

Rosai-Dorfman Disease of the Lung Overlapping with IgG4-related Disease: The Difficulty in Its Differential Diagnosis

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Abstract

We herein report a case of Rosai-Dorfman disease (RDD) overlapping with IgG4-related disease (IgG4-RD), which presented as diffuse interstitial lung disease with a perilymphatic pattern, followed by submandibular gland and eyelid swelling. The pathological findings of the submandibular gland biopsy specimen were indicative of IgG4-RD alone. We diagnosed the patient with RDD with overlapping IgG4-RD. However, the optimal method for differentiating between these two entities is still controversial. It is important that clinicians are aware that RDD should be included in the differential diagnoses of diffuse interstitial lung disease with a perilymphatic pattern and that RDD can overlap with IgG4-RD.

Key words: Rosai-Dorfman disease, IgG4-related disease, diffuse interstitial lung disease

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Introduction

Rosai-Dorfman disease (RDD) is a non-malignant histiocytic disorder characterized by monocyte/macrophage proliferation, mostly in the lymph nodes, that usually presents with cervical lymphadenopathy (1, 2). Intrathoracic RDD is rare, and most cases present with mediastinal lymphadenopathy (3). Recently, cases involving overlapping RDD and IgG4-related disease (IgG4-RD) or IgG4-positive plasma cell infiltration in RDD have been reported (4-6). We herein report a case in which RDD presented with diffuse interstitial lung disease overlapping with IgG4-RD.

Case Report

A 64-year-old woman was referred to our institution for

evaluation after bilateral abnormal shadows were incidentally detected on a chest X-ray. Her medical history included hypertension and hyperlipidemia, and she had never suffered from allergies. She was asymptomatic and exhibited normal physical findings. Laboratory tests showed elevated IgE (670 mg/dL), IgG (2,140 mg/dL) and IgG4 (293 mg/mL) levels. Her serum complement level was within the normal range. Screening tests for Epstein-Barr virus, cytomegalovirus, human herpes virus (HHV)-6, HHV-8, and human immunodeficiency virus all produced negative results or indicated that the infection had been resolved. Chest computed tomography (CT) revealed smooth thickening of the bronchovascular bundle and interlobular septa accompanied by multiple nodules, predominantly in the upper pulmonary lobes (Fig. 1A). The mediastinal lymph nodes were slightly enlarged (Fig. 1B). The other organs and lymph nodes all appeared normal on chest/abdominal CT. Video-assisted thoracic sur-

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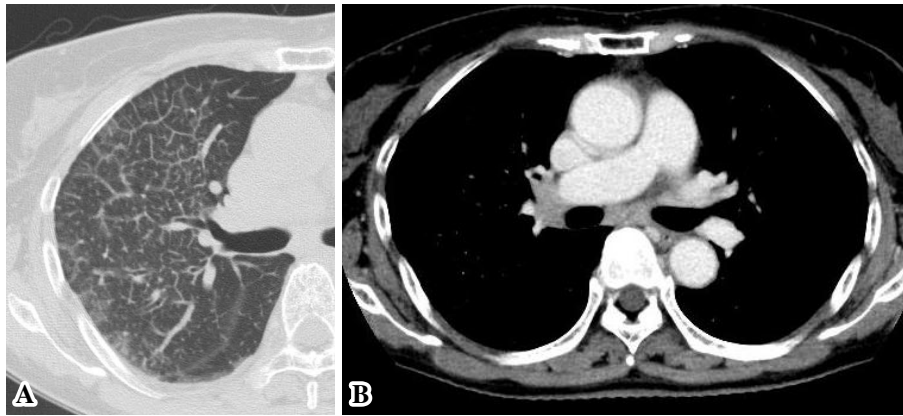


Figure 1. Chest CT revealed smooth thickening of the bronchovascular bundle and interlobular septa accompanied by multiple nodules, predominantly in the upper pulmonary lobe (A). Slight enlargement of the mediastinal lymph nodes was also observed (B).

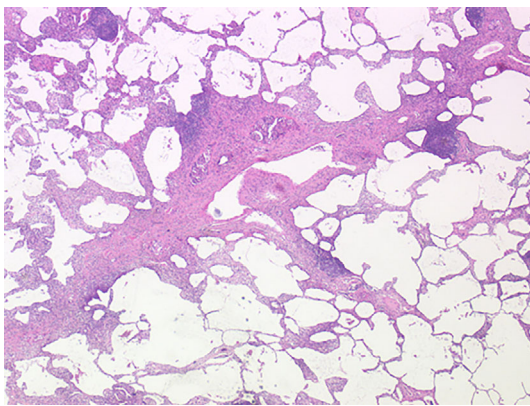


Figure 2. Hematoxylin and Eosin staining of the surgical lung specimen revealed histiocyte, lymphocyte, and plasma cell infiltration along the lymphatic structures together with fibrosis.

gery was performed to obtain a biopsy specimen from the right upper pulmonary lobe. A histological analysis showed histiocyte, lymphocyte, and plasma cell infiltration along the lymphatic structures and fibrosis (Fig. 2). The stromal lymphatic vessels were dilated and filled with histiocytes, which displayed lightly eosinophilic cytoplasm and emperipolesis. Immunohistochemical staining demonstrated that the histiocytes were positive for S100, but negative for CAM5.2, CD1a, and BRAF V600E (Fig. 3, 4). Negative staining for CAM5.2 indicated that these cells were not of epithelial origin. In addition, negative staining for CD1a allowed us to exclude Langerhans cell histiocytosis, while negative staining for BRAF V600E ruled out Erdheim-Chester disease (ECD). The infiltrative plasma cells that were detected in the interlobular connective tissue and thickened alveolar septum were strongly positive for IgG4 (IgG4/IgG ratio: 40%), and obliterative phlebitis was also observed (Fig. 5). Although these results were suggestive of RDD overlapping with IgG4-RD, secondary IgG4-positive plasma cell infiltration could not be ruled out. The patient was observed because she was asymptomatic; however, 5 months later she pre-

sented with swelling of the bilateral submandibular glands and eyelids. This was accompanied by a worsening of her lung infiltration (Fig. 6). A submandibular gland biopsy sample revealed marked IgG4-positive plasma cell infiltration with IgG4/IgG ratios of 70% accompanied by fibrosis with a storiform pattern, which was indicative of IgG4-RD alone (Fig. 7). Although the patient did not have any respiratory complaints, 0.5 mg/kg oral corticosteroids were administered. The lung infiltration and submandibular gland and eyelid swelling all improved within 2 weeks.

Discussion

There have only been four reported cases of RDD involving diffuse bilateral lung lesions (5, 7, 8). One case exhibited bilateral pulmonary consolidation, predominantly in the upper lungs. The second case mainly involved lower lung reticulation. Multiple nodules and cysts together with septal thickening were seen in the third case, and bilateral interstitial infiltrates were the only reported finding in the last case. The radiological features of our case included smooth thickening of the lymphatic interstitium mimicking lymphangitis, lymphoproliferative disease, and ECD. These findings are indicative of RDD in which lymphatic channel infiltration by histiocytes is often seen (9).

It has recently been reported that marked IgG4-positive plasma cell infiltration is observed in a subset of RDD cases (10, 11). Although the underlying pathophysiology of such IgG4-positive plasma cell infiltration remains unclear, it has been suggested that RDD and IgG4-RD might overlap to some extent (4-6). Conversely, Liu et al. reported that RDD does not belong to the IgG4-RD spectrum, even though some cases exhibit increased numbers of IgG4-positive plasma cells and higher IgG4/IgG ratios, since these cases do not meet the other histological criteria for IgG4-RD, such as storiform fibrosis or obliterative phlebitis (12). In the present case, the lung lesions exhibited pathological features of both RDD and IgG4-RD, but only IgG4-RD was seen in the submandibular gland. The histopathological fea-

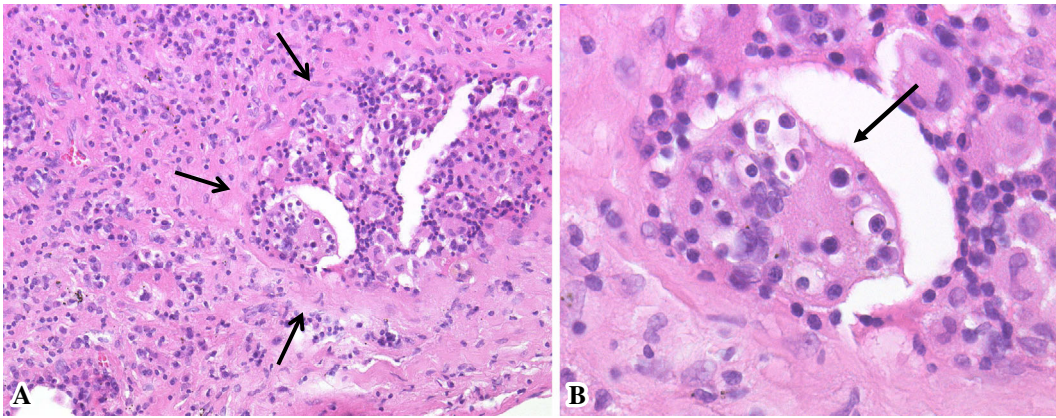


Figure 3. A shows that the stromal lymphatic vessels were dilated (surrounded by arrows) and filled with histiocytes. B shows a high-power field of histiocytes, which displayed a slightly eosinophilic cytoplasm and emperipolesis (arrow).

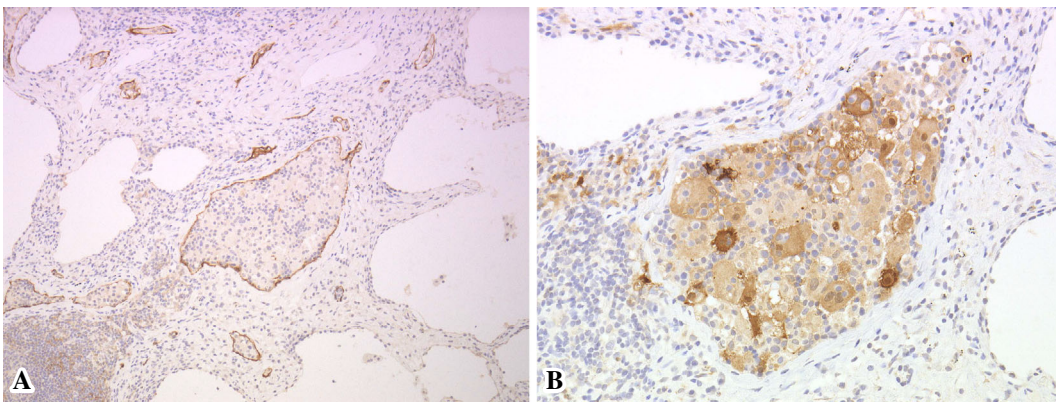


Figure 4. A and B show D2-staining and S100 staining, respectively. D2-40 is a marker of lymphatic vessel endothelial cells. A shows dilated lymphatic vessels, and B shows lymphatic vessels filled with S100-positive histiocytes.

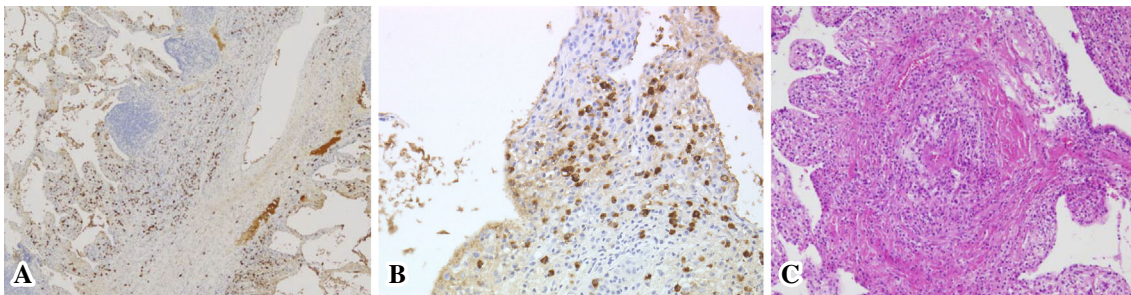


Figure 5. IgG4 staining of the surgical lung specimen shows infiltrative plasma cells in the surgical lung specimen, which were strongly positive for IgG4. These cells were located in the interlobular connective tissue and thickened alveolar septum (A, B). Obliterative phlebitis was also observed (C).

tures of IgG4-RD might arise in several other diseases, such as malignancies or multicentric Castleman's disease. It is therefore important to exclude these diseases when diagnosing IgG4-RD (13). Thus, although our patient's lung lesions satisfied the pathologic criteria for IgG4-RD, our case should be considered as RDD with a secondary increase in IgG4-positive plasma cell infiltration. On the other hand, the pathological findings of the submandibular gland were in-

dicative of IgG4-RD alone. Accordingly, our patient was finally diagnosed with RDD overlapping with IgG4-RD. In the present case, we considered that there were three possible causes of the patient's lung lesions: (1) RDD alone, (2) IgG4-RD alone, and (3) overlapping RDD and IgG4-RD. The infiltration of a large number of IgG4-positive plasma cells and the detection of obliterans phlebitis were inconsistent with an RDD lesion alone. Furthermore, the pathologi-

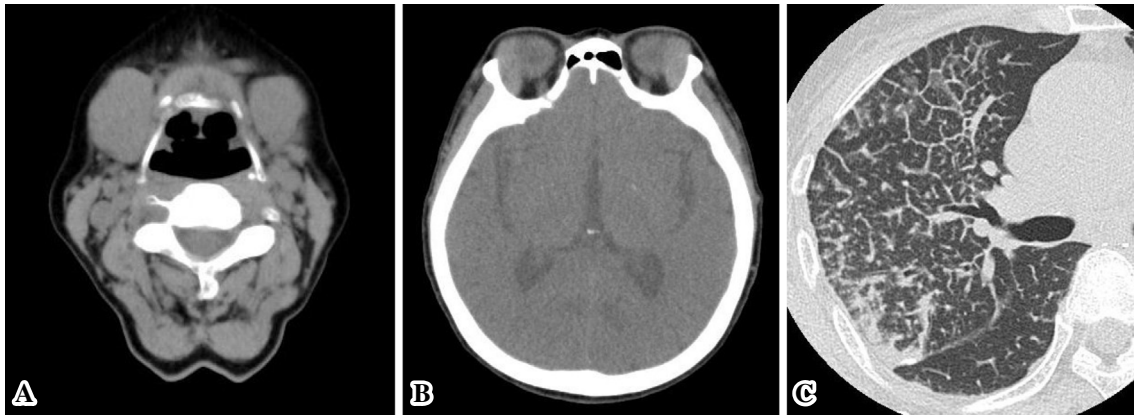


Figure 6. CT showed the swelling of the bilateral submandibular glands (A) and a soft tissue density in the lateral regions of both orbits (B). A chest CT scan obtained at the same time also showed the worsening of lung infiltration (C).

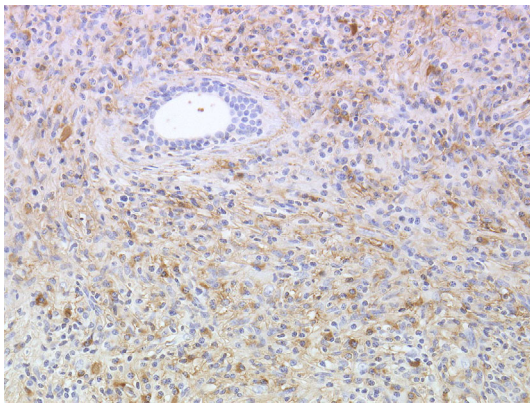


Figure 7. IgG4 staining of the submandibular biopsy specimen shows infiltrative plasma cells that were strongly positive for IgG4.

cal detection of dilated stromal lymphatic vessels containing histiocytes that exhibited emperipolesis was inconsistent with an IgG4-RD lesion alone. We therefore concluded that the lung lesions in this case were consistent with overlapping RDD and IgG4-RD. However, the optimal method for differentiating between these two entities and their exact relationship are disputed, and further study is essential.

We assume that some cases of RDD overlapping with IgG4-RD are misdiagnosed as IgG4-RD alone, since most clinicians are unfamiliar with the clinicoradiopathological features of pulmonary RDD. RDD with respiratory tract involvement may exhibit a worse prognosis than cases of IgG4-RD that are treated with corticosteroids (3, 14). Accordingly, it is important to differentiate between RDD that overlaps with IgG4-RD and IgG4-RD alone.

In conclusion, RDD should be included in the differential diagnoses for diffuse interstitial lung disease with a perilymphatic pattern. Furthermore, RDD can overlap with IgG4-RD and vice versa.

The authors state that they have no Conflict of Interest (COI).

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