Case Report

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A case of immunoglobulin G4-related lung disease with normal serum immunoglobulin G4 level and hybrid radiological findings

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Abstract:

Pulmonary involvement in immunoglobulin (Ig) G4-related disease is very rare and usually in the form of parenchymal infiltrates. Symptoms vary according to the location and severity of the infiltration. Previously, the radiological findings were categorized as solid nodule or mass, ground-glass opacity, interlobular septal, or bronchovascular bundle thickening. However, in some patients, all forms of radiological findings present at the same time. We do not know whether it is a type of disease or whether there is a difference in the disease course. Here, we present a patient, with normal serum IgG4 level, acute-subacute respiratory symptoms, extensive parenchymal consolidation in chest computed tomography, and intensive IgG4-positive-lymphoplasmocytic-infiltration in lung biopsy and the result of 6-month methylprednisolone and methotrexate treatment for IgG4-related lung disease.

Keywords:

Immunoglobulin G4, immunoglobulin G4-related lung disease, pulmonary nodule, radiological manifestations, steroid

Introduction

Immunoglobulin G4-related disease (IgG4-RD), described by Hamano in a patient with pancreatitis in 2001, is now a better-known fibro-inflammatory disease.[1] However, there are still many unknowns about the disease. Symptoms vary according to the location and severity of the infiltration. Pulmonary involvement is very rare and usually in the form of parenchymal infiltrates. Radiological findings were categorized as solid nodule or mass, ground-glass opacity, interlobular septal, or bronchovascular bundle thickening. However, in some patients, all forms of radiological findings present at the same time. These radiological hybrid findings make the diagnosis of this disease even more difficult. We do not know whether there is a difference in the disease course in cases with hybrid radiological findings. A biopsy is required because it is not possible to make a definitive diagnosis with current clinical, laboratory, and radiological findings. Even after biopsy, a multidisciplinary evaluation is mandatory. Here, we present a patient, with normal serum IgG4 level, acute-subacute respiratory symptoms, extensive parenchymal consolidation in chest computed tomography (CT), and intensive

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IgG4-positive-lymphoplasmocytic-infiltration in lung biopsy and the result of 6-month methylprednisolone and methotrexate treatment for IgG4-related lung disease.

Case Report

A 43-year-old female with dyspnea, cough, and sputum for a month administered to our outpatient clinic. She was a housekeeper and a smoker. She had no major comorbidity. She was taking ergotamine for migraines. She denied having a hobby or a pet. There was no feature in family history.

She used antibiotics for pneumonia in the last month, but there was no improvement in her symptoms. The oxygen saturation was 98% at room air and the respiratory rate was 20 per minute. The blood pressure and the heart rate were in normal ranges. There were crackles over the bases of the chest wall. Biochemical tests and blood cell count revealed mild leukocytosis. C-reactive protein, sedimentation, IgG, and IgM levels were high. There was no peripheral eosinophilia. Serum IgG4 (121 mg/dL) level was normal. Posterior-anterior chest X-ray showed bilateral radio-opacity in lower zones. We observed enlarged lymph nodes in the mediastinum, consolidations located in the peripheral region of the lungs and nodules and thickened-bronchovascular bundles in the lower lobes and minimal pericardial and pleural effusion [Figure 1]. Peritonitis and hepatomegaly and a nodular lesion in the adrenal gland were present in abdominal CT. We determined hypermetabolic activity in lower lobes of the lung, aortic arch, ascending aorta, and mesenteric fat tissue in positron emission tomography CT. She had a moderate restriction (forced vital capacity [FVC]: 58%). We performed bronchoalveolar lavage and cytologic evaluation revealed 61% alveolar macrophages, 20% lymphocyte, 16% neutrophil, 3% eosinophils, and 3% with no any atypical or malignant cell. The microbiological cultures were negative. She had no symptom or sign, suggestive of rheumatological disease. The serum levels of anti-nuclear antibody, anti-neutrophil cytoplasmic antibody (ANCA), anti-cyclic citrullinated peptide, and rhemotoid factor were all normal. Surgical biopsy revealed lymphohistiocytic inflammatory infiltrate and scattered fibrotic areas containing a large number of plasmocytes distributed throughout the pleura, interlobular septum, bronchovascular bundles, intimal endothelial inflammation in vessels within the lung parenchyma [Figure 2]. The number of IgG4-positive plasma cells was evaluated as an average of 51 in 3 high-power fields. After a multidisciplinary council, we considered IgG4-related lung disease. She started on methylprednisolone (40 mg/day) and methotrexate (15 mg/week). Her respiratory symptoms improved and she is still taking methylprednisolone (4 mg/day) and methotrexate with some acceptable side effects. Just before the initiation the treatment, forced expiratory volume in 1 s (FEV1) was 47% and FVC was 41% and at the 6 months of the treatment, FEV1 was 40% and FVC was 41%. Most of the radiological findings improved and were replaced by fibrotic sequelae [Figure 3].

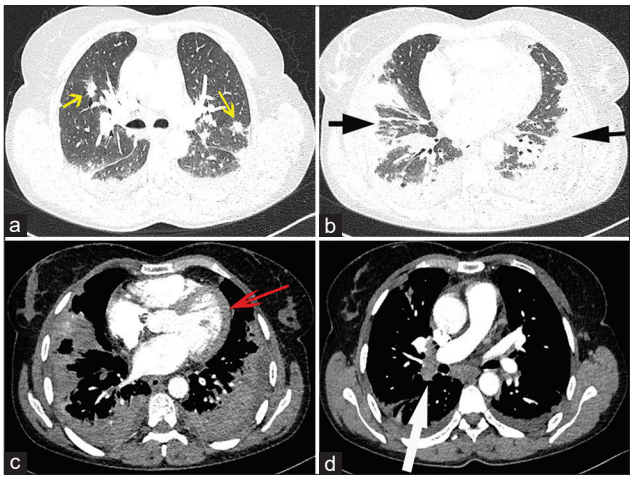

Figure 1: (a) Pulmonary nodules surrounded by ground-glass opacity, shown by a yellow arrow (b) Bilateral subpleural consolidations, shown by black arrows (c) Pericardial effusion, shown by a red arrow (d) Hilar lymph nodes, shown by a white arrow, in chest computed tomography

Discussion

IgG4-RD is a multisystemic inflammatory disease characterized by intense IgG4-positive lymphoplasmocytic infiltration in various tissues, often accompanied by high serum IgG4 levels.[2] The most

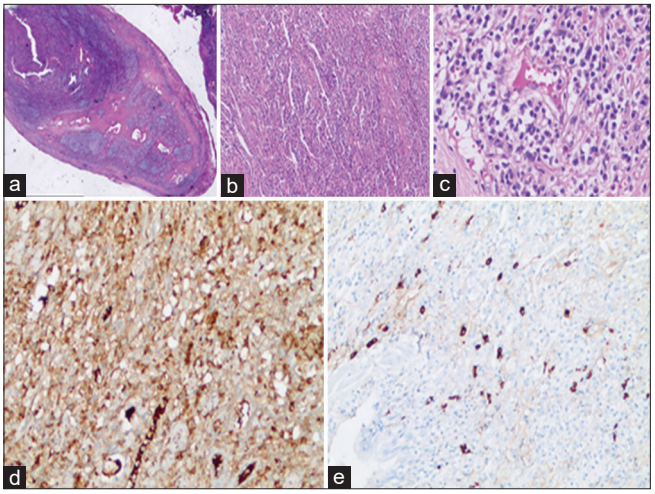

Figure 2: Lymphohistiocytic inflammatory infiltrates with numerous plasmocytes distributed throughout the pleura, interlobular septum, and bronchovascular bundles were shown (a) ×20 H and E, (b) ×100 H and E, (c) ×400 H and E. The plasma cells were diffusely positive with immunoglobulin G (d) whereas scattered immunoglobulin G4 immunoreactive plasma cells were detected (e) ×200

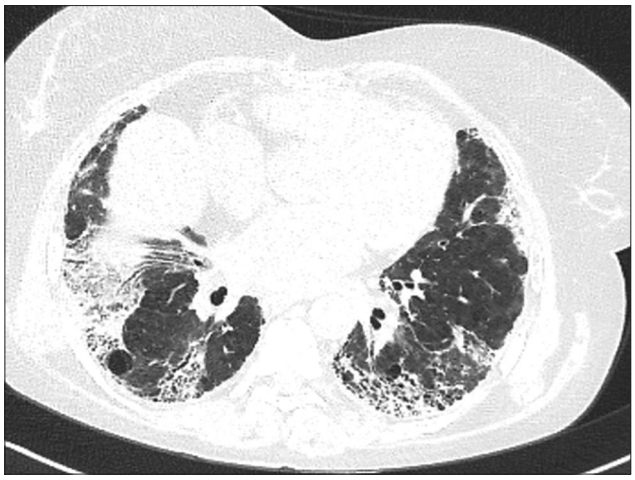

Figure 3: Fibrotic changes with bronchiolectasis and peribronchial thickening in the control chest computed tomography

commonly affected organs are the pancreas and salivary glands. Lung involvement is relatively uncommon.[3] The symptoms vary based on the involved organ and the severity of the involvement. Even some patients are asymptomatic. Almost every organ involvement has been reported so far.[4] IgG4-RD develops usually in the middle-ages and more common in males.[5] Patients with lung involvement may have symptoms such as cough, dyspnea, hemoptysis, and chest pain. Serum IgG4 is usually high, with a level of more than 140 mg/dL. Besides, it can be normal in 25%.[6] Hence, elevated IgG4 levels support the diagnosis but are not essential for it. In a previous study, researchers used the IgG4/IgG ratio and suggested that IgG4/IgG ratio >0.08 had a high sensitivity (97%) and specificity (95.5%).[7] Our patient was a young female, suffering from dyspnea and cough for a month and she had a normal serum IgG4 level and IgG4/IgG ratio was 0.052.

The most common chest CT finding is mediastinal lymphadenomegaly that is present up to 40%–90%. Previously, the radiological findings of the patients were divided into 4 different categories: solid nodular mass, ground-glass opacities, alveolar interstitial type, and bronchovascular type.[8] Nodularity in pleura, pleural effusion, and fibrosing mediastinitis are the other forms of intrathoracic involvement that has been reported so far. Later, Zhou *et al*. reported a case with all types of radiological features (nodule, mass, halo sign, and interlobular septal thickening) and suggested that this hybrid type of IgG4-RD was different from other reported cases.[9] Similarly, our patient also had a hybrid of near all radiological findings. The radiological findings were more suggestive for eosinophilic pneumonia or cryptogenic organizing pneumonia rather than IgG4-RD, and moreover, serum IgG4 level was also normal. However, she had all the characteristic histopathological features of IgG4-RD. Biopsy was not compatible with Castleman disease, lymphoma with lymphomatoid granulomatosis, or inflammatory myofibroblastic tumor, which are the mimickers of IgG4-RD. Multicentric Castleman's disease, ANCA-associated vasculitis, nonspecific interstitial pneumonia, and Rosai–Dorfman disease were in the differential diagnosis because in also these diseases, IgG4 positive cell infiltration in the lung is possible. However, the histopathological findings of IgG4-related lung disease are well described, and critical histopathologic features of IgG4-RD are a dense lymphoplasmacytic infiltration, storiform fibrosis, and phlebitis with obliteration. Clinicians and pathologists on this council decided, based on clinical, laboratory, radiological, and pathological findings, that it was unlike the diseases mentioned above and that it was IgG4-associated lung disease. Sometimes, even in the case of tissue sampling, the diagnosis may be challenging, therefore, the pathological diagnosis should be confirmed by clinicians in a multidisciplinary council.

The clinical course and effective treatment of this hybrid type may be different. In general, the mainstay of the IgG4-RD treatment is steroids. Patients with IgG4-RD lung disease generally respond favorably to prednisone treatment. Cyclophosphamide, azathioprine, and mycophenolate mofetil can be added to the treatment in case of resistance or steroid-sparing effect. Bortezomib has been reported to enable symptomatic improvement recently.[10] In our patient, we started methylprednisolone and methotrexate. After a while, with methylprednisolone and methotrexate, symptoms and respiratory functions improved significantly and radiological findings regressed with widespread fibrotic changes.

Conclusion

IgG4-RD is a rare fibro-inflammatory disease with various symptoms, radiological findings. Serum IgG4 is generally high but can be normal. Radiological findings may mimic eosinophilic pneumonia, cryptogenic organizing pneumonia, granuloma, hamartoma, sarcoidosis, and lung cancer. We do not know the importance of hybrid radiological findings. Besides this, the pathological differentiation of IG4-RD from some other diseases with IgG4-positive-lymphoplasmocytic-infiltration may not be so easy. Hence, a multidisciplinary approach is essential for a correct diagnosis.

Informed consent

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Declaration of patient consent

The authors certify that they have obtained all appropriate

patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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