CASE REPORT

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Immunoglobulin G4-Related Lung Disease Presenting with a Mediastinal Mass

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ABSTRACT Immunoglobulin G4-related disease (IgG4-RD) is a recently identified systemic disease characterized by increased IgG4 level in serum and plasma cell infiltration resulting in "storiform fibrosis". Although lung involvement is rare, clinical presentation is highly variable, including mediastinal lymphadenopathy, interstitial pneumonia, and pleural effusion. Glucocorticoid therapy is accepted as the mainstay treatment in IgG4-RD. Here, we present an IgG4-related lung disease (IgG4-RLD) case who was admitted to the hospital with chest pain; found out to have a mediastinal mass. IgG4-RLD was diagnosed based on histopathological features and a high blood IgG4 level. The patient's steroid therapy was effective and there were no steroid-related side effects.

Keywords: Immunoglobulin G4-related disease; lung diseases; glucocorticoids; mediastinal diseases

As a recently identified systemic disease, immunoglobulin G4-related disease (IgG4-RD) is defined by elevated serum IgG4 levels and IgG4+ plasma cell infiltration in multiple organs, leading to "storiform fibrosis".[1] Although virtually every anatomical region may be affected, the most common manifestations of the disease are sialadenitis, autoimmune pancreatitis (AIP), and dacryoadenitis.[2] Even though lung involvement is uncommon in IgG4-RD, interstitial pneumonia, mediastinal lymphadenopathy, and pleural effusion are some forms of pulmonary manifestations.[3] We present a case of IgG4-related lung disease (IgG4-RLD) with a mediastinal mass in this paper.

CASE REPORT

A 26-year-old Caucasian man presented with dyspnea and chest pain ongoing for 3 months. He denied a history of chronic disease, smoking, and drug abuse. His physical examination was not remarkable except for his respiratory sounds were slightly decreased on the left. His room air saturation was 97% at rest and his respiratory rate was 14/min. No palpable lymph node (LN) was detected. His laboratory results were as follows: white blood cells 7,330/mL; C-reactive protein 27 mg/L (normal range 0-5); hemoglobin 13.3 g/dL; platelet count 298,000/mL; eosinophil 220/mL; lymphocyte 2,030/mL; IgE 127

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IU/mL (normal range 0-87); IgG4 level of 196 IU/mL (normal range 40-80), IgG 423 mg/dL (normal range 639-1,349). His tumor markers and extractable nuclear antigen antibodies profile results were negative.

In the patient's chest computed tomography (CT), a hypodense mass lesion (approximately 8*6*3.5 cm in size) in the left anterior mediastinum surrounded the vascular structures filling the aortopulmonary window and hilar region was observed. There was an increase in reticulonodular density, starting from the left hilar area accompanied by peribronchial thickening along the bronchovascular interstitium, interlobular septal prominence, and ground glass density. Upon that an ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) scan was performed; the hypodense mass had an increased ^{18}F-FDG uptake with a standardized uptake value (SUV_{max}) of 6.5. There was no extrathoracic invasion (Figure 1).

Bronchoscopy was performed due to peribronchial thickening in the left hilar region on thorax tomography, however, no endobronchial lesion was seen. Bronchoalveolar lavage specimen analysis resulted as negative for tuberculosis polymerase chain reaction and normal for cytology. CD4/CD8 ratio was 2.1.

A tru-cut biopsy was performed from the mass in the superior left mediastinum, adjacent to the aorta under local anesthesia. Lymphoma, thymic carcinoma, and other mediastinal masses were considered as preliminary diagnoses. The pathological examination resulted as "Eosinophils in collagenized/sclerosing stroma, lymphoplasmacytic cells, and histiocytes." Histologic analysis of the lung biopsy material revealed infiltration of IgG4-positive plasma cells with a 40% IgG4 to IgG ratio (Figure 2). Histopathological findings and a high blood IgG4 concentration were used to make the diagnosis of

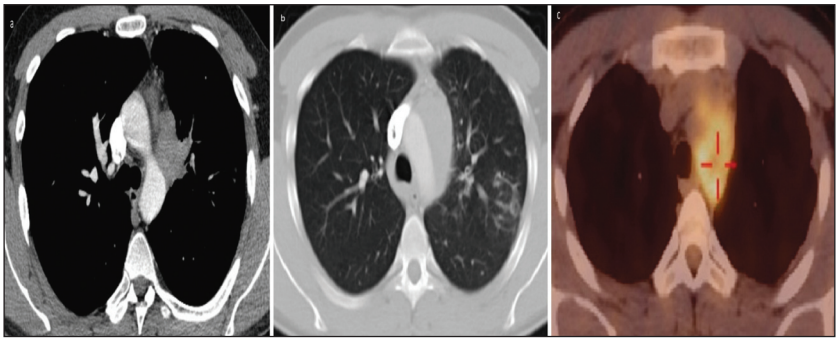

FIGURE 1: A) A hypodense mass lesion (approximately 8*6*3.5 cm in size) in the anterior mediastinum surrounded the vascular structures filling the aortopulmonary window and the hilar region is seen. **B)** There is an increase in reticulonodular density, starting from the left hilar area accompanied by peribronchial thickening along the bronchovasculary interstitium, interlobular septal prominence, and ground glass density. **C)** The hypodense mass had an increased ^{18}F-fluorodeoxyglucose uptake with a standardized uptake value (SUV_{max}) of 6.5.

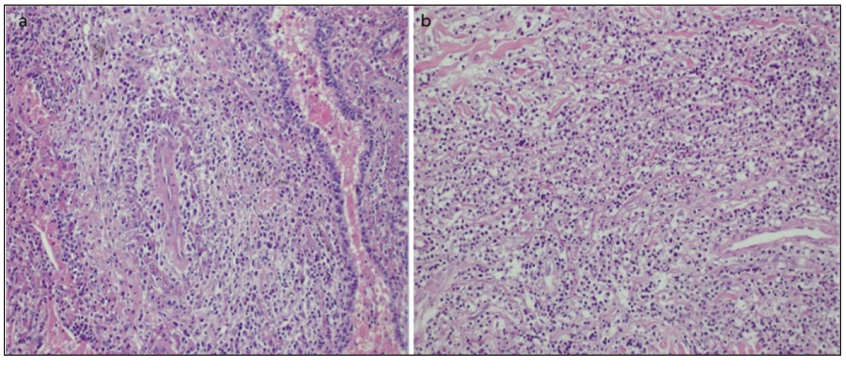

FIGURE 2: The biopsy material. Vasculitis characterized by intense plasmacytic inflammation accompanied by concentric fibrosis surrounding the peribronchiolar vessels can be observed (H&E x200).

IgG4-RLD. Methylprednisolone was then administered in the dose of 0.5 mg/kg for 1 month; then 0.25 mg/kg following month and 0.125 mg/kg for 3 months.

The patient was called for control after 3 months. The symptoms were almost entirely disappeared. In addition to the resolution of mediastinal mass and lung parenchymal infiltrations, high serum levels of IgG4 decreased to normal (79 mg/dL) and there was no increased ^{18}F-FDG uptake in the PET-CT scan (Figure 3).

Before publishing, the patient signed a written informed consent form.

DISCUSSION

IgG4-RD is a recently identified systemic condition presenting usually with multiple-organ involvement. Disease characteristics include IgG and IgG4-stained lymphoplasmacytic cell infiltration, fibrosis of the affected tissues, increased serum IgG4 levels, and a positive response to steroids.[1,2] AIP, sialadenitis, dacryoadenitis, and retroperitoneal fibrosis are the most common and distinctive presentations of IgG4-RD. Although the percentage of single-organ involvement is unknown, multi-organ involvement is prevalent and almost all organs can be affected by the disease.[2] Our case was an example of an IgG4-RLD of single organ involvement.

Lung parenchyma, airways, pleura, and mediastinum are known to be affected in IgG4-RD; however, the exact pulmonary involvement rate of IgG4-RD is unclear. Mediastinal LN is the most common intrathoracic manifestation of IgG4-RD, affecting approximately 40-90% of IgG4-RD patients.[3] Pulmonary involvement may imitate malignancy by showing nodules and masses radiographically, pleural lesions, or ground-glass opacities. In our patient, there was no additional lesion other than the anterior mediastinal mass.

The clinical symptoms of IgG4-RLD may change based on where the lesion is located.[3] Cough, dyspnea, fever, and chest pain can be counted among the possible symptoms as our patient was administered to the hospital with chest pain and dyspnea.

IgG4-RD has been associated with higher ^{18}F-FDG uptake in affected tissues. Although SUV may increase in inflammatory and malignant lesions, PET-CT is still a helpful method for determining the extent of the disease.[1,4] Although there was no extrathoracic involvement in our case, increased ^{18}F-FDG (SUV_{max} 6.5) shed light on the diagnosis.

Eosinophilia and elevated serum IgE levels were detected in 40% of patients, although the pathogenesis of IgG4-RD remains unknown. Therefore, autoimmunity is supposed to be linked to the disease.[5,6] In our case there was an increased IgE level although the eosinophil level was in the normal range.

Histopathological examination is required for a definitive diagnosis of IgG4-RD. The major morphological characteristics include dense lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and mild-to-moderate eosinophil infiltrates. The characteristic storiform fibrosis, on the other hand, may not be visible in the lungs.[3] In this case,

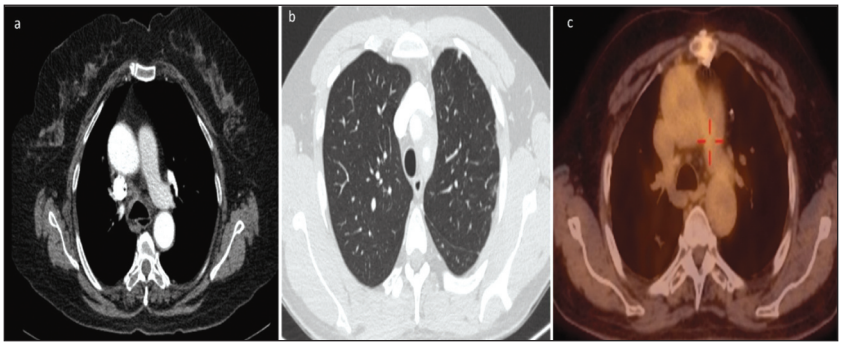

FIGURE 3: A) The lesion in the left anterior mediastinum is resolved after steroid treatment of 3 months. **B)** The reticular density and the peribronchial thickening seem to recover. **C)** There was no ^{18}F-fluorodeoxyglucose uptake on the positron emission tomography-computed tomography scan after steroid treatment.

IgG4-rich plasma cells in the lung biopsy material led to a definitive diagnosis. In our case, vasculitis characterized by intense plasmacytic inflammation accompanied by concentric fibrosis surrounding the peribronchiolar vessels was observed. Focal fibrin deposition, Type II pneumocyte hyperplasia, isolated histiocytic giant cells, and sparse loose granuloma structures in the surrounding alveoli were observed.

While there are no universally accepted diagnostic criteria, previous literature suggests 2 diagnostic criteria: Either serum IgG4 concentration higher than 135 mg/dL or IgG4/IgG plasma cell ratio higher than 40%.[4] In our case, the lung biopsy material revealed IgG4-positive plasma cell infiltration with a 40% of IgG4: IgG ratio in the mediastinal lesion, as well as elevated serum IgE levels, which led us to the proper diagnosis.

Glucocorticoid therapy is accepted as the mainstay treatment in IgG4-RD. It was shown to be effective in both intra- and extrapulmonary IgG4-RD.[7] AIP caused by IgG4-RD has also been treated with immunosuppressive drugs such as azathioprine, mycophenolate mofetil, and cyclosporine.[3,8] Following general opinion; we started a steroid treatment for our patient which helped the disease to recover.

In conclusion, IgG4-RD may affect the lungs as well as the other organs. Although single organ involvement is rare and the pulmonary manifestation rate is not clear; our case indicates that in patients with mediastinal mass, IgG4-RD should come to mind among differential diagnoses.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gülçehre Oğuztürk, Ekrem Cengiz Seyhan, Mehmet Zeki Günlüoğlu;* ***Design: Control/Supervision:*** *Gülçehre Oğuztürk, Ekrem Cengiz Seyhan, Mehmet Zeki Günlüoğlu;* ***Data Collection and/or Processing:*** *Gülçehre Oğuztürk, Ekrem Cengiz Seyhan, Mehmet Zeki Günlüoğlu;* ***Analysis and/or Interpretation:*** *Gülçehre Oğuztürk, Ekrem Cengiz Seyhan, Mehmet Zeki Günlüoğlu;* ***Literature Review:*** *Gülçehre Oğuztürk, Ekrem Cengiz Seyhan;* ***Writing the Article:*** *Ekrem Cengiz Seyhan;* ***Critical Review:*** *Gülçehre Oğuztürk, Ekrem Cengiz Seyhan, Mehmet Zeki Günlüoğlu;* ***References and Fundings:*** *Gülçehre Oğuztürk, Ekrem Cengiz Seyhan, Mehmet Zeki Günlüoğlu;* ***Materials:*** *Gülçehre Oğuztürk, Ekrem Cengiz Seyhan, Mehmet Zeki Günlüoğlu.*

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