>
<thead>
<tr>
<th>NHL Manifestation</th>
<th>Alternative Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial effusion</td>
<td>Pericarditis (infection, autoimmune disease, radiation, drugs)</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Pericardial nodules or thickening</td>
<td>Pericarditis</td>
</tr>
<tr>
<td></td>
<td>Postinflammatory or postsurgical change</td>
</tr>
<tr>
<td></td>
<td>Metastases</td>
</tr>
<tr>
<td>Cardiac mass</td>
<td>Cardiac sarcomas</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
</tr>
</tbody>
</table>

### Table 9: Distinguishing Imaging Features and Problem-solving Strategies for CT Findings of Pericardial and Cardiac NHL

<table>
<thead>
<tr>
<th>Pericardial effusion</th>
<th>Consider PEL in patients with severe immune compromise and unexplained effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effusion alone is nonspecific, but likelihood of involvement is high without an identifiable benign cause in patients with known NHL</td>
</tr>
<tr>
<td></td>
<td>Almost certainly malignant if solid cardiac or pericardial lesions are present (9)*</td>
</tr>
<tr>
<td></td>
<td>Pericardiocentesis is falsely negative in one-third of cases (12)*</td>
</tr>
<tr>
<td></td>
<td>18F-FDG PET/CT may demonstrate solid pericardial lesions occult at routine CT</td>
</tr>
<tr>
<td>Pericardial nodules or thickening, cardiac mass</td>
<td>Right cardiac mass infiltrating along epicardial surfaces and encasing coronary arteries suggests NHL over other diagnoses</td>
</tr>
<tr>
<td></td>
<td>ECG-gated CT or MR imaging reduces motion artifact and better demonstrates lesion morphology</td>
</tr>
<tr>
<td></td>
<td>Focal 18F-FDG uptake at PET increases specificity for malignant involvement</td>
</tr>
<tr>
<td></td>
<td>Biopsy is required for most primary cardiac lesions, particularly if pericardiocentesis is nondiagnostic or effusion is absent</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are references.
Differential Considerations and Diagnostic Strategies

Imaging manifestations of primary esophageal NHL are not distinct from those of more common esophageal tumors, and biopsy is required for diagnosis in essentially all cases (Tables 10, 11).

Esophagitis is an important differential consideration for focal or diffuse esophageal thickening at CT in the setting of known NHL. Opportunistic infection, chemotherapeutic agents, and radiation therapy are potential causes relevant to patients undergoing treatment of NHL. Conversely, esophageal thickening contiguous with lymphadenopathy or a gastric mass should raise higher suspicion for secondary involvement. Esophageal dilatation and retention of fluid or debris suggest obstruction, which can occur from either direct esophageal involvement or extrinsic compression from lymphadenopathy (Fig 14a). CT may not allow distinction between these due to limited tissue resolution, but retained fluid in the lumen can act as a negative contrast agent to help outline mural nodularity (Fig 14b).

Intense circumferential esophageal uptake of 18F-FDG at PET/CT is highly suggestive of involvement in the setting of known aggressive NHL (Fig 14c). Various causes of inflammatory esophagitis can produce similar patterns of uptake, although typically the intensity is lower than that of aggressive NHL.

Endoscopic biopsy may be necessary to confirm involvement if staging and therapy are affected. Mediastinoscopy or thoracotomy may be indicated in the setting of complications suspected at imaging, such as esophageal rupture or fistulization (Fig 14) (53).

Chest Wall and Spine

Clinical Features

Primary bone lymphoma represents 3%-5% of all primary bone neoplasms and 5% of all extranodal NHL (2,3,55,56). Regions of bone containing persistent hematopoietic marrow are affected (57). DLBCL comprises the majority of cases (2,3,58). Patients of all ages are affected, with the most cases occurring in the 50-70-year age range. Localized bone pain is the most common presentation, but a minority of patients present initially with a palpable mass, pathologic fracture, or neurologic compromise (2). The spine is the most common site in the chest, although generally the
axial and appendicular skeleton are involved with similar frequency (2). Approximately one-fourth of cases are polyostotic (2).

Primary muscular lymphoma is extremely uncommon, representing approximately 0.1% of all lymphomas in one large study (56,59) and accounting for less than 2% of primary chest wall tumors (60). Most cases are NHL, with DLBCL being the most common subtype (61). Middle-aged and older adults are most often affected (56,61). Muscular lymphoma may be initially detected at physical examination as a discrete firm mass. Diffuse infiltration and enlargement of muscle occur in some cases (56).

Secondary chest wall involvement of bone and muscle is far more common than primary NHL and often occurs by direct extension of pleural, pulmonary, or mediastinal disease. This is more likely with aggressive NHL subtypes such as DLBCL. Some cases of suspected primary chest wall disease may actually originate as pleural lymphoma, mainly in the form of PAL. Hematogenous and lymphatic spread are also seen, particularly in the setting of widespread aggressive disease. Bone is secondarily involved in 10% of patients with disseminated NHL. Unlike primary bone NHL, secondary bone NHL occurs mostly in the axial skeleton. Secondary muscular involvement occurs in 1.4% of cases (56).

**Imaging Findings**

For primary bone lymphoma, a lytic-destructive pattern is most common at radiography and CT (Fig 15) (3,55,56,62), representing 70% of cases in one large series (63). Margins are often permeative or moth-eaten but occasionally are well-defined (3,55,56). A mixed lytic-sclerotic pattern is the next most common (56,63). Purely sclerotic bone changes are usually due to treatment response of initially lytic lesions and only rarely represent untreated NHL, despite the classic association of lymphoma with the *ivory vertebra* sign (56,58,63,64). For all bone lesions, radiologists should carefully note the presence or absence of cortical breach and extension into surrounding soft tissues. This is present in up to one-half of cases and suggests a more aggressive NHL subtype (Fig 15) (2). Periosteal reaction is often present (3). In some cases, there is minimal trabecular destruction despite extensive marrow replacement, and radiographs and CT scans may be essentially normal (65).

Spinal involvement in lymphoma may appear as a draping paraspinal soft-tissue mass associated with extensive involvement of a vertebral body but with limited cortical bone destruction or height loss (64,65). This appearance has been termed the *wraparound* sign (Fig 16) and is thought to represent extensive marrow disease infiltrating through the vertebral cortex into the paraspinal tissues with relatively little involvement of the structural bone (65). It is a specific feature that allows the radiologist to make a relatively confident diagnosis of lymphoma (65). The paraspinal mass may elevate the aorta off the spine without causing stenosis or invasion (Fig 16a), producing an appearance that has been termed the *floating aorta* sign and is also characteristic of lymphoma (66,67).

At MR imaging, lymphomatous lesions replacing marrow are typically hypointense on T1-weighted images and hyperintense on T2-weighted and STIR (short inversion time inversion-recovery) images. Areas of enhancement are typically seen on postcontrast T1-weighted images (Figs 15, 16) (8,56,58).

---

**Table 10: Differential Diagnosis for CT Findings of Esophageal NHL**

<table>
<thead>
<tr>
<th>NHL Manifestation</th>
<th>Alternative Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal mass or thickening</td>
<td>Esophagitis (infection, radiation, drug-related, reflux)</td>
</tr>
<tr>
<td></td>
<td>Esophageal carcinoma</td>
</tr>
<tr>
<td></td>
<td>Leiomyoma</td>
</tr>
<tr>
<td></td>
<td>Metastatic disease</td>
</tr>
</tbody>
</table>

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**Table 11: Distinguishing Imaging Features and Problem-solving Strategies for CT Findings of Esophageal NHL**

| CT features do not allow reliable distinction of NHL from other esophageal neoplasms |
| Distal esophageal involvement and direct spread from nodal or gastric NHL characterize most cases |
| 18F-FDG PET may demonstrate additional lesions occult at CT (4,5)* |
| Endoscopic biopsy is indicated for diagnosis of a suspicious esophageal mass |

*Numbers in parentheses are references.
Primary and secondary intramuscular lymphoma share similar imaging features and can easily be missed with CT. Lesions usually manifest as discrete iso- or hypodense, intramuscular masses or diffuse infiltration and demonstrate a variable degree of enhancement (Fig 17) (55,56,61). Review of multiplanar images, use of intravenous contrast material, and a careful search for muscular asymmetry can increase detection. MR imaging can be used to confirm an equivocal CT finding. At MR imaging, lesions are typically isointense or slightly hyperintense to normal muscle on T1-weighted images and show signal intensity intermediate between that of muscle and fat on T2-weighted images. Enhancement is usually homogeneous but can demonstrate a peripheral band-like pattern (56,61). Associated deep fascial enhancement is common (61). Extension of tumor to the adjacent bone marrow is notably uncommon (61).

Differential Considerations and Diagnostic Strategies
Permeative patterns of bone lymphoma can be similar to those of other small round cell neoplasms such as plasmacytoma or Ewing sarcoma at imaging (56). Osteosarcoma and metastatic disease can also appear similar (Tables 12, 13) (58). Generally, lymphoma should be high in the differential diagnosis for solitary permeative lesions near the ends of long bones with layered periostitis (58).

In the setting of a near-normal CT appearance and high clinical suspicion for osseous lymphoma, MR imaging and radionuclide scintigraphy should be considered, as they usually demonstrate more marked abnormalities (58). MR imaging is ideal for characterization of lytic lesions and definition of soft-tissue extension. MR imaging should be routinely considered in the setting of vertebral involvement, especially when focal neurologic signs or symptoms are present, to exclude cord or nerve root compromise. Radionuclide scintigraphy is helpful to exclude distant lesions when a focal abnormality is identified at CT or radiography and may guide further MR imaging.

The primary differential diagnosis for muscle lymphoma typically includes soft-tissue sarcomas, metastases, sarcoidosis, and myositis (61,68). Occasionally, the appearance of muscle lymphoma can mimic that of necrotizing fasciitis (61). MR imaging features particularly suggestive of lymphoma include long segmental involvement, traversing vessels within the lesion, multicompartiment involvement, and subcutaneous stranding (Fig 17b) (61).

$^{18}$F-FDG PET/CT is highly sensitive for chest wall involvement and may indicate lesions in both bone and muscle not visible at CT alone. Because most cases of primary and secondary chest wall NHL are aggressive subtypes, lesions are usually highly $^{18}$F-FDG avid (8,56,68). PET is also sensitive for pure bone marrow involvement in $^{18}$F-FDG–avid NHL and has replaced
bone marrow biopsy in some settings (7,8). Diffuse marrow activity secondary to treatment with colony-stimulating factors can persist for longer than 4 weeks after administration and can obscure focal lesions, particularly in low-grade NHL (7). If present, focal uptake should be regarded as suspicious (7). In some cases of suspected bone, bone marrow, or muscle involvement, PET results may direct MR imaging evaluation or biopsy (7).

Secondary chest wall involvement by extension of nodal, pleural, or pulmonary NHL can usually be identified at CT (Fig 5b). Focal soft-tissue convexity or fat infiltration adjacent to other disease sites should be regarded with suspicion. However, reactive inflammatory changes may appear similar, particularly in the setting of treatment or superimposed infection. MR imaging and PET may not help clarify the diagnosis, and tissue sampling or follow-up imaging may be preferred. Isolated chest wall involvement is less susceptible to this ambiguity, but small lesions are more easily missed at CT due to inconspicuous appearance and location. Specific features of soft-tissue lymphomatous involvement such as the floating aorta or vertebral wraparound signs are helpful if present (65–67).

For lesions arising in bone or muscle for which primary lymphoma is a consideration, biopsy is generally recommended (2). When secondary involvement of bone or muscle is suspected in the setting of known NHL, biopsy may be necessary only when staging and management are affected and there is doubt as to the diagnosis.
Table 12: Differential Diagnosis for CT Findings of Chest Wall NHL

<table>
<thead>
<tr>
<th>NHL Manifestation</th>
<th>Alternative Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular mass</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Hematoma</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
</tr>
<tr>
<td>Diffuse muscular enlargement</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Myositis</td>
</tr>
<tr>
<td>Lytic bone lesion</td>
<td>Metastasis</td>
</tr>
<tr>
<td></td>
<td>Plasmacytoma</td>
</tr>
<tr>
<td></td>
<td>Ewing sarcoma</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Mixed or sclerotic bone lesion</td>
<td>Metastasis</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
</tr>
</tbody>
</table>

Table 13: Distinguishing Imaging Features and Problem-solving Strategies for CT Findings of Chest Wall NHL

- Bone NHL is usually lytic with permeative margins
- Purely sclerotic lesions are uncommon
- Intramuscular NHL tends to preserve rather than invade traversing vessels, unlike other aggressive tumors
- If present, the floating aorta and vertebral wraparound signs suggest lymphoma over other diagnoses
- MR imaging is indicated in most cases for better lesion characterization and assessment of extent
- $^{18}$F-FDG PET is highly sensitive for bone marrow involvement occult at CT and may replace or guide bone marrow biopsy
- Biopsy is required in essentially all cases of isolated primary bone or muscle NHL

**Figure 17.** Primary muscle DLBCL in a 68-year-old man with right chest wall pain and a palpable firm mass that increased in size over several months. (a) Axial nonenhanced CT scan (soft-tissue window) shows diffuse enlargement of the intercostal muscles and serratus anterior with loss of normal striations and fat planes (arrows). There is mild nodular pleural thickening continuous with the muscular enlargement (arrowheads), but the chest wall disease is dominant. Surgical biopsy demonstrated DLBCL. No remote sites of disease were identified at $^{18}$F-FDG PET/CT (not shown). (b) Axial contrast-enhanced CT scan (soft-tissue window) 2 months later without interval treatment shows marked progression of the mass with surrounding soft-tissue edema, increased nodular pleural thickening, and a new pleural effusion.

**Breast**

**Clinical Features**

Given that the breast contains relatively little lymphoid tissue, it is not surprising that breast lymphoma accounts for only 0.1%–0.7% of all breast malignancy and less than 2% of primary extranodal lymphomas (69–71). Secondary involvement is seen in 2% of extranodal lymphomas (5). The median age at diagnosis is 55–65 years
Figure 18. Primary breast EMZL detected at screening mammography in a 58-year-old asymptomatic woman. (a) Left mammogram (cranio-caudal view) shows an oval isodense mass with indistinct margins in the inner hemisphere (arrow). This is of intermediate suspicion for malignancy (BI-RADS [Breast Imaging Reporting and Data System] category 4b). (b) Targeted US image shows a round hypoechoic mass with partially indistinct margins (arrow). The lesion was vascular at color Doppler imaging (not shown). (c) Axial CT scan (soft-tissue window) shows a nonspecific round soft-tissue mass in the left breast (arrow). There was no evidence of lymphoma elsewhere, leading to a diagnosis of primary breast NHL. The findings with each modality are typical of breast lymphoma.

As with breast carcinoma, the vast majority of patients are female (2,70,72). Most cases are DLBCL with EMZL being the next most common (2,70,72,73). Anaplastic large cell lymphoma is increasingly recognized in association with the fibrous capsule surrounding breast implants but is extremely uncommon in the breast otherwise (73).

Breast NHL typically manifests as a solitary mass. Multiple or bilateral masses are occasionally seen in primary NHL (72) but are much more common in secondary disease (36% of secondary breast lymphoma cases in one series) (69). Focal or global asymmetric tissue and diffuse breast enlargement are occasional manifestations (3,69–71). Occasionally, the breast lesion arises within an intramammary lymph node and in this case would not be considered primary extranodal disease, but the distinction is not typically made until histologic examination.

The clinical presentation is similar to that of breast carcinoma, with many lesions being asymptomatic and detected at screening mammography (70). These cases are usually low grade (2). Symptomatic lesions most commonly manifest as a painless palpable lump (70,72). Pain, skin changes, nipple retraction, and discharge occur occasionally (69–71). Between 11% and 50% of patients have axillary adenopathy, which does not preclude a diagnosis of primary extranodal breast NHL (2,8,71).

Imaging Findings
Primary and secondary breast lymphoma share similar imaging features (70,71). At mammography, a lobulated or irregular isodense or high-density mass with indistinct (Fig 18a) or circumscribed (Fig 19a) margins and without calcification is typical (3,70,71). Notably, spiculation and focal architectural distortion are uncommon (69,71). Asymmetric tissue without a discrete mass is an occasional mammographic presentation (69).

At US, most lesions appear as an irregular solid hypervascular mass with indistinct margins (Fig 18b) or an echogenic boundary (Fig 19b) (5,70). A significant minority demonstrate posterior acoustic enhancement (69). Diffuse parenchymal distortion is an occasional US manifestation (69). CT findings reflect these characteristics, with most lesions appearing as nonspecific soft-tissue nodules (Figs 18c, 19c).

Differential Considerations and Diagnostic Strategies
Primary breast carcinoma is the main consideration for most suspicious breast nodules, with NHL being comparatively rare (Tables 14, 15). Although absence of spiculation, calcification, or
architectural distortion is typical of lymphoma, breast carcinomas lacking these features are still statistically more likely. Breast abscess may appear similar to lymphoma and other malignancy at CT and mammography. In these cases, US can be helpful. A complex cystic mass is extremely rare for lymphoma and favors abscess (71).

The diagnostic imaging workup of primary breast lymphoma is similar to that of other breast masses and typically involves mammography, with US and MR imaging as problem-solving tools. MR imaging does not reliably allow distinction of lymphoma from other malignant processes (69). The role of CT in workup is limited to staging, although it may be the modality of initial detection.

Secondary lymphoma should be considered in the differential diagnosis of any new breast mass in any patient with known aggressive or disseminated NHL (71). The appearance of multiple or bilateral lesions is particularly suspicious and favors lymphoma over breast carcinoma (70). 18F-FDG PET/CT can support secondary involvement if lesions show similar 18F-FDG avidity to that of other disease sites. PET also allows localization of lesions in dense breasts (7,12).

Even in the setting of suspected or known disseminated NHL, the high population prevalence of breast carcinoma must be taken into account when a suspicious breast lesion is encountered. Biopsy should still be performed when diagnosis and treatment of a potential breast cancer could affect life expectancy or when staging and management of the lymphoma would be affected by identification of breast involvement. Mastectomy does not improve survival in breast lymphoma and is typically not indicated (2,74).

**Conclusion**

Manifestations of extranodal NHL in the chest mimic a variety of other diseases at CT. However, certain combinations of clinical and imaging
Table 14: Differential Diagnosis for CT Findings of Breast NHL

<table>
<thead>
<tr>
<th>NHL Manifestation</th>
<th>Alternative Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary or multiple breast masses</td>
<td>Breast carcinoma</td>
</tr>
<tr>
<td></td>
<td>Fibroadenoma</td>
</tr>
<tr>
<td></td>
<td>Cyst</td>
</tr>
<tr>
<td></td>
<td>Normal intramammary lymph nodes</td>
</tr>
<tr>
<td></td>
<td>Metastasis</td>
</tr>
<tr>
<td>Focal or diffuse asymmetric tissue</td>
<td>Breast carcinoma</td>
</tr>
<tr>
<td></td>
<td>Mastitis</td>
</tr>
<tr>
<td></td>
<td>Normal variation</td>
</tr>
</tbody>
</table>

Table 15: Distinguishing Imaging Features and Problem-solving Strategies for CT Findings of Breast NHL

Absence of spiculation, calcification, and architectural distortion is typical of NHL.

Mammography is the first-line workup modality for any suspicious breast abnormality noted at CT. US helps distinguish cystic from solid masses; cystic lesions are unlikely to represent NHL.

Biopsy is indicated for suspicious breast lesions, even in patients with known NHL, to exclude breast carcinoma.

features should persuade radiologists to place lymphoma at or near the top of the differential diagnosis, which can lead to earlier characterization and treatment and may prevent unnecessary surgery. Similarly, knowing when to confidently diagnose secondary NHL at extranodal sites and when to direct further workup of suspicious findings can lead to improved staging and treatment.

Disclosures of Conflicts of Interest.—D.M. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: speaker for Roche. Other activities: disclosed no relevant relationships.

References
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