

## An unusual case of IgG4 Syndrome with a frontal mass

Zahra Mirfeizi<sup>1</sup>, Elham Atabati<sup>2\*</sup>, Mohammad Reza Hatef<sup>1</sup>, Kamila Hashemzadeh<sup>3</sup> and Zhaleh Shariati-Sarabi<sup>1</sup>

<sup>1</sup>Associated Professor of Rheumatology, Rheumatic Diseases Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; <sup>2</sup>Fellowship of Rheumatology, Mashhad University of Medical Science, Mashhad, Iran; <sup>3</sup>Assistant Professor of Rheumatology, Rheumatic Diseases Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

IgG4-positive plasma cell infiltration has been observed in patients with other conditions, including retroperitoneal and mediastinal fibrosis, inflammatory pseudotumor of the lungs and liver, Küttner tumors, and interstitial nephritis, indicating that these diseases and conditions collectively constitute a new disease concept known as "IgG4-related disease". The aim of this study was to present a case of a typical IgG4 syndrome. The case presentation involves a 33-year-old man with a soft tissue mass (3×4 cm) on the right side of his frontal area which had enlarged over the space of a year. He had not experienced any allergic disorder, weight loss, night sweating, or anorexia, and did not smoke or use illicit drugs. On examination his vital signs were normal. He had no complains of fever, rash or urticaria. The soft, round mass in the right side of the frontal area had no pain and tenderness, redness, or discharge for the year. Other examinations gave normal results. He was then referred to a rheumatologist. In further laboratory work, high IgG4 level (119.6; normal range: 5.9-86) was detected and in histopathological studies, chronic inflammation, fibrosis, lymphomononuclear and eosinophilic infiltration with a dilated vascular network were reported.

**Keywords:** chronic inflammation, frontal mass, IgG4-RD.

### Introduction

In 1892, Dr. Johann von Mikulicz, also known as Jan Mikulicz-Radecki, published a paper describing a patient with symmetrical swelling of the lacrimal, parotid, and submandibular glands, along with massive infiltration of these glands by mononuclear cells [1]. Following reports describing similar patients, this condition was named "Mikulicz's disease" (MD). In contrast, patients with similar symptoms, but with diseases such as leukemia, malignant lymphoma, and sarcoidosis were reported to have Mikulicz's syndrome [2]. In 1930, Dr. Henrik Sjögren, an ophthalmologist, published a paper describing a woman with rheumatoid arthritis accompanied by keratoconjunctivitis sicca and severe swelling of the parotid glands, a condition that has been recognized as Sjögren's syndrome (SS) [3]. In 1953, Morgan and Castleman examined 18 patients with MD and concluded that this condition is another manifestation of SS [4]. Since then, MD has attracted very little interest in western countries. In Japan, however, there have been many patients suffering from

MD, such that the differences between MD and S S have been clarified [5, 6]. For example, their gender distribution is quite different and MD occurs in both men and women. Following the description of a patient with chronic pancreatitis caused by an autoimmune mechanism [7], lymphoplasmacytic sclerosing pancreatitis (LSP) was found to be a characteristic histopathological finding in patients with autoimmune pancreatitis (AIP) [8]. These findings led to the concept of AIP, which has characteristics similar to those of other autoimmune diseases, such as hypergammaglobulinemia, the presence of various auto antibodies, lymphocytic infiltration into pancreatic tissue, and good responsiveness to steroids [9]. Following a report showing elevated serum IgG4 concentrations in patients with AIP [10], the pancreatic research team of the Ministry of Health, Labor and Welfare of Japan (MHLW Japan) disclosed that AIP was related to IgG4 levels [11].

IgG4-positive plasma cell infiltration has also been observed in patients with other conditions, including retroperitoneal and mediastinal fibrosis [12, 13],

\* Corresponding Author: Elham Atabati, Email: [atabatiE931@mums.ac.ir](mailto:atabatiE931@mums.ac.ir), Tel: +98 5138012753, Fax: +98 5138410136

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inflammatory pseudo tumor of the lungs and liver [14], Küttner tumor [15], and interstitial nephritis [16], thus indicating that these diseases and conditions collectively constitute a new disease concept known as IgG4-related disease (IgG4-RD).

These findings have led to the establishment of two study groups by the MHLW Japan to analyze the condition of IgG4-RD and to establish the diagnostic criteria for IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS).

The two teams reached a consensus which stated that IgG4-RD can occur in various organs, including the central nervous system, salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tract, kidneys, prostate gland, retroperitoneum, and lymph nodes, but that clinical symptoms depend on the location of the lesion (Table 1). IgG4-RD mainly affects middle-aged to elderly men. Its clinical symptoms are relatively mild, and the condition usually comes to clinical attention as a result of organ swelling or damage. Many patients with IgG4-RD are treated effectively with steroid therapy. Although the infiltration of IgG4-positive cells and increased serum concentrations of IgG4 are characteristics of IgG4-RD, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis and obliterative phlebitis are characteristics of pancreatic, biliary tract, and retroperitoneal lesions, but are very seldom found in the salivary glands or lymph nodes.

**Table 1.** Clinical Manifestations of IgG4-related disease

Salivary glands
Mikulicz disease
Chronic sialadenitis (Küttner tumor)
Orbit
Lacrimal glands
Mikulicz disease
Chronic dacryoadenitis
Idiopathic orbital inflammation (pseudotumor)
Lymphoid hyperplasia
Perineural spread (trigeminal nerve branches)
Sinonasal cavities
Thyroid gland
Hashimoto thyroiditis
Riedel thyroiditis
Pituitary gland
Hypophysitis (pituitary stalk/gland)
Larynx (submucosal lesion)
Lymph nodes

## Case report

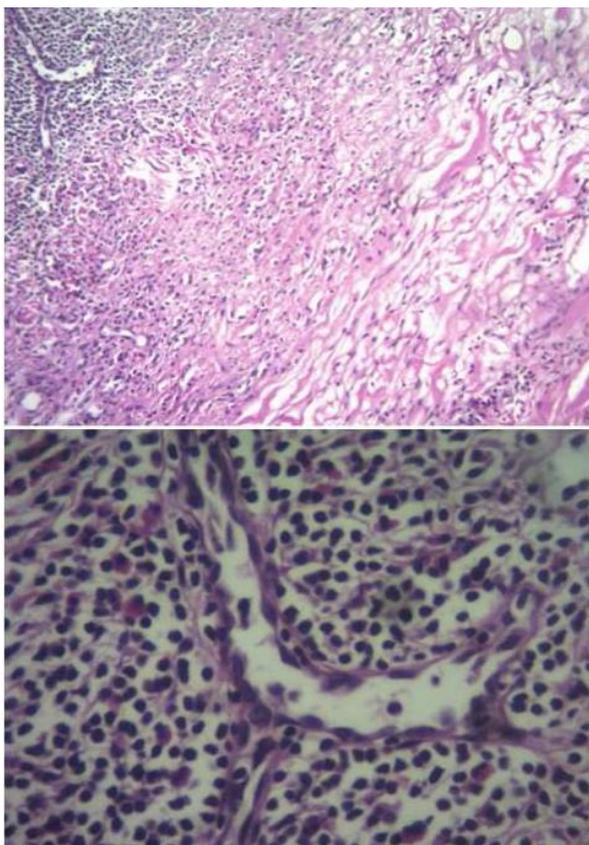
The case presentation involves a 33-year-old man with a soft tissue mass (3×4 cm) on the right side of his frontal area which had enlarged over the space of a year (Table 1). He had not experienced any allergic disorder, weight loss, night sweating, or anorexia and did not smoke or use illicit drugs. On examination his vital signs were normal. He had no complaints of fever, rash or urticaria. A soft, round mass was present on the right side of his frontal area without any pain, tenderness, redness, or discharge over the year. Other examinations were immaterial.

Regarding lab studies, white blood cell count was 8,300 with normal differentiation; hemoglobin level was 16.4g/dl, the platelet count was 204,000 per cubic millimeter; the blood urea nitrogen level was 15 mg/dl, and the creatinine level was 0.6 mg/dl. A liver function test was performed and it showed an alanine aminotransferase level of 75 mg/dl, aspartate aminotransferase level of 30 mg/dl, and alkaline phosphatase of 179 mg/dl. The C-reactive protein level and the erythrocyte sedimentation rate were both normal. Anti-nuclear profile matching was carried out and was also found to be normal. PCR for tuberculosis and the serology test results for viral hepatitis, EBV, CMV and HIV were all negative.

A brain and posterior nasal CT scan was done and showed no abnormality. The patient was then admitted to the otorhinolaryngology ward to undergo a diagnostic biopsy where the fine needle aspiration result was reported as negative for malignant cells. He was then referred to a rheumatologist, by whom a multi-organ evaluation was carried out, which resulted in no major findings. In further laboratory work, the rheumatologist found high IgG4 levels (119.6; normal range: 5.9-86) and in histopathological studies, chronic inflammation and fibrosis infiltrated by lymphomononuclear cells and many eosinophils with a dilated vascular network were reported (Fig. 1).

## Discussion

Immunoglobulin G4 (IgG4)-related disease is a systemic disease that is characterized by the abundant infiltration of IgG4-positive plasma cells and lymphocytes with associated fibrosis, leading to organ dysfunction. It has recently been established as a distinct clinico-pathological entity [17, 18]. IgG4-RD occurs predominantly in elderly men and is frequently associated with elevated serum IgG4 levels [19, 20]. One of the characteristics of IgG4-RD is its excellent response to corticosteroid therapy.



**Fig. 1.** Perivascular lymphoplasmocytic infiltration with eosinophils and fibrosis (H&E: a- $\times 100$ , b- $\times 400$ )

The head and neck are commonly involved with the IgG4-RD. Manifestations may occur anywhere in the head and neck, however, the disease most commonly involves the salivary glands, lacrimal glands, orbits, thyroid gland, lymph nodes, sinonasal cavities, and the pituitary stalk (Table 1) [21, 22], and less frequently, other areas such as the larynx.

The following pathologic entities have recently been included as part of the IgG4-RD spectrum:

**Table 2.** IgG4-related diseases are a family of immune-proliferative disorders

Type 1 autoimmune pancreatitis or AIP (IgG4-related pancreatitis)
IgG4-related sclerosing cholangitis
Mikulicz's disease (IgG4-related dacryoadenitis and sialadenitis)
Sclerosing sialadenitis (Küttner's tumor, IgG4-related submandibular gland disease)
Inflammatory orbital pseudotumor (IgG4-related orbital inflammation or orbital inflammatory pseudotumor)
Chronic sclerosing dacryoadenitis (lacrimal gland enlargement, IgG4-related dacryoadenitis)
A subset of patients with "idiopathic" retroperitoneal fibrosis (Ormond's disease) and related disorders (IgG4-related retroperitoneal fibrosis, IgG4-related mesenteritis)
Chronic sclerosing aortitis and periaortitis (IgG4-related aortitis or periaortitis)
Riedel's thyroiditis (IgG4-related thyroid disease)
IgG4-related interstitial pneumonitis and pulmonary inflammatory pseudotumors (IgG4-related lung disease)
IgG4-related kidney disease (including tubulointerstitial nephritis and membranous glomerulonephritis secondary to IgG4-RD)
IgG4-related hypophysitis
IgG4-related pachymeningitis

idiopathic orbital inflammation (inflammatory pseudotumor), orbital lymphoid hyperplasia, Mikulicz disease, Küttner tumor, Hashimoto thyroiditis, Riedel thyroiditis, and pituitary hypophysitis [8, 11, 14, 16, 17, 19, 20].

When IgG4-RD is suspected in a patient where the manifestations are in the head and neck, a search for further manifestations in other areas is very important as multiorgan involvement is frequently observed in such cases.

At present, the diagnostic criteria for IgG4-MD (Table 2), and those for IgG4-AIP type 1, have been established. Moreover, a consensus has been reached on two main diagnostic criteria for IgG4-RD, these are: serum IgG4 concentration  $> 135$  mg/dl; and  $> 40\%$  of IgG-positive plasma cells being IgG4-positive. The MHLW Japan team has proposed the guidelines for the diagnosis of IgG4-RD [21].

IgG4-RD usually presents itself subacutely and most patients are not constitutionally ill. Fever and increases in C-reactive protein levels are unusual. The disorder is often identified incidentally through radiologic findings or unexpectedly in pathological specimens.

In certain patients the disease is confined to a single organ for many years. Others may have known, or subclinical involvement, of other organs, in addition to the main organ involved. Patients with autoimmune pancreatitis may have pancreatic disease as the major focus of their illness, whereas additional examinations have revealed that 30% also have tubulointerstitial nephritis, indicated by a distinctive radiologic appearance and the presence of mild proteinuria and nonglomerular hematuria [22, 23].

The involvement of multiple organs may be evident at diagnosis but can also evolve in a metachronous manner over several months or years. Spontaneous improvement is reported in a minority of cases and sometimes leads to a clinical resolution of certain organ-system manifestations [24]. A condition identified in the 1960s as multifocal fibrosclerosis [25] is now regarded more appropriately in most cases as IgG4-RD.

Two common findings in IgG4-RD are tumefactive lesions and allergic diseases. IgG4-RD appears to account for a substantial proportion of tumorous swellings in many organ systems [18, 21, 25]. Many patients with IgG4-RD have allergy related issues such as atopy, eczema, asthma, and modest peripheral-blood eosinophilia [23]. Up to 40% of patients with IgG4-RD have allergic diseases such as bronchial asthma or chronic sinusitis [17].

IgG4-RD often causes major tissue damage and can lead to organ failure, but it generally does so subacutely. Untreated IgG4-related cholangitis can lead to hepatic failure within a matter of months. Similarly, IgG4-related aortitis can cause aneurysms and aortic dissections, and is believed to be associated with around 10 to 50% of cases of inflammatory aortitis. The natural history of IgG4-related tubulointerstitial nephritis has not been defined comprehensively, but substantial renal dysfunction, and even renal failure, can ensue [16]. Destructive bone lesions that mimic granulomatous polyangiitis (formerly known as Wegener's granulomatosis) or tumors in the sinuses, head, and middle-ear spaces have also been reported [26], but less aggressive lesions take precedence in most organs.

Over the past decade a number of previously thought unrelated diseases have been recognized as a spectrum of a single disease. Terminology and diagnostic criteria have since been worked out. However, as with every "new" disease, a lot of enthusiasm arises, which can lead to the situation that uncommon conditions are not only not under-diagnosed, but are eventually over-diagnosed. While it is straightforward for most IgG4-RD manifestations to be accepted as part of the IgG4-RD spectrum, for other manifestations, no final conclusion can yet be drawn, as only few cases have been reported so far.

Therefore, within the future it has to be clarified whether all of the nowadays suspected diseases truly belong to the IgG4-RD spectrum.

Currently, glucocorticosteroids are considered as the first line therapy, but randomized trials to determine the optimal dose and duration are still warranted. In addition, data on the effect of other immunosuppressants are very limited. Further points that need to be addressed in the reached as to whether all organ manifestations respond similar to treatment. Furthermore, it remains unclear whether non-Asian populations behave similar to Asian patients, on whom most data to date is published.

Accordingly, the follow-up of IgG4-RD patients remains unclear. IgG4 seems to have certain characteristics of a biomarker in patients with elevated IgG4 levels, but it is unclear whether IgG4 levels can be used in guiding the therapeutic approach [27]. Future research will include the search for other biomarkers for the diagnosis and/ or follow up of IgG4-RD patients. One possible useful biomarker seems to be circulating plasma blasts [26, 27]. Whether expensive imaging modalities, such as PET-CT, will become part of the routine care of IgG4-RD patients or not, also needs to be further investigated [28, 29]. Finally, we have not yet understood the pathophysiology of the disease, the understanding of which could result in the founding of specific therapies for this rare condition.

In a recent recommendation [21] the diagnostic criteria for IgG4-RD disease has been based on a biopsy showing lymphoblastic infiltrates enriched with plasma cells, storiform fibrosis, obliterative phlebitis, and mild to moderate tissue eosinophilia (Table 3).

Our clinical suspicion of according to the new information makes to be diagnosed by rheumatologist. We wanted to use a specialized detective pathologic method for IgG4 staining, but unfortunately such a method was not available.

### **Conflict of interests**

Authors have no conflict of interests.

### **Acknowledgment**

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**Table 3.** New Guideline for diagnosis of IgG4-RD

A consensus statement from a multi-national, multi-disciplinary group of experts on IgG4-RD describes guidelines for the diagnosis of the disease and the histopathologic findings important in making the diagnosis [9].

The histopathological findings include:

a dense lymphoplasmacytic infiltrate, storiform fibrosis,

obliterative phlebitis,

all critical features for establishing the diagnosis in affected tissues other than lymph nodes [10].

The presence of these findings, often together with mild tissue eosinophilia, is strongly suggestive of IgG4-related disease if accompanied by an increase in the volume of IgG4-positive plasma cells [11].

The number of IgG4-positive plasma cells per high-power field (HPF) that can be regarded as sufficient, varies somewhat from tissue to tissue. Tissue IgG4-positive cell counts and the ratios of IgG4- to IgG-positive cells are considered secondary in importance.

Generally, the minimum for making the diagnosis for most tissues is from 30 to 50 IgG4-positive cells/HPF. However, in some organs or tissues, including the kidneys and others, only 10 IgG4-positive plasma cells/HPF may be sufficient.

The diagnosis cannot be predicated entirely on the number of IgG4-positive plasma cells because a large number of other entities can have such cells. Nor can the diagnosis of IgG4-RD be based up on serum concentrations of IgG4 alone [10, 12].

Serum IgG4 concentrations are neither sufficiently sensitive nor specific to this disease. Thus, we strongly prefer the confirmation of the diagnosis to be done with a biopsy of an involved organ whenever this is possible

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