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IgG4-Related Disease and the Spectrum of Mimics in Rheumatology

Agata Sebastian, Piotr Donizy and Piotr Wiland

Abstract

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is an immune-mediated condition that can affect almost any organ. It is a chronic, systemic, inflammatory condition of unknown etiology. Pseudotumor formation is the most common and characteristic clinical symptom. The variable organ dysfunction reflects the clinical presentation. Because there are not specific antibodies for this disease, histopathological assessment provide the pivotal role in the diagnosis. IgG4-RD is characterized by a lymphoplasmacytic infiltrate composed of IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis and mild to moderate eosinophilia. In this chapter we present the newest knowledge of the IgG4-RD pathogenesis and then concentrate on clinical symptoms which can mimic many other conditions in rheumatology, e.g., this common as Sjögren syndrome or rare as vasculitis or idiopathic retroperitoneal fibrosis.

Keywords: IgG4-related disease, Mikulicz syndrome, Kuttner’s disease, pseudotumor

1. Spectrum of IgG4-related disease

IgG4-related disease (IgG4-RD) belongs to quite new disease entities; its name was introduced in the 21st century. In the course of the disease, characteristic infiltrates are formed, composed of mononuclear cells, mainly IgG4 cells. Also, fibrosis of affected organs is observed. In the majority of patients, concomitant increase in serum IgG4 concentration is found, but not in every patient [1, 2].

Location of lesions	Name of IgG-RD disease
- pancreas	- Autoimmune pancreatitis type 1, AIP
- biliary ducts	- IgG4-related sclerosing cholangitis
- parotid glands, submandibular glands and lacrimal glands	- IgG4-related sialadenitis, IgG4-related dacryoadenitis
- lacrimal glands and oculomotor muscles and orbit	- IgG4-related pan-orbital inflammation, IgG4-related orbital pseudotumor
- retroperitoneal space	- IgG4-related retroperitoneal fibrosis
- aorta	- IgG4-related aortitis/periaortitis
- kidneys	- IgG4-related kidney disease
- lungs	- IgG4-related lung disease
- lymph nodes	- IgG4-related lymphadenopathy

Table 1.
Current nomenclature of most common clinical forms of IgG4-RD.

In 2011, classification criteria were presented with a spectrum of diseases described so far in medicine that may correspond to IgG4-RD. The first relationship between autoimmune pancreatitis and increased serum IgG4 was observed in 2001 and it is one of the most common manifestations of IgG4-RD-type 1 of autoimmune pancreatitis [3]. Currently, there is a tendency to introduce the name IgG4-RD disease depending on the location of the lesions (**Table 1**) [4].

Due to possible location of pathologic lesions in most of the organs, every physician may have contact with IgG4-RD, independent of his/her speciality.

2. Epidemiology

The disease develops mostly in men, middle-aged or older. The ratio of disease incidence in men vs. women is between 1:0.77 and 4:1 [5, 6]. The disease incidence is not fully known and it seems that it varies significantly for different parts of the world. The highest number of IgG4-RD cases has been reported so far for Asia. In Japan, based on the register of patients with IgG4-RD, the disease incidence was determined to be 0.28–1.08 in 100,000 people [7]. Despite the fact that the disease is not often seen in children, there were more than a dozen such cases reported in the world [8]. In the case of an affected aorta, lesions in the course of IgG4-RD were observed in 4–20% of patients, depending on a publication [9–11].

3. Pathogenesis of IgG4-RD

Pathogenesis of IgG4-RD is not fully understood. It seems that many factors contribute to disease development, including allergic, autoimmune and genetic factors [12].

The observed positive response to drugs blocking B-lymphocyte activity and monoclonal increase of IgG4 concentration suggested a significant role of B lymphocytes in the initiation and maintenance of the disease process [13]. However, current research indicates inappropriate activation of T lymphocytes causing autoimmune defect.

The first publications indicated an increase of Th2 cytokine production in patients with IgG4-RD [14, 15]. However, it turned out that this effect is seen only in patients with IgG4-RD and concomitant allergic symptoms [16]. It was shown that in response to Th2-dependent cytokines, such as interleukin 4, 5, 10, and 13, as well as transforming growth factor beta (TGF- β), the eosinophil number and concentration of IgG4 and IgE increase and fibrosis progresses [17]. Eosinophilia, similarly to allergy, may occur in 1/3 of patients with IgG4-RD. However, the correlation between the increased number of eosinophils and clinical symptoms of allergy was not confirmed. Similarly, allergic symptoms did not correlate in patients with IgG4-RD with increased IgE concentration [18]. Allergic symptoms included allergic rhinitis, nasal polyps, bronchial asthma and atopic dermatitis [19]. Further studies showed that a key role in the pathomechanism of IgG4-RD play T follicular helper cells (Tfh) and regulatory T cells (Treg). Their role is particularly seen in relation with class switching of B cells and induction of aberrant lymphoid follicle formation in tissue. However, IL-21 and IL-4 related to Tfh play a great role in the formation of germinal centers, differentiation of B lymphocytes, induction of plasmoblasts and the phenomenon of class switching leading to the production of IgG4 [20, 21]. This is in the Tfh germinal centers of lymph nodes that IL-4 is produced and long-lasting memory lymphocytes responsible for disease recurrences proliferate [22, 23].

The analyses of immunophenotyping of Thf subclasses showed that in IgG4-RD, cytokines type Th2 (IL-4, IL-5, IL-13) are produced by cells not expressing CXCR3 and CCR6 [24]. The number of Th2 cells is increased in IgG4 and correlates with increased IgG4 concentration in serum and IL4, the number of plasmocytes and the number of affected organs [21, 25]. However, in AIP, an increased number of CD4+ and CD25+ Treg was observed [21, 25]. In the most recent reports, attention has been paid to cytotoxic lymphocytes CD4+ (CTLs) [26–29] as well as the possibility of participation of annexin A11 in the pathogenesis of AIP [30].

The role of plasmoblasts and IgG4 itself is still not known in the pathomechanism of IgG4-RD. It is thought that they are more of disease markers than factors of disease development [5, 22]. Among IgG, there are 4 subclasses in humans (IgG1-IgG4). Normally, IgG4 constitute about 2–3% of all IgG, and their serum concentration is 35–51 mg/dL on average. Higher serum concentration of IgG4 was observed in men and in the elderly [31]. IgG4 and IgE are usually produced as a result of chronic exposure to antigens [32] or after allergy immunotherapy [33]. IgG4 is not able to form immunocomplexes which could stimulate antigen-presenting cells and enhance immunological response. Moreover, it does not initiate the classic pathway of complement activation [34]. The IgG4 antibodies bind weakly to complement C1q and Fcγ receptors. As a consequence, they are not involved in antibody-dependent cell-mediated cytotoxicity [35]. Additionally, IgG4 antibodies are dynamic molecules—altering their properties by spontaneous exchange of one of the two Fab fragments between individual immunoglobulin molecules. This process involves dissociation of immunoglobulin G4 heavy-chain dimers and a subsequent bonding of each IgG4 half-molecule with a different IgG4 half-molecule. This half-molecule exchange yields bi-specific antibodies able to bind with two different antigens, but monovalent for each of them. These properties of IgG4 molecules are the reason why IgG4 antibodies do not bind to the complement directly, do not initiate the classic pathway of complement activation, or why they are poor Fc receptor activators. This reduced IgG4 effector function has been responsible for these antibodies being considered anti-inflammatory [31]. IgG4 are believed to constitute a veritable antigen “garbage disposal” system, which can attenuate inflammation or protect against type I hypersensitivity by inhibiting IgE activity, as well as prevent type II and III hypersensitivity by blocking immune complex formation [36, 37].

Genetic studies seem to confirm some genetic background of IgG4-RD. Until present, differences in the expression of different genes have been found in salivary glands of patients with Sjögren syndrome and in patients with IgG4-RD, compared to healthy population. Only in a group of patients with IgG4-RD, overexpression of genes related to cell proliferation, organization of extracellular matrix and tissue fibrosis was confirmed [38]. Also, the relationship was found between AIP and class II antigen of the major histocompatibility complex HLA-DRB1*0405-DQB1*0401 and nuclear factor κB gene polymorphism and a molecule for type Fc-3 receptor on B cells [39].

4. Clinical manifestations of IgG4-RD

In the course of IgG4-RD, infiltrations composed mainly of IgG4 are formed, and characteristic fibrosis of affected organs is seen. These lesions usually form pseudotumors, which may occur in every organ. Most commonly observed locations of IgG4-RD are shown in **Table 2**. Single clinical cases of disease occurrence in the brain and cerebrospinal meninges, as well as intestines, causing ileus, have also been reported [40, 41]. IgG4-RD may affect one organ or occur in a generalized form. It seems that some locations may be more common for a particular sex. For example, lesions in the pancreas are more common in men, while sialadenitis

1. Characteristic symptoms of organ affection with its enlargement, or abnormal function of organ/organs
2. Increased serum IgG4 concentration ≥ 135 mg/dL
3. Characteristic changes in histopathological examination: <ul style="list-style-type: none">• infiltration composed of lymphocytes and plasmatic cells and fibrosis• infiltration of IgG4+ cells: >10 cells IgG4+ hpf in a high-resolution microscope and quantitative ratio of IgG4+/IgG $> 40\%$
Certain diagnosis of IgG4-RD: meeting the requirements of 1, 2, 3
Probable diagnosis of IgG4-R: meeting the requirements of 1 and 3
Possible diagnosis of IgG4-RD: meeting the requirement of 1 and 2

Table 2.
Criteria of IgG4-RD diagnosis.

and dacryoadenitis in women [42]. Patients with IgG4-usually do not present general symptoms such as fever, night sweats, or weight loss [43].

5. Criteria of IgG4-RD diagnosis

Criteria of IgG4-RD diagnosis were developed in 2012 (Table 2) [44].

Summing up the criteria of IgG4-RD diagnosis: one of the most important examinations in case of an appropriate clinical picture of the disease is the histopathological examination of the affected organ. It is now believed to be the key examination. In the next chapter, the principles of histopathological examination are presented, depending on the location of the pathological lesions.

In the second point of the criteria, IgG4 serum concentration was also included. It should be minimum 135 mg/dL in an affected individual. The probability of IgG4-RD diagnosis is significantly increased when this concentration is higher than 270 mg/dL [45]. However, it should be remembered that in some patients with IgG4-RD, an increase of serum IgG4 is observed. This percentage may be as high as 40% [46, 47]. IgG4 production depends mainly on the action of interleukin 6 and 10. Moreover, it was observed that in some autoimmune diseases, the concentration of IgG4 is also increased. Among others, in primary Sjögren syndrome, in systemic lupus erythematosus, and rheumatoid arthritis. A similar situation was also observed in 2% of patients with cancers and in healthy population [46, 47].

In IgG4-RD, no other immunologic markers observed in rheumatoid diseases are found, including antinuclear antibodies, ANCA antibodies or decreased complement components C3 and C4 [48].

In 1/3 of patients, eosinophilia in the peripheral blood is observed [18]. However, it does not correlate with the allergic symptoms [19].

In the diagnostics of IgG4-RD, imaging plays an important role, depending on lesion location, e.g., PET, magnetic resonance, computed tomography, EUS, bronchoscopy. However, the disease has no sufficiently characteristic image in any of the imaging methods, therefore these examinations are helpful in the evaluation of the affected organs and selection of the biopsy site, but they cannot be the only methods of disease diagnosis.

Another most important component of the criteria is their application only after exclusion of all other diseases that may suggest IgG4-RD disease, including cancer. It was evaluated that neoplastic lesions may occur even in 7% of patients with IgG4-RD. Development of neoplastic lesions, including lymphomas, was reported even after 5 years from diagnosis of IgG4-RD in the orbit, with affected salivary glands and cerebrospinal meninges [49, 50]. On the other hand, there are publications denying the increased risk of cancer development in IgG4-RD [51, 52].

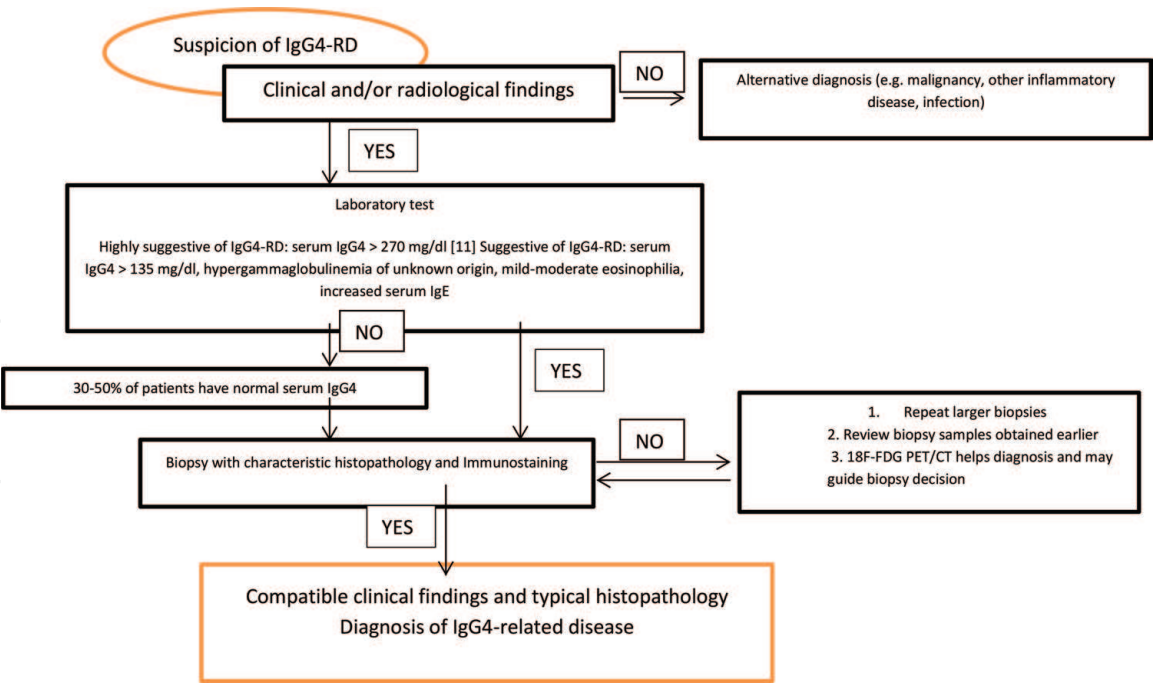


Figure 1.
Diagnostic scheme in IgG4-RD [22, 37, 54].

An interesting fact is that most cancers observed in patients with IgG4-RD do not contain IgG4 cells [5]. At present, there are no well-designed observational studies confirming these findings. Therefore, patients with lesions in the clinical picture or patients not responding to basic treatment, should have their diagnosis verified.

The diagnostics of lesions within large salivary and lacrimal glands should take the primary Sjögren syndrome into consideration. One of the key clinical differences is the lack of symptoms of dryness confirmed in objective examinations in patients with IgG4-RD [47, 53] and the lack of immunological markers characteristic for the Sjögren syndrome.

Taking the above into consideration, diagnostic and therapeutic procedures were developed in 2015 in patients with suspected IgG4-RD, which is presented in **Figure 1** [22, 54].

New classification guidelines were presented, during the ACR meeting in Chicago in October 2018. It were developed by 79 experts from five continents and are awaiting approval by ACR and the EULAR. The guidelines based on clinical findings, bloodwork, radiologic findings and exclusion criteria for other mimickers.

6. Organ location of lesions in IgG4-RD

The lesions may occur individually or in many organs at the same time. From the point of view of rheumatologists, the most important locations include the below mentioned organs.

6.1 IgG4-RD of the head and neck

Lesions located within the head and neck belong to the most common clinical manifestation of IgG4-RD [55, 56]. They can affect large salivary glands (submandibular salivary glands, parotid glands), thyroid, lacrimal glands, orbit with oculomotor muscles, nasal sinuses, and upper airways. Mikulicz's disease is an enlargement (usually symmetrical) of lacrimal glands, parotid and submandibular glands, and sometimes sublingual glands. In the past, Mikulicz's disease was

believed to be a subtype of Sjögren syndrome. Today we know that these are two different disease entities with a different treatment response. Diagnostic criteria of Mikulicz's disease include: symmetric oedema of at least two pairs of lacrimal glands, parotid or submandibular glands, present for at least 3 months, and increased serum concentration, of IgG4 > 135 mg/dL, as well as a typical histopathological picture of the affected tissues.

The term Kuttner's tumor is used in case of submandibular salivary gland enlargement.

In case of lesions located in the orbit, vision disturbances, orbital pain, swelling of the eyelids caused by infiltration of oculomotor muscles and infiltration of tumor mass in the orbit may occur. Sometimes these changes may occur in tissues around the orbit as painless facial swelling. Cases of IgG4-RD were reported with infiltration and destruction of bone tissues, resulting in a saddle-shaped nose [57]. The basis for diagnosis is always a histopathological examination.

Involvement of the thyroid in IgG4-RD is possible. Recently, a lot of effort was put into this issue. First, based on case reports, it was found that Riedel thyroiditis belongs to IgG4 diseases. Some authors suggest also that the form of Hashimoto's thyroiditis with fibrosis, leading to hypothyroidism is also caused by IgG4-RD. This could be indicated by more common occurrence of hypothyroidism in patients with autoimmune pancreatitis and IgG4-RD [58–60].

6.2 Location in the lungs, mediastinum and pleura

Lesions located in the lungs may occur in the form of pseudotumors, “milk glass” lesions, lesions resembling interstitial lung disease or honeycomb lung. Less commonly, thickening of bronchovascular bundles and interlobular septa may occur. Also, involvement of the pleura and mediastinum was reported—infiltration with lymph node enlargement. In case of disease diagnosis in this location, biopsy with a thorough differential diagnosis is needed, including cancer, vasculitis [61–63].

6.3 IgG4-RD in the alimentary tract

The first organ in which IgG4-RD was reported was pancreas. Autoimmune symptoms of pancreatitis type I include jaundice, abdominal pain, pruritus, de novo diabetes and fatty diarrhea [64–67].

Lesions characteristic for IgG4-RD may be also located in other parts of the alimentary tract, e.g., gallbladder or intestines. Clinical symptoms depend on the location of lesions and organ dysfunction caused by infiltration. They may be symptomless, as in the case of IgG4-RD findings in the removed gallbladders, or present as full-blown intestinal obstruction [47]. Involvement of bile ducts is well documented in the literature as IgG4-RD sclerosing cholangitis [68].

6.4 Lesions in the kidneys

Most commonly, tubulointerstitial inflammation is found in the course of IgG4-RD (IgG4-TIN) [69]. Rarely tumor masses in the kidneys or damage to the glomeruli are observed. However, such locations of IgG4-RD may be found in the literature too [70]. Moreover, involvement of the kidneys may be divided into directly related to the location of infiltration in the parenchyma, and indirectly related to infiltration of structures of the urinary system in the course of retroperitoneal fibrosis. Recently, also a case of renal amyloidosis AA in the course of IgG4-RD was reported. It is estimated that kidney involvement occurs in about 15% patients with IgG4-RD [70]. Besides symptoms of renal insufficiency in patients

with IgG4-TIN, increased serum concentration of IgG and IgG4 is observed. In 60% of patients also hypocomplementemia is observed, in 40% eosinophilia and even in 32% antinuclear antibodies [71, 72]. In the imaging examinations, lesions in the course of IgG4-RD had a form of numerous hypodense lesions [69, 73]. At present, in diagnostics of renal lesions typical for IgG4-RD, criteria proposed by Mayo Clinic or criteria of the Japanese Society of Nephrology may be used [69, 74]. Their use does not require unconditional kidney biopsy. Considering the fact that lesions in the course of IgG4-RD are most commonly located also in other organs, biopsy of other organs is acceptable.

The most common histopathological form of IgG4-RD in the kidneys is membranous nephropathy (IgG4-MGN). Lesions in the glomeruli may be isolated or occur together with TIN, which is seen more often. The infiltrate observed in IgG4-MGN composed of IgG4 cells in the wall of glomerular capillaries may imitate primary membranous nephritis. Detection of antibodies against phospholipase A2 receptor (anti-PLA2R), which do not occur in IgG4-MGN, may be then helpful [70].

6.5 Involvement of the vessels in IgG4-RD

Lesions of IgG4-RD type usually locate in the aorta in the form of periaortitis, aortic dilatation, and aneurysm. The lesions are usually found in the abdominal aorta [9]. Inflammatory aortic aneurysm is characterized by thickening of the aortic wall, partial fibrosis of adventitia and infiltration composed of inflammatory cells [75]. Similar changes without enlargement of vessel diameter are called periaortitis [9]. The most characteristic location of inflammatory infiltrations for IgG4-RD is the adventitia (external fibrous membrane). In case of thoracic aorta involvement, separation of the aortic layers, lymphoplasmacytic aortitis and isolated aortitis are observed [76, 77]. Arterial wall thickening is relatively low compared to lesions found in the abdominal section. In some patients, aorta involvement may occur as unexpected separation of the aortic layers or sudden cardiac death; other changes in the course of the disease were rarely reported in vessels such as carotid artery, coronary arteries, pulmonary arteries, visceral vessels, mesentery vessels, iliac and vertebral arteries, brain vessels. If present, they were reported as vasculitis or aneurysms [78, 79].

The relationship between IgG4-RD and ANCA-associated vasculitis (AAV) has not been fully explained. It is known that these diseases have a similar clinical picture (asthma symptoms, involvement of nasal sinuses, involvement of lungs and kidneys) and may proceed with increased serum IgG4 concentration and eosinophilia in the peripheral blood. Most publications were dedicated to eosinophilic granulomatosis with vasculitis (EGPA) [9].

6.6 Location of IgG4-RD in the nervous system

Lesions in the central nervous system are rare. If present, they are usually found in the meninges of the brain or cranial nerves. The symptoms concerning cranial nerve involvement are most commonly caused by the presence of pseudotumors and pressure on or infiltration of the nerves [80].

6.7 Skin lesions in IgG4-RD

Skin lesions in the course of IgG4-RD are rarely observed and occur mainly in systemic forms. So far, the following skin lesions in the course of IgG4-RD were reported on: erythematous papules, tarsus and brown papules resembling nodular prurigo [81, 82].

6.8 Retroperitoneal fibrosis and IgG4-RD

Retroperitoneal fibrosis was reported in 13% of patients with multi-organ involvement in the course of IgG4-RD. Most of the lesions were periaortic or located around iliac vessels. In 33% of patients, hydronephrosis was found, more commonly of one kidney than two [83]. Classifying all cases of IgG4-RD as Ormond's disease is controversial if not confirmed by histopathology, and requires a further well-designed medical analysis. However such a suggestion was made in one publication [84].

6.9 Summary of the clinical picture

IgG4-RD is a disease of multiple systems. It may be located in one or in many organs at the same time. In case of suspected IgG4-RD, all other diseases which may mimic IgG4-RD should be excluded. For rheumatologists it is important to exclude in the differential diagnosis the following: neoplasms including solid lesions and lymphomas, inflammatory and infectious changes, sarcoidosis, vasculitis including granulomatous vasculitis, Sjögren syndrome, Castleman's disease, eosinophilic angiocentric fibrosis. As IgG4-RD may involve many organs, imaging diagnostics should always be carried out in order to determine all locations of the disease after diagnosis of the disease.

7. Histopathological evaluation in IgG4-RD

Histopathological evaluation is a crucial element of an accurate diagnosis of IgG4-RD due to their nonspecific clinical and laboratory features. Irrespective of the anatomic site, histopathologic presentation is similar and consists of five main histomorphological and immunohistochemical parameters evaluated in the tissue specimen (both biopsy and postoperative specimens) [1, 85, 86]:

1. dense lymphoplasmacytic infiltrate,
2. fibrosis with prominent storiform pattern,
3. obliterative phlebitis,
4. increased number of IgG4+ plasma cells/HPF - different cutoffs depending on the anatomic site and the type of evaluated material (biopsy vs. postoperative specimen),
5. IgG4+/IgG+ plasma cell ratio of >40%;

Most of the analyzed cases do not show all histopathologic features characteristic for IgG4-RD. The presence of two or more of the parameters listed above suggests the diagnosis of IgG4-RD [1].

The inflammatory infiltrate in IgG4-related diseases primarily consists of mature plasma cells, dispersed T lymphocytes and focally aggregated macrophages. In some cases, eosinophils are observed [1].

It must be underlined that the isolated elevated IgG4+ plasma cell count is non-specific and insufficient for the diagnosis of IgG4-RD. Elevated IgG4+ plasma cell count is observed in many cancers and infectious diseases, which is why a range of detailed clinical and laboratory tests is crucial in differential diagnosis [85, 86]. Full clinician and pathologist cooperation is indispensable as well since incomplete patient history may delay or in some cases even prevent establishing the accurate diagnosis.

Fibrosis in IgG4-related diseases is very characteristic, being storiform with whorled or cart-wheel appearance [1, 56]. No cytologic atypia is observed within proliferating fibroblasts, which is an important element in differential diagnosis of potentially malignant lesions that may imitate IgG4-RD.

Obliterative phlebitis is the most specific but most rare histopathologic feature of IgG4-RD. In hematoxylin and eosin stained specimens a chronic intramural inflammatory infiltrate is observed with fibrosis and obliteration of the vessel lumen [1]. Elastic stain, which is a histochemical stain outlining the wall elements of the vessel damaged by the chronic inflammatory infiltration, may aid if it is difficult to accurately identify the pathologically altered and totally obliterated vein.

The accurate histopathologic diagnosis of IgG4-RD can be made when two quantity parameters for IgG4+ plasma cells are observed at the same time [4]. According to the current recommendations, the number of IgG4+ plasma cells should be determined within three high-power fields with the highest density of IgG4+ plasma cells and then the average should be determined based on three measurements [1]. For the core-needle biopsy specimen the minimal number of IgG4+ plasma cells is 10/HPF and one of the two histopathologic parameters (storiform fibrosis and/or obliterative phlebitis) must be observed. Different cutoffs are used for postoperative material, for example the cutoff within the resected salivary gland is >100 IgG4+ plasma cells/HPF [1, 56].

The key parameter, apart from elevated number of IgG4+ plasma cells is the accurate determination of IgG4+ plasma cells/total number of IgG+ plasma cells ratio. It is only the ratio of >40% that may suggest the diagnosis of IgG4-RD. The isolated elevated IgG4+ plasma cell number not accompanied by the required increase of IgG4+/IgG+ ratio does not meet the criteria for the diagnosis of IgG4-RD.

It must be stressed that plasma cells in IgG4-RD are polytypical. If a monotypic population of plasma cells is identified (even if it meets IgG4-RD criteria), a more extended histopathologic diagnosis for plasmacytic neoplasms is required—it is necessary to perform immunohistochemical staining for potential lambda and kappa light chains restriction [87].

From the point of view of histopathology and histopathologic-clinical correlations, three categories of diagnosis were enumerated [1, 56]:

- histologically highly suggestive of IgG4-RD;
- probable histologic features of IgG4-RD; and
- insufficient histopathologic evidence of IgG4-RD.

The diagnosis of “histologically highly suggestive of IgG4-RD” requires the presence of a typical storiform fibrosis or obliterative phlebitis with a high number of IgG4+ plasma cells and elevated IgG4/IgG ratio.

Histopathologic diagnosis of “probable histologic features of IgG4-RD” is based only on a high number and elevated global percentage of IgG4+ plasma cells with the lack of typical storiform fibrosis or obliterative phlebitis. A detailed correlation with clinical, laboratory and radiological data is necessary.

The third histopathologic category (“insufficient histopathologic evidence of IgG4-RD”) is applied when microscopic examination does not show dense lymphoplasmacytic inflammatory infiltrate, storiform fibrosis, obliterative phlebitis or elevated number of IgG4+ plasma cells. It must be remembered though, that such diagnosis does not preclude IgG4-RD in a given patient since the primary lesion may not have been represented in the specimen taken for evaluation [1, 56].

The histopathological features of IgG4-RD in liver biopsy (**Figures 2-5**).

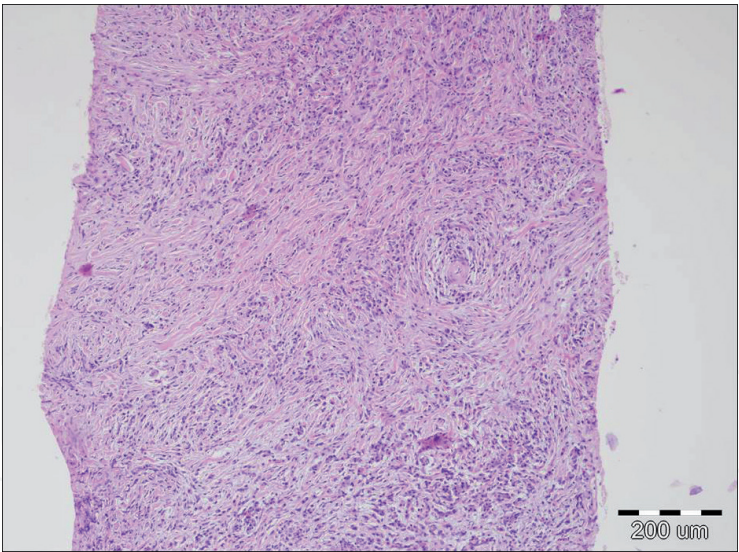


Figure 2.
Extensive fibrosis with storiform appearance and chronic inflammatory infiltrate (H&E, 200×).

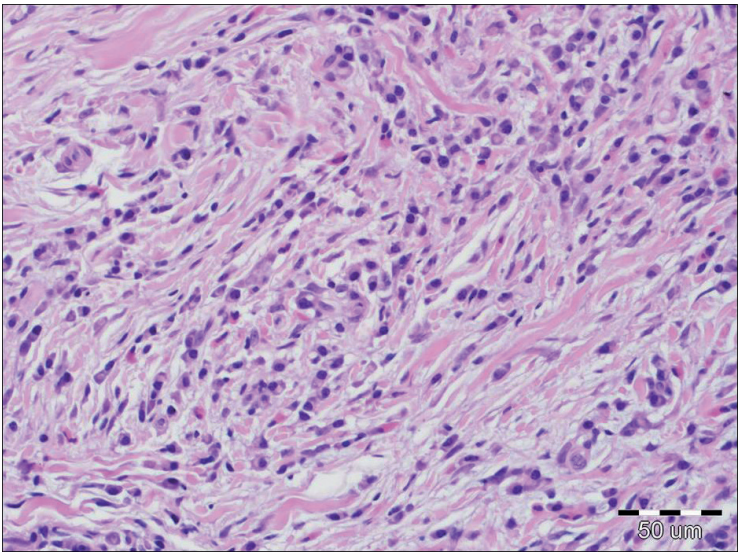


Figure 3.
Extensive fibrosis with storiform appearance and chronic inflammatory infiltrate (H&E, 400×).

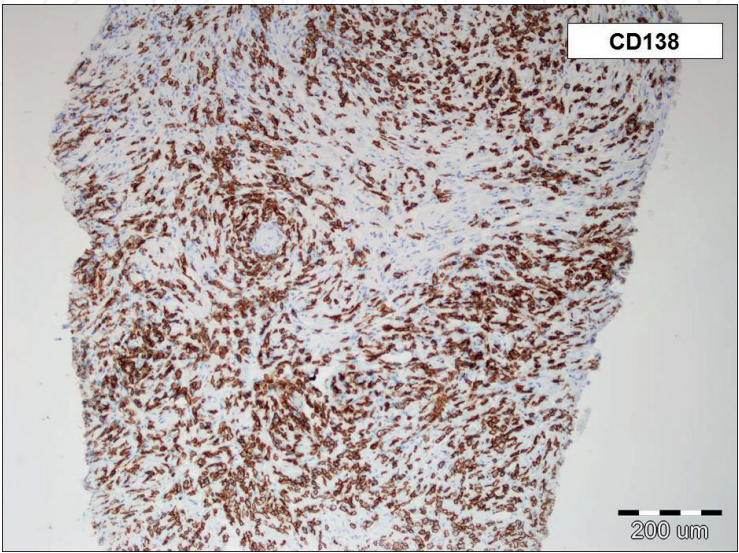


Figure 4.
Immunohistochemical staining for CD138 revealed that majority of the cells are plasmacytes (hematoxylin, 200×).

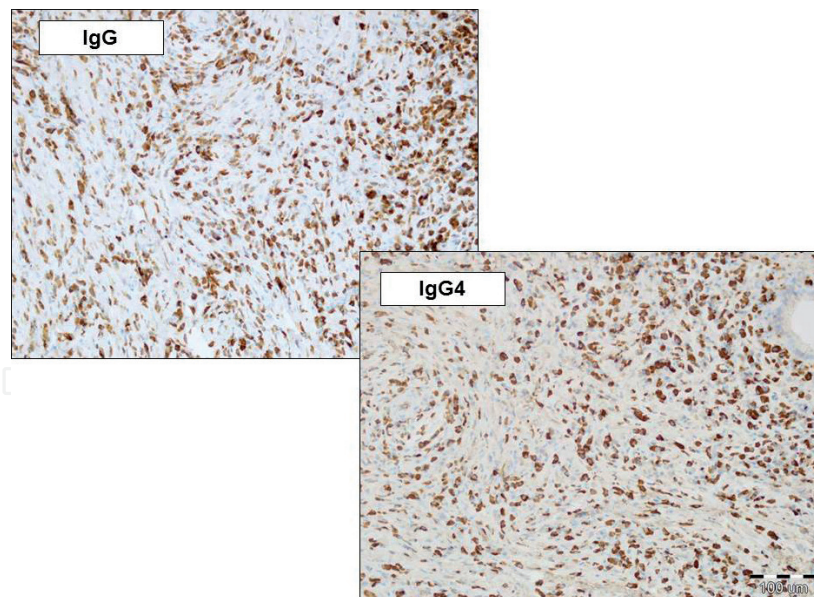


Figure 5.
A prominent component of IgG4+ plasmocytes (hematoxylin, 100×).

8. Treatment

Treatment of IgG4-RD is based on the experience of the attending physicians and opinions of the experts, as there are no large controlled clinical trials covering this problem so far. Moreover, the exact molecular pathomechanism of IgG4-RD is not known, so determination of targeted therapies is not possible at the moment. In every patient, treatment should be individually planned, depending on the location and organ damage, coexisting diseases and contraindications to immunosuppressive treatment. Another aspect of IgG4-RD therapy is that the disease tends to recur in case of treatment withdrawal. In the group of patients with the highest recurrence rate, increased baseline level of serum IgG4, IgE and eosinophils was observed [5]. At present, the experts recommend pharmacologic treatment in patients with active lymphoplasmatic infiltrations in histopathological examination. Surgery may be considered in patients with a long-lasting disease with predominant fibrosis, poorly responding to basic treatment [13, 83]. Therapy including careful observation without rapid initiation of treatment may be considered in moderate lymphadenopathy and with moderate enlargement of the submandibular salivary gland. In case of subclinical forms with involvement of the bile ducts, kidneys, aorta, retroperitoneal fibrosis, pancreas, pachymeningitis, pericarditis, treatment must be started even with a lack of clinical symptoms due to progressive, irreversible organ damage.

According to international guidelines of IgG4-RD treatment, the first-line medicines are glucocorticoids: oral prednisone, at an initial dose of 0.6 mg/kg daily maintained for 2–4 weeks and gradually reduced for 3–6 months [83, 84]. In Japanese guidelines, glucocorticoids in small maintenance doses (5–10 mg daily) are recommended even for 3 years [88]. In case of recurrences, repeated administration of glucocorticoids is proposed in the above schedule [83]. Most of the patients show fast improvement after glucocorticoid use. As soon as after several weeks of treatment, improvement of functional parameters of the involved organs is observed, with a reduction of the infiltration mass and a decrease of serum IgG4 concentration.

There are no publications which would constitute guidelines for the application of disease modifying antirheumatic drugs in patients not responding to or not tolerating treatment with glucocorticoids or who experience frequent disease

recurrences. In 46% of patients with IgG4-RD who have their glucocorticoid doses decreased, the disease recurs [89]. As in other rheumatic diseases, the disease modifying antirheumatic drugs are tried in such cases. The adjunctive therapy has so far applied most drugs used in rheumatology, including methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide. However, the results and their efficacy are different. Adjunctive treatment with disease modifying antirheumatic drugs is currently based mainly on the experience of attending physicians and is experimental. At present, there are no well-designed clinical trials summarizing this problem. Moreover, the disease modifying antirheumatic drugs were always used as adjunctive treatment to glucocorticoid therapy and not as first-line therapy, therefore their efficacy is even more difficult to evaluate. In 2017, a summary of observations in patients treated with glucocorticoids vs. glucocorticoids and cyclophosphamide orally was published [90]. It turned out that a combination of disease modifying antirheumatic drugs decreased the risk of disease recurrence by 70% as compared to the group treated with glucocorticoid monotherapy.

In case vascular location and lesions in the aorta, there are no explicit guidelines concerning treatment. Similarly as in other forms of IgG4-RD, steroids are used, most commonly prednisone at a dose of 0.6 mg/kg daily. This dose is gradually reduced to the maintenance dose of 5 mg/kg daily. There are no guidelines concerning therapy duration. Steroid administration does not protect against development and progression of aneurysms in patients in whom vascular wall widening was found initially [9, 80]. In this group of patients, surgery is performed in case of confirmation of indications by vascular surgeons.

Due to participation of T and B lymphocytes in the pathomechanism of the disease, the first biological drug which turned out to be effective in the treatment of IgG4-RD was rituximab (RTX). Typically this drug is used intravenously at a dose of 1 g every 15 days, up to a dose of 2 g [91]. In a prospective open-label clinical trial, RTX was effective in 97% of patients with IgG4-RD after 6 months of therapy despite no glucocorticoids used [80]. Also, the efficacy of RTX in patients with involvement of cerebrospinal meninges was reported on [92]. Currently RTX is recommended by experts for use as a second-line therapy in patients with recurrent disease or not responding to basic treatment [92].

So far, the data from a clinical trial with XmAB5871, i.e., a reversible inhibitor of CD19+ on B lymphocytes, were not published.

The patients with IgG4-RD are shown in **Figure 6**, before and after treatment.



Figure 6.
Typical Mikulicz disease (IgG4-related disease) with lacrimal enlargement at the diagnosis (A, B) and after 10 months of treatment (C, D) with prednisone 0.6 mg/kg/day.

9. Evaluation of disease activity and efficacy of the therapy

For evaluation of disease activity and efficacy of the therapy, IgG4 Responder index is used. This index includes 25 domains, regarding organ location of lesions and general symptoms. For every domain, 0 to 3 scores may be assigned. The disease is active if the index score is 3 or higher [93].

The prognosis regarding IgG4-RD is not known. There are no long-term, well-designed observational studies. It seems that spontaneous remissions rarely occur. However, the disease recurrences are frequently observed when glucocorticoids are reduced. The disease, if not diagnosed, may lead to irreversible fibrosis and damage of the involved organs. It should be remembered that due to the diversity of clinical pictures in IgG4-RD, all physicians may encounter this entity in their practice, regardless of their specialty.

Conflict of interest

None declare.

Author details

Agata Sebastian^{1*}, Piotr Donizy² and Piotr Wiland¹

¹ Department of Rheumatology and Internal Medicine,
Wroclaw Medical University, Wroclaw, Poland

² Department of Pathomorphology and Oncological Cytology,
Wroclaw Medical University, Wroclaw, Poland

*Address all correspondence to: agatasebastian@vp.pl

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