Case Report

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High Level of IgG4 in a Patient with Extensive Pulmonary Involvement

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ABSTRACT

Immunoglobulin G4-Related Disease (IgG4-RD) is a systemic fibro-inflammatory disease that has been proposed as a separate entity since the beginning of this century. The disease is often manifested by increased serum IgG4 levels and certain histopathological manifestations. The patient mentioned in this article is a 29-year-old man from Tajikistan, who has had a chronic cough since the beginning of 2018 without a previous history of the disease. At first, he was diagnosed with pneumonia for a long time and then underwent a lung biopsy due to exacerbation of symptoms and the spread of lung lesions in radiology but no abnormalities were found in these evaluations. The patient traveled to Iran to continue his treatment. He was re-evaluated and then the previous samples taken from the patient's lung tissue were re-examined. Here are the key findings in favor of diagnosing IgG4 RD. Evaluations did not confirm the involvement of other organs. He was first treated with steroids and due to recurrence of symptoms, he was treated with rituximab once which was significantly effective in improving the patient's clinical symptoms. In general, it can be concluded that the diagnosis of IgG4-RD is very challenging and if it has not been diagnosed and treated in time, it can lead to irreversible fibrosis and permanent loss of function of the involved organ.

Keywords: Fibro-inflammatory disease, Immunoglobulin G4-related disease, Rituximab

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INTRODUCTION

IgG4-RD with a fibro inflammatory mechanism is mostly seen in middle-aged and elderly people that 90% of cases fall into the age group of 50-80 years (1). It should be noted that IgG4-RD in children is generally unknown among pediatricians, nevertheless, several cases have been described (2). The proportion of men to women varies, according to the involvement of different organs. Autoimmune pancreatitis is more common in men (3) and Sialadenitis and Dacroadenitis are more common in women (4). IgG4-RD first appeared in 2001 in patients with sclerosing pancreatitis with elevated IgG4 levels in serum (5) In addition, cases such as Mikulicz's disease (6) Riedels' thyroiditis (7), which was later included in this classification, were known around the 1800S. Since 2008,

a new classification called IgG4 positive multi-organ lymphoproliferative syndrome has been proposed by Japanese experts that could explain a wide range of previous involvements in various organs.

The basis of the pathogenesis of the disease is defined as the interaction of the innate immune system with adaptive immunity in the patient. Initially, foreign (exogenous) antigens which known as pathogen-associated molecular patterns (PAMP) and endogenous autoantigens as damage-associated molecular patterns (DAMP) are recognized by surface receptors on peripheral blood mononuclear (PMN) cells, including Toll-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptor (NLR), which can induce the production of B-cell-activating factor (BAFF) by activating B cells, leading to increased production of IgG4 (8). The interaction of B cells and the T cells are also an important part of the pathogenesis. Two types of T cell CD4, that are effective in the development of the disease, consist of cytotoxic CD4 (CTLs) and follicular T-helper (TFH). CTLs can interfere with the secretion of profibrotic proteins such as IFN-γ, IL-1β, and TGF-β in the process of fibrosis. The interaction and activation of B and T cells can increase the production of IL-4 and IL-10, which are capable of inducing more IgG4 production by plasma cells (9).

In 40% of cases, the disease affects only one organ (10) and in other cases, several organs are involved. The symptoms in each case can be the result of organomegaly or organ dysfunction due to cell infiltration and fibrosis (11, 12). Since 2012, an international consensus has defined the general criteria as comprehensive diagnostic criteria for the diagnosis of the disease (13). However, the diagnosis of the disease is very difficult and challenging, especially in organs that are not available for biopsy, so new criteria called organ-specific diagnostic criteria are designed, which are defined separately for each organ (14). The progression of the disease is very slow and gradual, therefore the organ dysfunction may be irreversible at the time of diagnosis as seen in the patient reported in this article. Furthermore, the occurrence of secondary amyloidosis in some of the organs such as kidneys following the increase and deposition of serum amyloid A (SAA), is another complication observed during the disease (15)

CASE REPORT

The patient was a 29-year-old athlete man from Tajikistan, who has had a history of consecutive sputum cough and hemoptysis without any history of lung disease since the first months of 2018. The patient was diagnosed with pneumonia and treated with antibiotics several times. Gradually, the hemoptysis was stopped, but the cough was continued. For this purpose, he was hospitalized in Tajikistan to study the etiology of the disease and according to the extent of the lesion in the radiology performed, he was a candidate for a lung biopsy (Figure 1A, Figure 1B). The tissue sample obtained was negative for common and unusual infections, especially Mycobacterium Tuberculosis (MBT) and the possibility of lung malignancy. The sample was sent to Russia for further evaluation, which ultimately ruled out the diagnosis of lung cancer for the patient. With the intensification of cough and increased sweating and pain, the patient occasionally traveled to Iran to continue his treatment and was admitted to a hospital in Tehran. Owing to the patient's reluctance to repeat the lung biopsy, the slides taken in Russia were re-observed.

The result of the new report was as follows: Fibro inflammatory process associated with obliterative inflammation of vessel, presence of polyclonal lymphoplasmacytic population, and IgG4-positive plasma cells (up to 40/HPF), and the presence of few necrotizing granulomas. Thus, no changes in favor of malignancy were reported in the pathology specimen. A complete evaluation

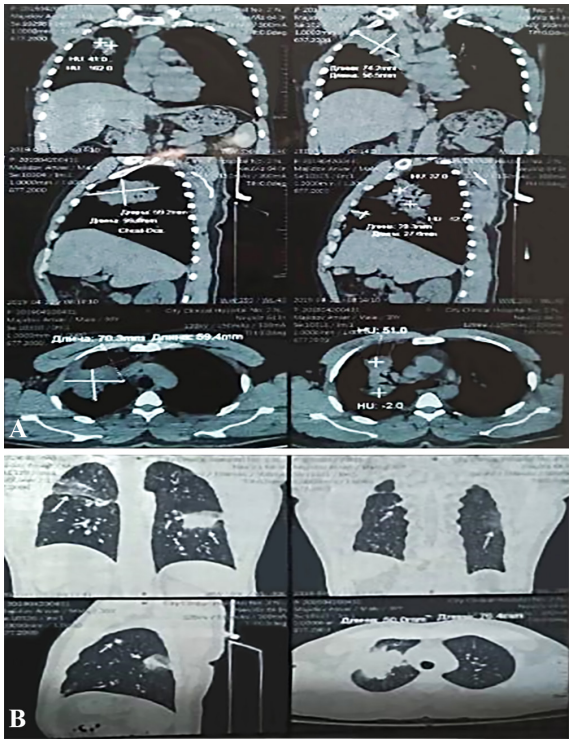

Figure 1. Description of lung lesions in the patient. Initial contrast-enhanced CT revealed a mass-like lesion in the right lung (A). Initial CT. A lung window scan reveals mass-like lesions in right and left lung (B).

was performed for the patient in terms of infections and collagen vascular diseases such as Antineutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis, but the results were not in favor of a specific disease. The only positive point in all examinations was that abnormal ESR and CRP were reported, for which no reason was found. The patient was then referred to another medical center for further evaluation. In the second center, a complete examination was performed several times, and the clue of immune dysregulation was reported in the patient's pathology results, possibly due to primary and secondary immune defects. According to the report of plasma cells containing IgG4 in pathology, humoral immunoassay was performed with more accuracy. The initial responses obtained from the measurement of patient immunoglobulins were as follows: Total IgG: 1015 (700-1600), IgA: 219 (70-400), IgM: 124 (40-230), IgE: 36 (<188), IgG4: 447 (62-1127) and IgG4/IgG: 0.44. Finally, based on histopathology, clinical signs, and IgG4> 135, the diagnosis of definite IgG4-RD was made for the patient based on comprehensive diagnostic criteria.

The patient was first treated with high-dose corticosteroids and then the dose was gradually reduced. The patient had significant clinical improvement at the beginning of treatment, but due to the recurrence of symptoms on corticosteroid therapy, the patient was a candidate for treatment with B cell-depleting biologic drugs such as rituximab. The clinical manifestation of the patient significantly improved after the first course of rituximab and his ESR was significantly reduced. Finally, the patient returned to his country while receiving low-dose corticosteroids for a long time and his clinical and radiological improvements are being followed up in the next visits.

DISCUSSION

IgG4-RD is a fibro-inflammatory disease in which the main trigger of the immune system is not exactly known. Most patients diagnosed as middle-aged and elderly men are often in the 6th decade of their life (1). However, our patient is one of the few cases of this disease in his youth. Typical Histopathological change as mentioned earlier is the key to diagnose the disease in half of the patients (16). In contrast to the necrotizing feature of the disease, granulomatous inflammation and giant cells are atypical for the disease (10). Re-observation of the sample taken from our patient's lung tissue revealed both typical and atypical changes, which unfortunately were not mentioned in the initial pathology report.

According to studies, the disease is more common in organs such as lymph nodes, submandibular and lacrimal glands, pancreas, and retroperitoneum, and basically, the disease is systemic, which tends to involve several organs in the body (17). However, in our patient, the disease rarely started in the lungs and was not present in other organs

at the time of diagnosis. It should be noted that despite the general title of the disease, an increase in IgG4 level is not a specific criterion for this disease, and it is also increased in many non-IgG4-RD situations, including allergic diseases, collagen vascular diseases, autoimmune diseases, and malignancies (18). According to studies, although serum IgG4 level has a specific and low positive predictive value (PPV) for disease diagnosis (19), it is a good and reliable criterion for determining disease activity and predicting flare attacks. Primary serum IgG4 levels indicate the extent of the disease and the number of organs involved and are a reliable marker to determine the patient's response to treatment (20). But it is interesting to note that serum IgG4 levels are normal in about half of the proven cases of the disease (17).

The disease progresses slowly and even in cases of multi-organ involvement may be asymptomatic for a long time, as seen in our patient (10). The initial report of the radiologist for our patient was bronchoalveolar carcinoma, which was not confirmed in the pathology report. According to studies, IgG4-RD pulmonary involvement is radiologically divided into two general categories: 1) Inflammatory pseudotumor 2) Interstitial pneumonitis. In addition, ground-glass lesions and interstitial fibrosis are other patterns of pulmonary involvement in these patients (21). The report of the inflammatory pseudotumor in the patient's lungs was another valuable point in favor of the pulmonary diagnosis of IgG4-RD. A definitive diagnosis of IgG4-RD in the lung requires a biopsy to differentiate the disease from other cases such as neoplasms, sarcoidosis, and Castleman disease with a pattern similar to pulmonary involvement.

Our patient was finally treated with a definitive diagnosis of IgG4 pulmonary disease. Corticosteroids are the basis of IgG4-RD treatment and failure to respond to corticosteroids is one of the criteria for rejecting the diagnosis. It should be noted that IgG4-RD has a recurrent nature and the risk of recurrence varies depending on the number of organs involved and the concentration of IgG4 at the time of diagnosis (10). According to the same treatment plan, the reported patient was first treated with high-dose corticosteroids and then due to the recurrence of symptoms following a reduction in corticosteroid dose, he was once treated with rituximab which dermatologically improved the patient's symptoms. To prevent a recurrence, the patient underwent maintenance treatment with corticosteroids for a long time. Continuation of clinical and, radiological improvement and possible recurrence of symptoms in the lung or involvement of other organs will be followed up at subsequent visits.

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