Immunoglobulin G4-Related Disease Unilaterally Involving the Pulmonary Interstitium and Pleura: A Case Report
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Abstract

Immunoglobulin G4-related disease is a novel inflammatory entity involving multiple organs of the body. In the lungs, it is accompanied by infiltration of IgG4-positive lymphocytes and increased serum levels of IgG4. Previous studies have reported radiological findings of IgG4-related lung disease in the pulmonary parenchyma; however, there are few case reports of pleural involvement. Here, we report the case of a 66-year-old man with IgG4-related disease unilaterally involving the lung interstitium and pleura. Thoracic computed tomography images demonstrated pleural effusion and thickening resembling a primary or secondary pleural malignancy. The diagnosis of IgG4-related disease was confirmed by video-assisted-thoracoscopic biopsy. This rare disease should not be overlooked in patients with radiological findings that are suggestive of pleural malignancies.

Keywords: Immunoglobulin G, Pleural Disease, Pleural Effusion, Plasma Cells

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a rare and recently defined immune-mediated, systemic inflammatory disease characterized histopathologically by lymphoplasmacytic infiltration, storiform fibrosis, phlebitis, and abundant IgG4-positive plasma cells (1, 2). While it usually involves the pancreas and salivary glands, other organs may be affected as well including the lung; pachymeninges, orbit, liver, kidney, and prostate (3, 4). IgG4-RD of the lung is relatively rare and can be confined to the lung or develop in other organs simultaneously or metachronously.

The clinical and imaging findings of IgG4-related lung disease (IgG4-LRD) are highly variable. While lung parenchymal involvement (mass like lesion or interstitial lung disease) and mediastinal lymphadenopathy are typical, airway or pleural involvement is rare (2). In fact, there are only a few case reports of IgG4-LRD involving the pleura, most often bilaterally, with or without disease in the lung parenchymal interstitium (5, 6). Here, we present the case of a patient with IgG4-LRD unilaterally involving the pleura and lung parenchyma interstitium and radiologically mimicking malignant pleural effusion with lymphangitic metastasis or mesothelioma.

2. Case Presentation

A 66-year-old man was diagnosed endoscopically with early gastric cancer and underwent further evaluation for surgical treatment. He had no history of hypertension, diabetes mellitus, or occupational or environmental exposure to dust or asbestos. He had never smoked. His physical examination prior to surgery did not reveal significant findings. He had no abnormal respiratory symptoms such as dyspnea, cough, sputum, or fever. The results of laboratory tests, including measurements of white blood cell (WBC) levels, erythrocyte sedimentation rate, C-reactive protein levels, and tumor markers (CEA, CA19-9, and CA-125), were all in the normal range. To evaluate distant metastasis of the gastric cancer, he underwent contrast-enhanced computed tomography (CT) of the chest and abdomen.

The chest CT revealed a small amount of right pleural effusion as well as mildly enhanced thickening of both the pleura in the right lower hemithorax and the right bronchovascular bundles. Thoracentesis was performed to analyze the pleural fluid and rule out the possibility of malignancy. The pleural fluid was turbid, characterized by an exudate with a predominance of polymorphonuclear neutrophils (PMN), rather than lymphocytes, and eosinophils (WBC 1,296/mm³, PMN 20%, lymphocyte 5%, eosinophils 20%, other cells 55%). His adenosine deaminase level was within the normal limit (27 IU/L). Cytological examination...
Discussion

IgG4-RD is a novel multi-organ inflammatory disorder characterized by the subacute development of a mass-like swelling or enlargement of an organ, increased serum levels of IgG4, infiltration of IgG4-positive lymphocytes, and storiform fibrosis of tissue (3, 7, 8). It usually occurs in middle-aged Asian males and responds well to corticosteroid treatment (9).

The pathogenesis of IgG4-RD is poorly understood, as is the physiological role of the IgG4 antibody, including whether it has a stimulatory or inhibitory role in the inflammation and fibrosis of IgG4-RD (10). The disease is thought to be both an autoimmune and an allergic disorder, with previous studies reporting increased levels of autoantibodies including antinuclear antibody and rheumatoid factor. Peripheral eosinophilia, bronchial asthma, and rhinitis are other common findings in IgG4-RD patients (11).

In cases of IgG4-RD involving the lung and thorax, mild and nonspecific respiratory symptoms, such as cough, sputum or dyspnea, occur in about half of the patients. IgG4-RD can involve various structures of the thorax, including lung parenchyma, mediastinal lymph nodes, airway, and pleura, with corresponding variation in the radiological imaging patterns. This wide range of clinical and radiological features has complicated the diagnosis of IgG4-related lung disease (IgG4-RLD) (2, 12).

Few reports have described the radiological findings of IgG4-RLD characterized by lung parenchymal involvement. Inoue et al. described four major pulmonary radiological patterns that may aid in the differential diagnosis of IgG4-RLD versus other diseases (12): solid nodular type (mimicking lung cancer), round GGO (mimicking bronchiolar alveolar carcinoma), alveolar interstitial type (mimicking interstitial lung disease), and bronchovascular type (mimicking sarcoidosis or multicentric Castleman disease). However, the clinical symptoms and pathologic features do not differ among the four subtypes.

In their analyses of the radiological and pathologic features of IgG4-RLD, Matsui et al. mostly found mixed subtypes that hindered a straightforward characterization of the disease (13). Most patients with IgG4-RLD have hilar and mediastinal lymphadenopathy as well as thickening of the bronchovascular bundles and interlobular septa corresponding pathologically to a lymphatic infiltration of inflammatory cells. However, in most IgG4-RD patients the disease develops in the lung parenchyma whereas case reports or original articles demonstrating predominant pleural involvement of IgG4-RLD are rare.

In their pathologic study of 21 cases of IgG4-RLD, Zen et al. reported five cases in which the pleural lesions were accompanied only by visceral or parietal pleural nodules (9). However, only the histopathologic results of the pleural lesions, and not the imaging findings, were provided such that whether the lesion was visible on CT is not known.

To the best of our knowledge, there are only three case reports of IgG4-RLD characterized by pleural effusion (5,
A 66-year-old man with immunoglobulin G4-related disease (IgG4-RD) unilaterally involving the lung interstitium and pleura. Follow-up chest CT scan obtained with a contrast-enhanced mediastinal window setting of the axial (A) and high resolution computed tomography (HRCT) (B, C) images. A remnant right pleural effusion persists despite the insertion of a chest drainage catheter in the right hemithorax. Enhanced nodular thickening (arrow in A) along the right pleura is also present. Diffuse thickening of the bronchovascular bundles persists in the right lung (arrows in B), together with multiple tiny fissural nodules (arrowheads in C) in the right major fissure. [18F]-Fluorodeoxyglucose positron emission tomography-computed tomography fusion images. Multiple, heterogeneously increased (maximum standardized uptake value [SUVmax = 4.9]) foci are seen along the right pleura together with right pleural effusion (D).

6, 14) (Table 1). In two cases, the pleural involvement was bilateral, including one case in which there was a large bilateral pleural effusion and another in which the pleural effusion was unilateral, with pleural nodules in the contralateral lung. The current case is the first one of IgG4-RLD with pleural effusion, pleural nodules, and bronchovascular bundle thickening seen unilaterally on the CT scan. The differential diagnosis of patients with unilateral pleural effusion and perilymphatic interstitial thickening should include malignant pleural effusion with lymphangitis carcinomatosis, mesothelioma, and epithelioid hemangioendothelioma (15, 16). In our patient, the disease course was subacute rather than acute or rapidly progressive. Cytological evaluation of several pleural samples showed no evidence of malignancy. The pleural fluid analyses demonstrated the presence of an exudate, with negative microbiologic culture results. These features provided a clue to the diagnosis of IgG4-RLD. However, confirmation of a diagnosis of IgG4-RLD is difficult due to the variable organ involvement and imaging findings. In our patient, pathologic confirmation through video-assisted-thoracoscopic biopsy was essential to rule out a primary or secondary malignancy.

The histologic hallmark of IgG4-RLD is the infiltration of mononuclear cells and IgG4-positive plasma cells, fibrosis, a ratio of IgG4/IgG-positive cells > 40%, and > 10 IgG4-positive cells per high power field (17). In IgG4-RLD, IgG4 plasma cells abundantly and uniformly infiltrate pulmonary connective tissues, including the bronchovascular bundles, alveolar interstitium, interlobular septa, and pleura. The pleural lesions manifest as a diffuse pleural thickening accompanied by diffuse sclerosing inflammation and a chronic lymphoplasmacytic infiltration with or without fibrosis (9). Given the correlation between the radiological and pathologic findings in IgG4-RLD, the radiology results provide a window into the actual state of the
Figure 2. Microscopic findings of the wedge-resected pleura. Hematoxylin and eosin (H&E) staining reveals a pleura lesion. The pleura is diffusely thickened by dense inflammation and fibrosis (H&E, 40×) (A). A plasma-cell-rich inflammatory infiltration is present in the pleura (H&E, 200×) (B). Immunohistochemical stains for Immunoglobulin G (IgG) (C, 200×) and Immunoglobulin G4 (IgG4) (D, 200×) reveal a ratio of IgG4/IgG-positive plasma cells > 50% (C, D).

Table 1. Summary of Published Cases of Immunoglobulin G4 (IgG4)-Related Lung Disease with Pleural Involvement

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>Organ involvement</th>
<th>Chest computed tomography finding</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>74/M</td>
<td>Lung</td>
<td>Right-side pleural effusion</td>
<td>Visceral pleura and alveolar interstitium involvement with IgG4 positive lymphoplasmacytic infiltration</td>
</tr>
<tr>
<td>5</td>
<td>74/M</td>
<td>Lung</td>
<td>Pleural thickening with right-side pleural effusion and multiple patchy lesions in both lungs</td>
<td>Visceral pleura and alveolar interstitium involvement with lymphoplasmacytic infiltration and fibrosis</td>
</tr>
<tr>
<td>6</td>
<td>48/M</td>
<td>Lung, thrombophlebitis in the innominate vein, abdomen</td>
<td>Both pleural effusion</td>
<td>Chronic inflammation with lymphoplasmacytic infiltration and fibrosis</td>
</tr>
<tr>
<td>Present case</td>
<td>66/M</td>
<td>Lung</td>
<td>Right-side pleural effusion with thickening, interstitial thickening in the right lung</td>
<td>Parietal pleura and interstitium involvement with lymphoplasmacytic infiltration</td>
</tr>
</tbody>
</table>

lymphoplasmacytic infiltration along the intrapulmonary lymphatic system. IgG4-RLD lesions mostly develop in the peribronchial or perivascular connective tissues, interlobular septa, and pleura (17). This distribution is essentially a map of the intrapulmonary lymphatic drainage system and may be a significant step in understanding the pathogenesis and imaging features of IgG4-RLD.

Steroid therapy is the mainstay of treatment for IgG4-RLD (7) and almost always results in a dramatic improvement of the radiological abnormalities and clinical symptoms within 2 weeks to a few months. The dose of corticosteroid can be gradually tapered, but serial monitor-
IgG4-RLD involving the pleura is a rare radiological finding and the clinical relationship is unclear. Many different diseases, both benign and malignant, can be included in the differential diagnosis. Although infrequently seen, IgG4-RLD should not be overlooked, particularly because it is an emerging, treatable disorder. A subacute onset or exudative pleural fluid could be a clue in its diagnosis but pathologic confirmation by surgical biopsy is mandatory.

Footnotes

Authors’ Contributions: Seonghwan Byun reviewed the literature and prepared the radiological images and the manuscript. Kyung Eun Shin contributed to the basic concept of the report and proofread the manuscript. Jai Soung Park, Heon Lee, Jae Wook Lee supervised and reviewed the manuscript. Susie Chin, and Eun Suk Koh were responsible for technical and material support. All authors have read and approved the final version of the manuscript.

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