# Organizing Pneumonia Mimicking Pulmonary Involvement by Follicular Lymphoma

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**Authors' contributions**
Cibele Luna and Pritish Aher had the idea for the case. Cibele Luna did the literature research and wrote the first draft of the manuscript. Roberto Ruiz-Cordero contributed with pathology slides and description. All authors read, drafted, and critically revised the work with approval of the final manuscript.

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ABSTRACT

Follicular lymphoma is the most common indolent non-Hodgkin lymphoma. Pulmonary parenchymal involvement by lymphoma can be seen, among many presentations, as consolidation and ground-glass opacities. We present a case of a 61-year-old woman with follicular lymphoma who has never received therapy and now presents respiratory symptoms. Positron emission tomography demonstrated worsened splenomegaly and new radiotracer-avid pulmonary opacities, the latter resulting positive for organizing pneumonia. She initiated prednisone treatment, and pulmonary opacities improved.

# CASE REPORT

## BACKGROUND

The paper highlights the overlap in imaging and clinical presentations between organizing pneumonia and pulmonary involvement by lymphoma, raising awareness about this diagnostic pitfall. This is particularly valuable for radiologists and clinicians managing similar cases. Also, adding to the limited body of literature on organizing pneumonia in the context of lymphoma.

## CASE REPORT

A 61-year-old woman with a reported history of follicular lymphoma who has been in remission and never received therapy is now presenting respiratory symptoms. She had had upper respiratory symptoms for eight weeks. The main symptom had been coughing with greenish phlegm and no blood. She had no fever, chills, shortness of breath, night sweats, or weight loss. Her white count was low (2.9 10*3 µL) with elevated percentage of lymphocytes (44.1%). She also has a smoking history and

was advised to cessation. She had no significant improvement with antibiotics. The patient was referred to Pulmonology. Also, a PET/CT was pending for lymphoma follow-up.

### Imaging findings

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG-PET/CT) showed worsened splenomegaly with new lymphadenopathy and radiotracer-avid pulmonary nodular opacities (Figure 1).

### Management

The findings met GELF criteria (Groupe d-Etude des Lymphomes Folliculaires) for therapy, and the recommendation was bendamustine rituximab.

The pulmonary findings were concerning for lymphomatous involvement, and a biopsy was recommended. The patient underwent an endobronchial biopsy, and a lymph node resulted positive for low-grade B-cell lymphoma, and a lung nodule was positive for organizing pneumonia (Figure 2).

### Follow-up

She completed prednisone treatment for a total of 7 weeks with dose tapering, after which the cough resolved and the pulmonary opacities improved.

## DISCUSSION

### Etiology & demographics

Follicular lymphoma represents approximately 20% of Non-Hodgkin Lymphoma (NHL) [1]. Follicular lymphoma is an indolent neoplasm of germinal-center B cells usually with a follicular growth pattern and positive reaction to B-cell markers and bcl-2 on immunohistochemistry. Lung involvement with lymphoma may manifest less commonly as primary pulmonary lymphoma or as part of extrapulmonary lymphoma in a patient, with the latter being deemed more probable. Notably, extranodal follicular lymphoma without peripheral lymphadenopathy is infrequent [2,3]. Primary thoracic extranodal lesions are mainly mucosa-associated lymphoid tissue (MALT) NHLs [4]. There are few reports regarding pulmonary follicular lymphoma, including, most recently, a Clinical Analysis published by Hu et al. in 2022 [5].

When it comes to organizing pneumonia (OP), it presents as an inflammatory lung condition linked to collagen vascular disease, inflammatory bowel disease, HIV infection, chemotherapy, malignancy, post-transplant situations, or as a response to medication. The pathophysiology of OP has not been clearly described. However, alveolar epithelial injury due to an unknown insult is thought to cause leakage of plasma proteins into the alveolar space, resulting in the recruitment of inflammatory cells. It is called cryptogenic organizing pneumonia when no specific cause is identified [6,7]. The incidence is approximately 1 to 3 per 100,000 hospital admissions and usually presents in the fifth to sixth decade of life [8,9]. Hematologic malignancy has been implicated as a potential risk factor for OP [10].

### Clinical & imaging findings

Follicular lymphoma commonly exhibits an indolent course and carries a favorable prognosis. Marrow involvement is prevalent in over half of the cases, often presenting alongside painless lymphadenopathy. B symptoms, such as night sweats, fever, and weight loss, are reported in only 20% of patients [11].

Pulmonary involvement associated with extrathoracic or diffuse lymphoma is more common than primary pulmonary lymphoma [12]. In individuals with hematologic malignancies, pulmonary infiltrates may arise from various causes, such as infection, pulmonary edema, hemorrhage, or the underlying malignancy. Lymphoma's involvement of the pulmonary parenchyma can manifest in forms like consolidation, masses, nodules, ground-glass opacity, and lymphangitis/perilymphatic spread [13,14]. Frequently, a significant overlap exists in the presentation patterns, posing a diagnostic challenge for radiologists. Given that imaging plays a crucial role in staging and treatment decisions, radiologists' interpretation and management of suspicious findings are pivotal for effective patient care [15].

Regrettably, due to substantial imaging similarities with other conditions, diagnosing extranodal lymphoma solely through imaging poses challenges. The latest diagnostic framework for lymphomas outlines the significance of characterizing tissue architecture to accurately diagnose and classify lymphoproliferative disorders [16-18].

Typically, individuals affected by organizing pneumonia (OP) are in their fifth or sixth decade of life and may exhibit symptoms such as fever, dyspnea, and cough. Radiographic signs of OP are often nonspecific, commonly featuring patchy or nodular consolidative infiltrates with air bronchograms (present in 80-95% of cases) and ground glass opacities. Also, migratory, irregular, linear, or nodular opacities have been described. These infiltrates can manifest unilaterally or bilaterally, and they may appear in peripheral or central locations, occasionally shifting over weeks to months. Notably, the peripheral and basal regions are frequently affected. On CT, approximately 20% of cases demonstrate the classic atoll sign (reverse halo sign), characterized by a dense outer rim of consolidation around a focal ground-glass opacity. Other less common findings include irregular nodular opacities, cavitary lesions, pleural effusions, and bandlike and perilobular or polygonal consolidation. Additionally, OP typically demonstrates hypermetabolism on F-18 FDG PET/CT scans, and the degree of uptake usually corresponds to disease activity [19-22].

### Treatment & prognosis

Typically, confirming an OP diagnosis necessitates a biopsy, although patients are frequently treated empirically with steroids, with a favorable response often indicating the diagnosis. Patients exhibiting progressive symptoms and diffuse radiographic involvement are typically administered oral glucocorticoids, leading to significant improvement. OP treatment is linked to excellent long-term outcomes, with patients typically experiencing a swift symptomatic improvement and up to 80% achieving complete remission. Although relapses are

frequent, they do not significantly impact long-term outcomes regarding morbidity and mortality. Additionally, researchers have investigated the potential of macrolides' anti-inflammatory properties in treating individuals with mild symptoms [23-25].

**Differential diagnoses**

Other pneumonia etiologies include infectious agents like bacteria, fungi, or viruses. Inflammatory causes, such as nonspecific interstitial pneumonia (NSIP), often exhibit a lower lobe predominance with subpleural sparing. In the initial phases of NSIP, the chest radiograph may appear normal. However, CT scans typically reveal basilar-predominant peripheral ground glass opacities (GGO), sparing the subpleural regions. In fibrotic NSIP cases, reticulation and bronchovascular bundle thickening and traction bronchiectasis are evident, but honeycombing is typically absent. The honeycombing pattern on high-resolution CT scans is more indicative of advanced fibrotic lung disease, such as idiopathic pulmonary fibrosis, rather than organizing pneumonia or pulmonary lymphoma. NSIP also demonstrates hypermetabolism on FDG PET/CT [26,27].

Hypersensitivity pneumonitis typically presents with upper lobe-predominant radiographic changes alongside identifiable exposure history [28].

Other inflammatory causes, such as eosinophilic pneumonia, usually present with GGO and interlobular septal thickening, consolidative opacification, and centrilobular nodules and can also present bilateral pleural effusion. Of note, the lung opacities demonstrate increased FDG uptake on PET/CT [29].

Diffuse ground-glass opacities are a common feature of diffuse lung diseases but are not specific to organizing pneumonia [30]. The distribution of the opacities and clinical picture can guide the differential diagnosis.

Additionally, malignancies such as primary pulmonary lymphoma or adenocarcinoma in situ may mimic focal OP areas. On radiographs, pulmonary lymphoma can manifest as poorly defined opacification with air bronchogram or multiple pulmonary nodules. On CT, pulmonary lymphoma can demonstrate a mass or mass-like consolidation, ground glass opacification, pulmonary nodules, or solitary mass with irregular borders and peribronchial thickening. Pleural effusions and masses of pleural origin can also be seen, as well as lymphadenopathy. On FDG PET/CT, low-grade lymphomas can have mild FDG uptake. However, DLBCL can have marked increased FDG uptake. Differentiation between these conditions typically relies on clinical presentation and histopathological examination [31,32].

## TEACHING POINT

Recognizing the clinical and radiological presentation of OP in individuals with hematologic malignancies, such as migratory patchy consolidative infiltrates, is crucial for timely diagnosis and proper treatment.

## QUESTIONS

**Question #1**

Which of the following characteristics helps distinguish organizing pneumonia from pulmonary lymphoma?

1) Presence of fever
2) Ground glass opacities on chest imaging
3) Peripheral consolidation with ground glass halo sign (applies)
4) Honeycombing pattern on high-resolution CT scan
5) Mediastinal lymphadenopathy

Explanation:

1) The presence of fever is not specific to either organizing pneumonia or pulmonary lymphoma. [20% of the patients with follicular lymphoma experience B symptoms (night sweats, fever, weight loss). Patients with organizing pneumonia are usually within the 5$^{th}$ or 6$^{th}$ decade of life and can have fever, dyspnea, and cough.]

2) Ground-glass opacities on chest imaging can be seen in organizing pneumonia and pulmonary lymphoma, but it's not a distinguishing feature. [Organizing pneumonia presents with asymmetric migratory bilateral patchy peripherally located consolidations or ground glass opacities. Pulmonary lymphoma can present with mass or mass-like consolidation and ground glass opacification.]

3) Peripheral consolidation with ground glass halo sign is more characteristic of organizing pneumonia. [Organizing pneumonia presents with asymmetric migratory bilateral patchy peripherally located consolidations and can have the atoll sign or ground glass halo sign.]

4) [Honeycombing pattern on high-resolution CT scan is more indicative of advanced fibrotic lung disease, such as idiopathic pulmonary fibrosis, rather than organizing pneumonia or pulmonary lymphoma].

5) [Mediastinal lymphadenopathy is more suggestive of a malignant process like lymphoma] rather than organizing pneumonia.

**Question #2**

Which imaging findings are typically more characteristic of organizing pneumonia than nonspecific interstitial pneumonia?

1) Bilateral ground-glass opacities with subpleural sparing
2) Patchy consolidation with air bronchograms (applies)
3) Reticulation and traction bronchiectasis
4) Diffuse ground-glass opacities
5) Linear opacities with traction bronchiectasis

Explanation:

1) Bilateral ground-glass opacities with subpleural sparing indicate nonspecific interstitial pneumonia rather than organizing pneumonia. [Nonspecific interstitial pneumonia typically presents with bilateral ground-glass opacities with subpleural sparing.]

2) Patchy consolidation with air bronchograms is more characteristic of organizing pneumonia than nonspecific interstitial pneumonia. [Organizing pneumonia typically presents with patchy areas of consolidation with air bronchograms on imaging]. While [nonspecific interstitial pneumonia typically presents with bilateral ground-glass opacities] with a lower predominance of consolidation.

3) Reticulation and traction bronchiectasis. [The fibrotic nonspecific interstitial pneumonia shows reticulation with bronchovascular bundle thickening and traction bronchiectasis without honeycombing.] Such findings are not seen in organizing pneumonia.

4) [Diffuse ground-glass opacities are a common feature of various diffuse lung diseases but not specific to organizing pneumonia]

5) Linear opacities with traction bronchiectasis are more characteristic of advanced fibrotic lung disease and are often seen in nonspecific interstitial pneumonia rather than organizing pneumonia. [In fibrotic NSIP cases, reticulation and bronchovascular bundle thickening and traction bronchiectasis are evident.]

**Question #3**

Which imaging finding is more characteristic of organizing pneumonia rather than eosinophilic pneumonia?

1) Migratory peripheral consolidations (applies)
2) Ground glass opacities and interlobular septal thickening
3) Diffuse bilateral patchy opacities with pleural effusion
4) Peripheral ground glass opacities with subpleural sparing
5) Mass-like consolidation

Explanation:

1) Migratory peripheral consolidations. [Asymmetric migratory bilateral patchy peripherally located consolidations with air bronchograms or ground glass opacities are characteristic of organizing pneumonia].

2) [Ground glass opacities and interlobular septal thickening] are more characteristic of eosinophilic pneumonia than organizing pneumonia.

3) Diffuse bilateral patchy opacities with pleural effusion are not specific to either organizing pneumonia or eosinophilic pneumonia. [Eosinophilic pneumonia can have bilateral pleural effusions].

4) Peripheral ground glass opacities with subpleural sparing. [Basilar predominant peripheral ground glass opacities with subpleural sparing are more suggestive of nonspecific interstitial pneumonia].

5) Mass-like consolidation. [Mass or mass-like consolidation and ground glass opacification would be more suggestive of pulmonary lymphoma].

**Question #4**

Which imaging feature is more indicative of organizing pneumonia?

1) Solitary pulmonary nodule with irregular borders
2) Homogeneous consolidation with air bronchograms (applies)
3) Consolidative opacification and centrilobular nodules
4) Mediastinal lymphadenopathy
5) Peripheral ground glass opacities with subpleural sparing

**Explanation:**

1) Solitary pulmonary nodule with irregular borders. [Pulmonary lymphoma can present with nodules or solitary mass with irregular borders or mass-like consolidation.]

2) Homogeneous consolidation with air bronchograms indicates organizing pneumonia more than pulmonary lymphoma. [Organizing pneumonia typically presents with patchy areas of consolidation with air bronchograms] on imaging.

3) Consolidative opacification and centrilobular nodules are not typically seen in organizing pneumonia, which usually presents with patchy consolidations with air bronchograms. However, [consolidative opacification and centrilobular nodules are more characteristic of other lung diseases such as eosinophilic pneumonia].

4) Mediastinal lymphadenopathy is uncommon in organizing pneumonia and [can be seen with lymphomas].

5) Peripheral ground glass opacities with subpleural sparing. [Basilar predominant peripheral ground glass opacities with subpleural sparing are more suggestive of nonspecific interstitial pneumonia].

**Question #5**

Which of the following imaging features is the most frequently observed in organizing pneumonia?

1) Bilateral ground glass opacities with subpleural sparing
2) Diffuse reticular opacities with honeycombing pattern
3) Patchy consolidation with air bronchograms (applies)
4) Traction bronchiectasis without honeycombing
5) Linear opacities with traction bronchiectasis

**Explanation:**

1) Bilateral ground-glass opacities with subpleural sparing. [Basilar predominant peripheral ground glass opacities with subpleural sparing are a common feature of nonspecific interstitial pneumonia].

2) [Honeycombing pattern on high-resolution CT scan is more indicative of advanced fibrotic lung disease, such as idiopathic pulmonary fibrosis], rather than organizing pneumonia.

3) Patchy consolidation with air bronchograms is the most frequently observed imaging feature in organizing pneumonia. Typically, organizing pneumonia presents with [asymmetric migratory bilateral patchy peripherally located consolidations with air bronchograms].

4) Traction bronchiectasis without honeycombing. [The fibrotic nonspecific interstitial pneumonia shows reticulation with thickening of bronchovascular bundles and traction bronchiectasis without honeycombing].

5) Linear opacities with traction bronchiectasis are more characteristic of advanced fibrotic lung disease and are often seen in nonspecific interstitial pneumonia rather than organizing pneumonia. [In fibrotic NSIP cases, reticulation and bronchovascular bundle thickening and traction bronchiectasis are evident.]

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## FIGURES

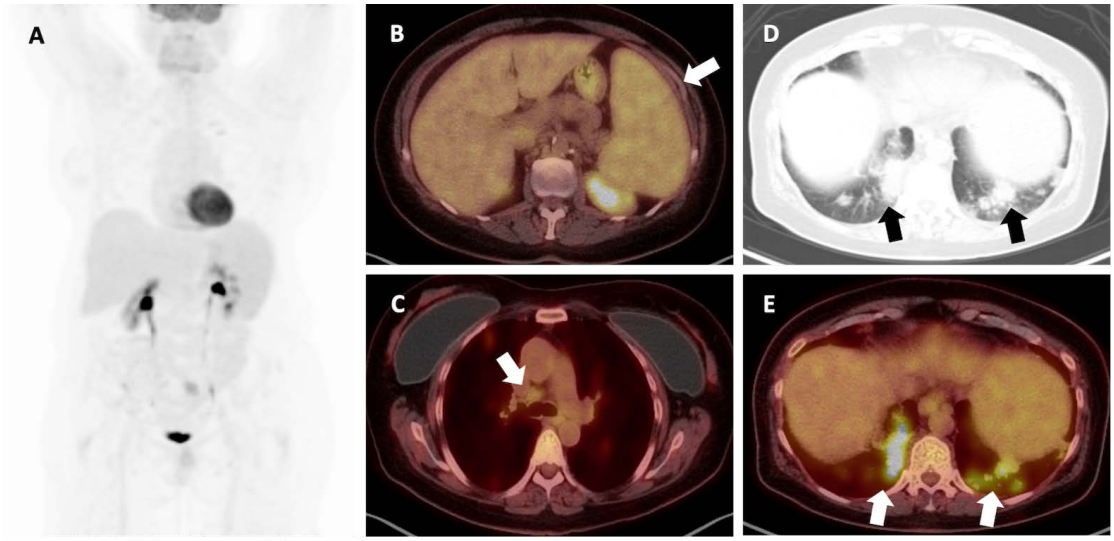


**Figure 1**: 61-year-old woman with a history of follicular lymphoma. Technique: F-18 FDG-PET/CT was performed with a dose of 14.67 mCi (images were obtained at 2:02 pm) and another scan with 14.3 mCi (images were obtained at 8:58 am). Imaging findings: F-18 FDG-PET/CT shows the prior state of remission (A). A new scan demonstrates worsened FDG-avid splenomegaly with SUVmax of 4.1 (arrow in B), new FDG-avid lymphadenopathy with SUVmax of 4.1 (arrow in C), and new radiotracer-avid pulmonary nodular opacities with SUVmax of 12.7 (arrows in D, E).

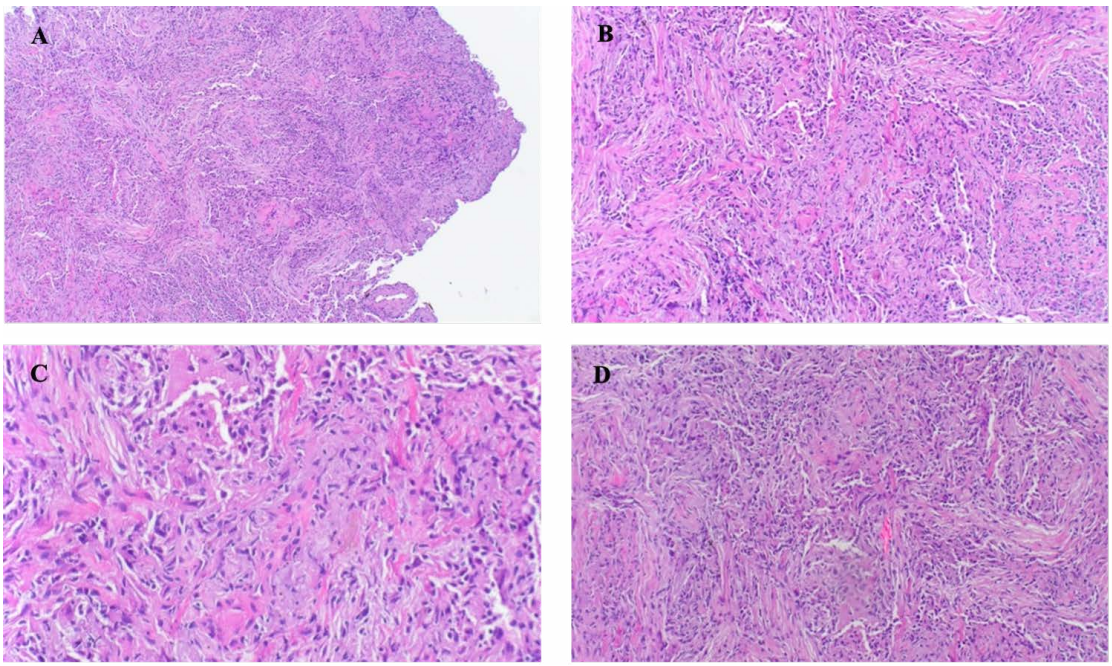


**Figure 2:** 61-year-old woman with a history of follicular lymphoma and new pulmonary opacities. Technique: endobronchial biopsy was obtained. Findings: Histologic sections stained with hematoxylin and eosin from right upper lobe nodular opacity show a benign proliferation of fibroblasts and myofibroblasts arranged in a haphazard pattern with associated extracellular collagen filling the distal air spaces, bronchioles, and adjacent alveoli (A-C, 20X & 40X). An inflammatory infiltrate consisting of few lymphocytes and occasional plasma cells and macrophages is noted (D, 60X). The findings are consistent with organizing pneumonia.

**Table 1:** Summary table

| **Organizing pneumonia (OP)** | |
|---|---|
| Etiology | This inflammatory lung condition can arise alongside collagen vascular disease, inflammatory bowel disease, HIV infection, chemotherapy, malignancy, post-transplant situations, or as a reaction to pharmacologic agents. When no identifiable cause is determined, it is termed cryptogenic organizing pneumonia. |
| Incidence | 1 to 3 per 100,000 hospital admissions. |
| Gender ratio | Both genders are equally affected. |
| Age predilection | Fifth to sixth decade of life. |
| Risk factors | Lately, hematologic malignancy itself has been associated as a potential risk factor. |
| Treatment | Patients with mild symptoms have been reported to experience spontaneous remissions. Additionally, researchers have investigated the potential of macrolides' anti-inflammatory properties in treating individuals with mild symptoms.<br>Patients exhibiting progressive symptoms and diffuse radiographic involvement are typically administered oral glucocorticoids, leading to significant improvement. |
| Prognosis | Treating OP yields excellent long-term outcomes. Spontaneous remissions are observed in approximately 50% of mild cases, while up to 80% of patients attain a complete cure. Although relapses are frequent, they do not significantly impact long-term outcomes regarding morbidity and mortality. |
| Imaging findings | **X-Ray**<br>Patchy diffuse consolidations mainly involve bilateral lower lung zones. Also, migratory, irregular, linear, or nodular opacities have been described.<br>**CT.**<br>Asymmetric migratory bilateral patchy peripherally located consolidations or ground glass opacities.<br>In approximately 20% of cases, the classic sign described is the atoll (reverse halo) sign, a nonspecific sign characterized by a dense outer rim of consolidation around a focal ground-glass opacity.<br>Other less common findings include irregular nodular opacities, cavitary lesions, pleural effusions, and bandlike and perilobular or polygonal consolidation. |

The summary table includes the most crucial facts about organizing pneumonia.
X-Ray: Radiograph; CT: Computed Tomography

**Differential table**

| **Imaging findings** | **Organizing pneumonia** | **Nonspecific interstitial pneumonia (NSIP)** | **Eosinophilic pneumonia** | **Pulmonary lymphoma** |
|---|---|---|---|---|
| X-Ray | Migratory patchy diffuse consolidations. | It can be normal in the initial stages. Patchy, reticulonodular, or mixed lower lobe-predominant opacities can be seen later. | Bilateral ground glass and consolidative opacities. | Poorly-defined opacification with air bronchogram.<br>Pulmonary nodules. |
| CT. | Asymmetric migratory bilateral patchy peripherally located consolidations with air bronchograms or ground glass opacities (GGO).<br>Atoll sign.<br><br>Bandlike and perilobular or polygonal consolidation can be present. | Basilar-predominant peripheral ground glass opacities (GGO) with sparing of the subpleural regions are usually present. In fibrotic NSIP cases, reticulation and bronchovascular bundle thickening and traction bronchiectasis are evident, but honeycombing is typically absent. | GGO and interlobular septal thickening.<br>Consolidative opacification and centrilobular nodules.<br>Bilateral pleural effusion. | Mass or mass-like consolidation and ground glass opacification.<br>Pulmonary nodules or a solitary mass with irregular borders can also be seen.<br>Peribronchial thickening.<br>Pleural effusions.<br>Masses of pleural origin.<br>Lymphadenopathy. |
| PET | Increased FDG uptake, with higher uptake in areas of consolidative opacification, is the usual finding. The degree of uptake usually corresponds to disease activity. | Increased FDG uptake within the GGO, consolidation, and reticulations. | Lung opacities can have increased FDG uptake. | Low-grade lymphomas can have mild FDG uptake. However, DLBCL can have a marked increased uptake. |

Differential diagnosis table, including the major causes of pneumonia.
X-Ray: Radiograph. CT: Computed tomography. PET: Positron emission tomography. GGO: ground glass opacities. NSIP: Nonspecific interstitial pneumonia. DLBCL: Diffuse Large B-cell Lymphoma.

KEYWORDS

F-18 FDG-PET/CT; Organizing pneumonia; Follicular lymphoma; Pulmonary opacities; Pulmonary lymphoma

ABBREVIATIONS

NHL: Non-Hodgkin Lymphoma, F-18 FDG-PET/CT: Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, CT: Computed Tomography, GELF criteria: Groupe d-Etude des Lymphomes Folliculaires, MALT: Mucosa-Associated Lymphoid Tissue, OP: Organizing Pneumonia, GGO: Ground Glass Opacities, NSIP: Nonspecific Interstitial Pneumonia, DLBCL: Diffuse Large B-cell Lymphoma

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