Turk Thorac J 2020; 21(4): 280-2 DOI: 10.5152/TurkThoracJ.2019.190115

Case Report

Immunoglobulin G4 Related Lung Disease

Ekrem Cengiz Seyhan[1], Mehmet Akif Özgül[1], Efsun Uğur[1], Demet Turan[1], Nur Ürer[2]

[1]Department of Chest Diseases, Ministry of Health, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey
[2]Department of Pathology, Ministry of Health, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey

Cite this article as: Seyhan EC, Özgül MA, Uğur E, et al. Immunoglobulin G4 related lung disease. Turk Thorac J 2020; 21(4): 280-2.

Abstract

Immunoglobulin G4 related disease (IgG4-RD) is a relatively newly defined disease known for multiple organ involvement. Histopathologically, the disease is characterized by lymphoplasmatic inflammation, fibrosis, and enhanced levels of IgG4-positive plasma cells in tissues. IgG4-RD has been reported in almost every organ system. With pulmonary involvement, lesions have been described in the lung parenchyma, airways, pleura, and the mediastinum. Glucocorticoids are the first choice of treatment, but additional immunosuppressive drugs may be administered in refractory patients. In this article, we report a patient with IgG4 syndrome who had lung parenchyma, mediastinum, aorta wall, and pancreatic involvement. Histopathological findings and high serum IgG4 level established the diagnosis of IgG4-related disease. The patient was treated successfully with glucocorticoids.

KEYWORDS: IgG4-related disease, pulmonary manifestation, glucocorticoids

Received: *01.10.2019* ***Accepted:*** *18.11.2019*

INTRODUCTION

Immunoglobulin G4 related disease (IgG4-RD) is a recently known fibroinflammatory condition that can involve single or multiple organs and is characterized by fibrosis with prominent lymphoplasmacytic infiltrates and dense IgG4-positive plasma cells [1]. Pulmonary manifestations of IgG4-RD appear to be miscellaneous due to the involvement of not only the lung parenchyma but also the lymph node (LN), mediastinum, and pleura [2]. Glucocorticoids are the mainstay of treatment. We reported a case of IgG4-related lung disease (IgG4-RLD) and reviewed the literature on this increasingly recognized entity.

CASE PRESENTATION

A 57-year-old man presented with a complaint of chest pain for 3 years. The patient had a medical history of asthma. Clinical examination revealed decreased breath sounds in the right upper area during lung auscultation. His laboratory findings showed eosinophilic leukocytes at 670/mm^3 (0-450) and C-reactive protein 29 mg/L (<5). Serum electrophoresis revealed hypergammaglobulinaemia of 5.31 g/dl (0.74-1.66). IgE level was higher than normal (131 IU/mL: <100).

A chest CT scan showed a 25-mm LN in the subcarinal (SC) region and areas of consolidation in the right upper lobe of the lung (Figure 1a). An 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG PET) scan showed increased 18F-FDG uptake in the SC LN (SUVmax 7.7) in the areas of consolidation of the lung (SUVmax 11.5) and in the right pleural effusion (Figure 1b). In the abdomen, there was increased 18F-FDG uptake around the abdominal aorta and at the pancreatic head (Figure 1. c, d). An endobronchial ultrasound detected a smooth-edged rounded LN with a diameter of 14 mm in the SC area. A transbronchial needle biopsy of these LN was reported as normal in the pathologic evaluation. Video-assisted thoracoscopic surgery was performed for the diagnosis of the patient. Histologic examination of the lung biopsy material and SC LN showed infiltration of IgG4-positive plasma cells with an IgG4 to IgG ratio of more than 40%. Hematoxylin and eosin-stained slides of our case was examined by the pathologist considering the diagnostic criteria for IgG4-RD [3] (Figure 2a). Blood examinations after histopathology results revealed a high serum IgG4 concentration at 977 mg/dL (8-140 mg/dL).

The diagnosis of IgG4-RLD was made based on histopathological results and the high serum concentration of IgG4. The patient was then managed with steroids. The patient was seen in the cardiology department due to chest pain 6 weeks after starting treatment. The patient underwent coronary artery bypass surgery at this center. At the end of histopathology of coronary artery biopsy, lymphaplasmociter infiltration with focal area IgG4 between large vessel structures surrounded by lipomatous tissues and striated muscle bundles was reported consistent with IgG4-RD (Figure 2 b). After six months, the patient was healthy and symptom free.

Address for Correspondence: Ekrem Cengiz Seyhan, Department of Chest Diseases, Ministry of Health, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Turkey
E-mail: drekremcs@yahoo.com

IgG4 serum levels, PET-CT results and Chest-CT scan showed that the symptoms had almost completely disappeared (Figure 3). The changes provided the meaning we intended.

Written informed consent was obtained from the patient for publication.

DISCUSSION

IgG4-RD is a systemic fibroinflammatory disease that has been recognized in recent years [1]. Autoimmunity is one of the potential immunostimulants in IgG4-RD [4]. High IgE and eosinophil levels and a history of allergic disease should be considered in the diagnosis of IgG4-RD [5]. We found that the IgE and eosinophil levels were high in our case. In addition, the patient had a history of asthma.

IgG4-RD has been described in almost every organ system [1]. Some patients may have a single organ involvement, whereas others may have several organs affected by IgG4-RD [6]. We found multiple organ involvement in our case: LN, pulmonary parenchyma, pleura, pancreas, and cardiovascular organ involvement.

IgG4-RLD can be found in various forms based on the organ system affected, i.e., parenchyma: nodules or masses or interstitial pneumonia and bronchiectasis; respiratory: tracheobroncheal stenosis; pleura: pleural nodules or effusions; and mediastinum: LN or fibrosing mediastinitis [7-9]. Reference is made to the affected area of the lung of the first element and the second to the form of the disease. For example, the pleura has been identified as the region, and pleural effusion has been identified as the disease form.

The most common intrathoracic manifestation in IgG4-RD is mediastinal LN, defined in 40 to 90% of the patients with IgG4-RD [10]. In our case, IgG4-RD had different manifestations such as LN, parenchymal consolidation, and pleural effusion.

Laboratory findings in IgG4-RD are generally not conspicuous. Polyclonal hypergammaglobulinemia is frequently observed in IgG4-RD. Increased serum IgE and eosinophil levels have been reported in approximately 30% of IgG4-RD patients [5]. We found that in our case, the IgE and eosinophil levels were high, and hypergammaglobulinemia was also present.

High IgG4 concentration (>140 mg/dL) is seen in most of the patients with IgG4-RD; however, 25% of the patients display normal IgG4 levels [11]. High serum IgG4 levels may support the diagnosis of IgG4-RLD but not necessarily so. One study

MAIN POINTS

- Immunoglobulin (Ig)G4-related disease (RD) is a newly recognized systemic fibroinflammatory disease that can affect any organ.
- Although the frequency of pulmonary involvement is not known, the disease can affect the lung parenchyma, airways, pleura and mediastinum.
- The presence of a dense lymphoplasmocytic infiltrate, irregular fibrosis and obliterative phlebitis are important for diagnosis. Definite diagnosis requires the presence of more than 40-50% IgG4 positive tissue plasma cells.
- A high index of suspicious is required particularly in the setting of patients with fibroinflammatory systemic involvement.
- The mainstay of treatment is corticosteroids, with most patients demonstrating a good initial response.

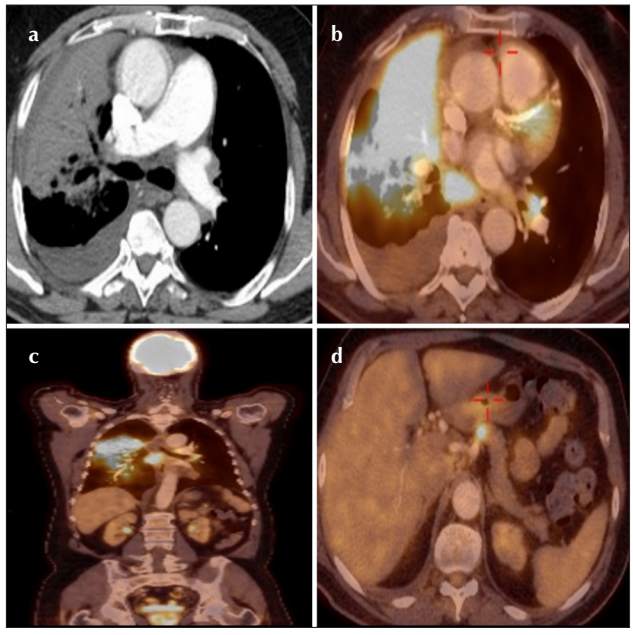

Figure 1. a-d. Chest CT scan showing areas of consolidation in the posterior segment of right upper lobe of the lung and pleural effusion (a). PET scan revealing increased 18F-FDG uptake in the subcarinal lymph nodes and in the consolidation areas in the posterior segment of right upper lobe (b), soft tissue formation around the abdominal aorta (c), and soft tissue area at the pancreatic head (d)

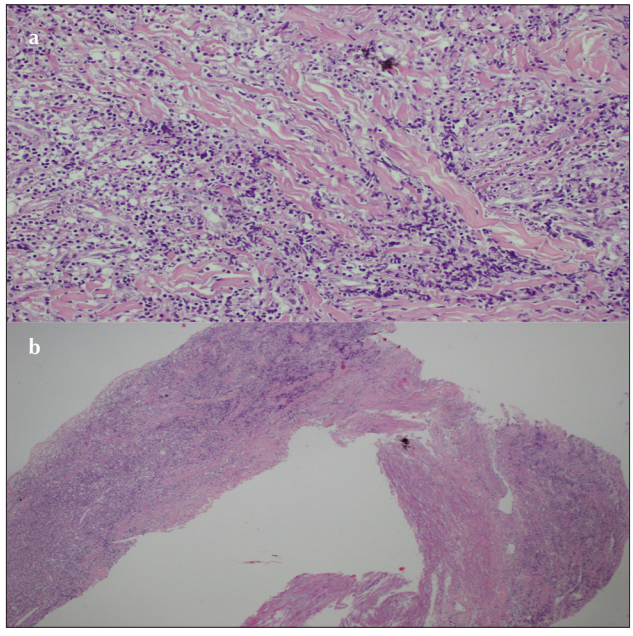

Figure 2. a, b. Histologic examination of lung specimens (right lung middle lobe) showing dense lymphoplasmacytic inflammation rich in plasma cells with storiform fibrosis and obliterative phlebitis (hematoxylin and eosin=H&E stain x 400) (a). Immunostaining also detected numerous aggregates of IgG4+ lymphocytes and plasma cells in the same sample of the coronary artery biopsy (H&E x 40) (b)

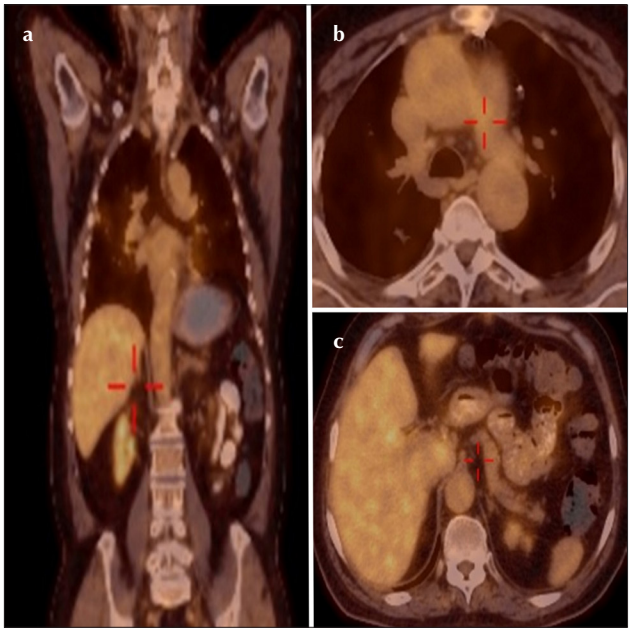

Figure 3. a-c. PET scan revealing metabolic involvement was not detected in the subcarinal regions, areas in the right lung, head of the pancreas, and around the abdominal aorta (a-c)

of IgG4-RD patients demonstrated that serum IgG4/IgG ratios >8 % had a sensitivity of 97.0 and 95.5%, respectively [12]. Our patient had high levels of IgG4 (977) and IgG4/IgG ratio >8 (9.1).

IgG4-RD has also been reported to show high 18F-FDG uptake in diseased sites [13]. Although SUV may increase in inflammatory and malignant lesions, PET-CT remains a valuable tool for determining the extent of a lesion in IgG4-associated disease [14]. The PET-CT findings can aid in the diagnosis of diseases of the pancreas and aorta, as in our case. The use of PET-CT was found to be very helpful in the involvement of the extrapulmonary organs in our case.

Histopathology is the gold standard for diagnosing IgG4-RD [3]. Histopathologic analysis includes lymphoplasmacytic infiltrates, storiform fibrosis, obliterative vascular lesions, as well as IgG4/IgG ratio ≥40 % and IgG4-positive plasma cell numbers per high-power field ≥10, meeting the criteria according to the Consensus Statement on Pathology of IgG4-RD [14]. Our case met the diagnostic criteria.

Glucocorticoids are the first drugs of choice for the treatment IgG4-RD, and most patients respond well to this treatment [15]. There have been reports about successful treatment with other immunosuppressive drugs in patients with resistant IgG4-RD [16]. We started systemic glucocorticoid therapy in our patient who showed clinical and radiological improvement at the end of treatment.

In conclusion, lung is the target organ of IgG4-RD, which should be considered as a differential diagnosis of unknown etiology in patients with diffuse or localized fibroinflammatory lung disease.

Informed Consent: Written informed consent was obtained from the patient who participated in this case.

Author contributions: Concept - E.C.S., M.A.Ö.; Design - E.C.S., D.T Supervision - M.A.Ö.; Resource - E.U., D.T.; Materials - N.Ü., E.U .; Data Collection and/or Processing - E.C.S., M.A.Ö.; Analysis and/or Interpretation- N.Ü; E.U; Literature Search - N.Ü., E.C.S.; Writing - E.C.S.; Critical Reviews - M.A.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support

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