Indonesian Journal of Rheumatology
Journal Homepage: https://journalrheumatology.or.id/index.php/IJR

Pathogenesis, Clinical Presentations and Diagnosis of IgG4-related Disease: A Review

Perdana Aditya Rahman[1*], Cesarius Singgih Wahono[1], Fajar Maulana Raharjo[2], Handono Kalim[1], Mokhamad Fahmi Rizki Syaban[2]

[1] Rheumatology and Immunology Division, Department of Internal Medicine, University of Brawijaya, Malang, Indonesia
[2] Faculty of Medicine, University of Brawijaya, Malang, Indonesia

ARTICLE INFO

Keywords:
IgG4-related disease
Lymphoplasmacytic infiltrate
Obliterative phlebitis
Storiform fibrosis
Tumefactive lesion

Corresponding author:
Perdana Aditya Rahman

E-mail address:
perdana.aditya@ub.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/IJR.v13i2.189

ABSTRACT

IgG4-Related Disease (IgG4RD) was identified by the International Classification of Diseases (ICD) in 2012. Numerous diseases, including Mikulicz's disease, Kuttner's tumor, Riedel's thyroiditis, and Ormond's disease, are pathologically associated with IgG4. Here, we present a review of the clinical presentation and pathogenesis of IgG4-associated disease. IgG4-RD term has been used to refer to a group of diseases involving multiple organs in which there is an abundant IgG4-positive lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, and mild to moderate tissue eosinophilia, all of which show clinically as a tumefactive lesion, usually in more than one organ. IgG4 exhibits a unique property called an unstable disulfide bond between its heavy chain, as described by Fab-arm exchange which enables the recombination of a single IgG4 heavy chain with other IgG4 heavy chains, resulting in a bispecific antibody incapable of cross-linking and thus of forming an immune complex. IgG4-RD pathomechanism that causes serum IgG4 increase and tissue IgG4-plasma-cell deposition that is pathogenic, rather than the IgG4 itself. Genetic predisposition, autoimmunity, T-cell dysregulation, infection, and dysbiosis are just a few of the underlying pathomechanisms. Clinical symptoms are also frequently complex and may involve many organs. Confirmation of a diagnosis required a comprehensive anamnesis and examination.

1. Introduction

The phenomena of IgG4-Related Disease (IgG4-RD) is a relatively recent issue, distinct clinical cases with identical histopathologic findings. The earliest known medical literature on the subject was discovered in the late nineteenth century. This phenomenon was first seen in a patient with autoimmune pancreatitis in 1995, who responded to steroids, and in 2001 among individuals with autoimmune pancreatitis and concurrent retroperitoneal fibrosis who exhibited a rise in blood IgG4 levels. Its multiorgan participation in nature has been documented as a result of this mechanism, according to various publications. The nomenclature for IgG4-RD was announced in 2012.[1,2]

IgG4-RD is a fibroinflammatory immune-mediated, affects a number of different organ systems at the same time. It is thus necessary to do a biopsy to obtain a definitive diagnosis of IgG4-RD. Due to the fact that the symptoms might resemble cancer, infection, or other inflammatory conditions, clinicians continue to have substantial difficulties in making a clinical diagnosis.[2] Elevated serum IgG4 levels continue to be used as a diagnostic tool, despite it also being detected in a variety of other conditions.[3] Elevated in serum levels have been

recommended as diagnostic criteria.[4] Understanding the disease's pathogenesis will enable the development of additional treatment options, as there are currently only a few randomized clinical trials (RCTs) for this condition.

Epidemology

Study in japan shows that IgG4-RD estimated affect 2709 patients with autoimmune pancreatitis. Study also reported 5190 patients with IgG4-RD in multiple organs, with Mikulicz's disease being the most prevalent in 2009.[5] Inoue *et al.* describe 486 IgG4-RD signs and symptoms in 235 patients at eight Japanese hospitals in 2015. This data demonstrates that the vast majority of patients with IgG4-RD exhibit multiple clinical manifestations.[6] The most common symptom of IgG4-RD is pancreatitis. Men were found to be more likely than women to be affected by this illness, according to these two Japanese studies. However, when the condition is categorized by organ involved, the male to female ratio might vary significantly (1 to 1.3 : 4), as demonstrated in head and neck diseases, where the ratio is almost similar.[1,5–7]

There are numerous symptoms associated with IgG4-RD, although it is unknown how frequently they occur. Over 10,000 patients have IgG4-RD, according to countrywide surveys. In 2011, they estimated 5,745 autoimmune pancreatitis patients.[8] This disease was found to be slightly more prevalent in males, 322 (65.3%) based on study in 2019.[9] Typically, most cases of IgG4-related orbital disease (ages 50 to 70) are found in elderly adults, but at least three pediatric cases (22 months to 17 years) have been reported. The exception is children, IgG4-related orbital disease become the most common manifestation.[10]

According to the findings of limited research, the pancreas appears to be the organ most commonly afflicted, followed by an exocrine gland. Two independent investigations conducted in Japan have provided epidemiologic information. There is no universally accepted nomenclature for determining whether the lacrimal gland is regarded as a component of orbital involvement or a distinct organ. Additionally, involvement of multiple organs is more common than involvement of a single organ as swhon in Table 1. In spite of the fact that fewer than 40% of pancreatic lesions are isolated and that the other isolated organ lesions account for more than 25% of all isolated organ lesions, solitary organ involvement is prevalent in the lung, orbital, paravertebral, salivary, and lacrimal glands.[6]

Table 1. Organs Involvement in IgG4RD (%)

Organs	**Study**		
	Ryu, *et al* (n = 29)[3]	Inoue, *et al* (n = 235)[6]	Wallace, *et al* (n=149)[9]
Pancreas	62	60	87
Bile duct	38	13	55
Orbit	14	4	<1
Salivary gland	10	34	-
Lymph node	7	-	15
Lung	7	13	2
Gastrointestinal	7	-	-
Kidney	3	23	11
Pleura	3	-	-
Sinus	3	-	3
Mesentery	3	-	-
Testis	3	-	-
Aorta	-	20	4
Paravertebra	-	5	-
Lacrimal	-	23	3
Artery	-	4	-
Other sites	-	3	-

Pathogenesis

Among the IgG subclasses, IgG4 has the least proportion. In particular, the hinges and upper CH2 domain of IgG interact with FcR and C1q, resulting in unique roles for each subclass of antibodies. A Th2 cytokine, IL-4, stimulates the production of IgG4 in response to prolonged and recurrent exposure to noninfectious antigens, as in allergic illness. IgG4 levels rise in response to parasite infection through IL-4, a Th2 cytokine, as do IgG1 and IgE levels. Symptom alleviation is associated with the production of IgG4 in immunotherapy settings, and transitioning to IgG4 controlled by IL-10 explains its association with the induction or downregulation of immunological tolerance in immunotherapy situations.[11]

IgG4 production is primarily mediated by Th2 cells and IL-10.[12,13] Cytokines such as IgE, IgG4, IL-4, and IL-13 are involved in this process. IL-10, IL-12, and IL-21 all mediated an increase in the ratio of IgG4 to IgE.[11,14,15] Apart from IL-13, T-cells secrete TGF, which promotes fibroblast activation and tissue fibrosis.[1,16]

In contrast, IgG4 other subclasses have a unique property called Fab-arm exchange (**Figure 1**), which is described as an unstable disulfide bond between its heavy chain. As a result of this unique feature, it enables a single IgG4 heavy chain with additional IgG4 heavy chains, yielding a bispecific antibody that, owing to its inability to cross-link, was incapable of forming an immune complex.[11,15]

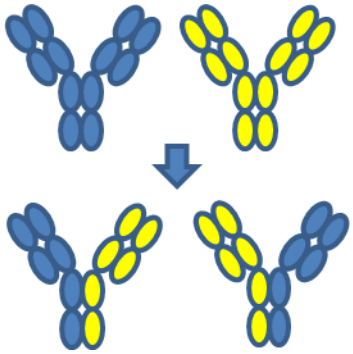

Figure 1. IgG4 Fab-arm exchange, also known as Half-arm exchange. This unique properties of IgG4 is the exchange of half-arm (one heavy chain and one light chain), this phenomenon resulting inability to form immune complex and receptor binding.[4]

Genetic

There have been several genetic loci identified that relate to IgG4RD, including several genes involved in regulation of T cells and fibroblast. In regulatory T cells (Treg), expression of mammalian homologs of yeast sterile 20 (STE 20)-like kinases (MST) was reduced due to hypermethylation in the promoter region, and an FGFBP2 variant was also found in circulating CD4+ T cells in a familial IgG4RD. KLF7, FRMD4B, LOC101928923, and MPPED2 have been identified as susceptibility genes in Japanese patients with type 1 AIP who develop lacrimal and salivary gland lesions.[17] A link was also discovered between AIP and the HLA-DRB1*0405-DQB1*0401 major histocompatibility complex class II antigen, the NF-κB polymorphism, and a molecule for the type Fc-3 receptor on B cells.[18]

Autoimmunity

B cells produce immunoglobulin, which is converted to IgG4 via IL-4 and IL-10 secreted by T cells. Numerous IgG4+ plasma cells are present in the affected organ, whereas the CD19+CD20–CD27+CD38+ plasmablast level correlates with disease activity in the peripheral circulation, implying a pathogenic role for plasmablast. IgG4RD has been

proposed to be caused by oligoclonal expansion and somatic hypermutation in response to common antigen stimulation. Additionally, IL-10 is inhibited by IL-21 and IL-27 produced by APC.[1,19]

Complement deficiencies were reported in 19–20% of IgG4-RD cases, 45.5% of kidney-related cases, and 36% of AIP cases. These phenomena are almost certainly the result of an increase in the number of other IgG subclasses, as IgG4 forms relatively few immune complexes.[1,20] There have been a number of laboratory investigations conducted to investigate the function of complement in IgG4-RD that have generated conflicting results. According to Muraki *et al.,* individuals with IgG4-related AIP had a substantially elevated MBL while receiving corticosteroid therapy; nevertheless, they concluded that this did not correspond with disease activity.[21] In contrast to IgG1, IgG4 does not normally bind to C1q and, as a result, should not contribute to complement activation. This supports the idea that complement activation may be induced by an elevated amount of IgG1 in the IgG4RD population. In contrast, Sugimoto *et al.* discovered that in IgG4-RD patients, complement activation occurred via multiple pathways.[15] An additional study, on the other hand, is required in order to fully understand the function of complement activation and the complement activation pathway in IgG4-related disease.

T-cell dysregulation

CD4+ T helper cells were found to be the most abundant cells in IgG4-RD tissues, besides CD4+ cytotoxic T cells and Tfh cells as the source of IL-1β, TGF-β1, and IFN-γ that promote fibrosis besides releasing granzymes that mediate cellular injury. Plasmablasts were found to be increased in IgG4-RD patients. It is hypothesized that activated B cells and plasmablasts are responsible for reactivating cytotoxic CD4+ T cells in injured tissues.[22,23]

In some cases, Tph cells have been implicated in pathogenesis, and Tph-like cells have been found to be significantly increased in IgG4-RD patients. According to some theories, another possible mechanism is IgG subclass switching, which is also regulated by T cells. One of the Tfh subsets, circulating Tfh2 (cTfh2), secretes IL-4 and IL-10. IL-4 is a cytokine that mediates IgA, IgE, and IgG isotype class switching, including IgG4. cTfh2 memory cells were found to be more abundant in IgG4-RD subjects. Tfh and its subsets have also been linked to disease activity.[21,23–25]

There is also a role for Treg-associated cytokines and circulating Treg (Foxp3+ T-cells), which secrete IL-10 and TGF-, which promote fibroblast activation and IgG4+ plasma cell infiltration, which are known as the clinical features of IgG4-RD.[7]

Other immune cells are also thought to play a part in IgG4-RD pathogenesis; immunostaining of IgE-positive mast cells revealed that they generate IL-4, IL-10, and TGF-, confirming the involvement of IgE. Fibrosis is promoted by macrophages that have been activated by interleukin-4 and interleukin-13. A class switch recombination pathway involving BAFF is activated and proliferated by toll and nucleotide-binding oligomerization domain-like receptors on macrophages, culminating in IgG4+ B cell activation and proliferation (B-cell activating factor).[1]

Infection

DRB1*0405 binding motif shared by Helicobacter pylori and pancreatic carbonic anhydrase, which are homologous portions of the DRB1* 0405 binding motif. Another similar protein is a plasminogen-binding protein from Helicobacter pylori, as well as the n-recognin 2 component of the ubiquitin-protein ligase E3 enzyme produced in pancreatic acinar cells which are both expressed in the same cell type. Linked between AIP and an IgG4-RD response to steroid treatment was described. Using gastric specimens from subjects with IgG4-RD and those from subjects with other inflammatory conditions as controls, Culver *et al.* discovered no significant difference in clinically relevant symptoms

(dyspepsia), ulceration, or histologic findings (including Helicobacter pylori), with the exception of duodenal IgG4+cells, which were significantly higher in subjects with IgG4-RD. Other bacterial infections, such as TB and Gram-negative bacteria, have been involved with IgG4-RD pathogenesis.[7,11,14,25,26]

The presence of IgA1 and λ-light chain along the glomerular capillary wall in the kidney of a hepatitis C patient with membranous nephropathy has been demonstrated by immunofluorescence investigation. The deposition of IgG4 is prominent in the capillary walls of the glomeruli.[27]

Dysbiosis

Hamada *et al* found that there are alterations of intestinal microbiome in AIP subjects, which is lower proportions of *Bacteroides*, *Streptococcus*, and *Clostridiu*m. The interactions between dysbiosis and immune dysregulation have become current interests, including in autoimmunity. Persistent exposure to PAMPs may initiate innate immunity; some microbial products may induce plasmacytoid dendritic cells to release IFN- and IL-33, resulting in an experimental model of AIP.[28]

According to current understanding, it is not IgG4 itself that is harmful, but rather the underlying pathomechanism that results in elevated blood IgG4 levels and deposition of IgG4+-plasma cells in tissues and other organs.

Diagnosis

IgG4-RD can present clinically in a variety of ways; it can affect multiple organs and is characterized by tumefactive lesions (tumors) that lack the characteristics of infection or malignancy. Musculoskeletal symptoms such as arthritis, enthesitis, or arthralgia are occasionally present in these patients. The major salivary glands, the pancreas, the orbits, the lymph nodes, and the retroperitoneum were all affected by IgG4-RD.[2] In a variety of situations, real-life emergency situations such as aortic dissection, pancreatitis, or meningitis may be shown. Swelling is frequently observed when the lacrimal gland, salivary gland, or lymph nodes are involved. While the disease may manifest as obstructive symptoms in pancreatobiliary and urethral involvement, it may also manifest as obstructive symptoms in other locations. Hypophysitis and kidney disease both exhibit organ dysfunction.[29]

Table 2. Histological Findings of IgG4RD.[14]

Major (1) Dense lymphoplasmacytic infiltrate (2) Fibrosis, arranged at least focally in a storiform pattern (3) Obliterative phlebitis
Other (1) Phlebitis without obliteration of the lumen (2) Increased numbers of eosinophils

The consensus on a uniform definition of IgG4-RD was reached in 2012; however, as knowledge continues to grow, several terminologies have been proposed to describe this disease as a clinical entity. The terms IgG4-associated systemic disease, IgG4-associated sclerosing disease, and IgG4-associated multiorgan lymphoproliferative syndrome are among those proposed. Consensus reached in 2012 agreed on histological findings and evidence of IgG4+ plasma cells within tissue as distinguishing features. Table 2 summarizes the major and most frequently encountered histopathological findings. When at least two of the three major criteria for IgG4RD are present, a pathologic diagnosis of IgG4-RD can be established. Elastin staining is preferable for detecting obliterative phlebitis; hematoxylin and eosin staining do not clearly show obliterated vessels.[14]

Although laboratory tests are not diagnostic, they can aid in diagnosis. Elevated IgG4 levels in the serum are extremely common, as are peripheral eosinophilia, elevated IgE levels, anti-nuclear antibody, and rheumatoid factors [1]. Tissue eosinophilia occurs as a result of increased IL-5 production, while IL-4 and IL-13 stimulate plasma cell IgE production as shown in Table 3.[14]

Table 3. Common Laboratory, Imaging, and Immunohistochemistry Findings.[30]

Laboratory
Eosinophilia
Elevated IgE levels
Hypergammaglobulinemia
Protein electrophoresis : mono/bi/poly-clonal band, beta-gamma bridging
Low complement levels
IgG4 levels >135 mg/dL
Flowcytometry: increased circulating plasmablasts ($CD19^{low}CD38+CD20-CD27+$)
Imaging
Solitary or multiple nodules/masses
Organ enlargement
Homogeneous lesions with well-defined margins
Enhancement/thickening patterns
T2-weighted hypointense lesions on magnetic resonance imaging
Immunohistochemistry
IgG4+ cells per high-power field >10
IgG4+/ total IgG+ cell ratio >40%

In 2019 ACR/EULAR published the classification criteria for IgG4-RD, consisting of 4 steps approach. The first step is to establish entry criteria, which should include typical clinical/radiological or pathologic findings. The second step is to establish exclusion criteria, which include clinical characteristics, serologic, radiologic, pathologic, and other confirmed diagnoses, in order to rule out alternative diagnoses that mimic IgG4-RD. The third step is scoring of clinical, serological, and pathological characteristics of IgG4-RD; this step is performed if it fulfills entry criteria (first step) and does not fulfill any criteria on exclusion step (second step). The fourth step is calculating total score from the third step; if the score ≥ 20, then the criteria fulfilled.[31]

Clinical Presentation

A tumefactive lesion in any organ is the most commonly observed clinical symptom of IgG4-RD. Mikulicz's disease, which was first identified in 1988, manifests as bilateral parotid and lacrimal gland enlargement with no infectious or malignant features. IgG4 was later found to be the causal factor of this disease. Unlike autoimmune pancreatitis, which was originally described in 1961, IgG4-related pancreatitis was not recognized until the 1990s.[32]

IgG4 related pancreatitis

Type 1 and 2 autoimmune pancreatitis (AIP) are recognized. Lymphoplasmacytic infiltration and sclerosing pancreatitis are characteristic of AIP-1. In comparison to AIP-2, AIP-1 is more prevalent in the Asian population, is frequently diagnosed in older adults, and has a high relapse rate. Nearly 40% of cases were isolated, while the remainder had multiple organ involvement. Apart from the clinical manifestations of IgG4RD, sclerosing ductopathy of the pancreatic duct with irregular lumen narrowing on imaging (ERCP/MRCP) is common in type 1 AIP.[15,33]

IgG4 related sclerosing cholangitis

Sclerosing cholangitis associated with IgG4 is frequently associated with pancreatitis associated with IgG4 (60–80% of cases). Men are affected eight times more frequently than women by this disease. According to cholangiographic features, there are four types of IgG4-related sclerosing cholangitis: Type 1 (Isolated distal stenosis of the common hepatic duct (CHD)**,** Type 2 (Diffuse stenoses**),** Type 3 (Hilar and distal CHD stenosis)**,** Type 4 (Isolated hilar CHD stenosis).

Surgical intervention is necessary, with a liver biopsy being performed in type 2 and a bile-duct biopsy being performed in the other type. A colonoscopy is also required in type 2 to rule out the possibility of co-existing inflammatory bowel disease (IBD) (IBD). Hepatobiliary cancer should be regarded as a possibility in the differential diagnosis of other diseases.[33,34]

IgG4 related orbital disease

It is possible that enlargement of the lacrimal gland, a retro-orbital pseudotumor, orbital myositis, or other orbital structures with tumefactive inflammatory lesions are manifestations of orbital involvement in this disease. Lesions of the ocular adnexa with well-defined borders and isoattenuation on precontrast CT, T1-isointense and T2-hypointense MRI lesions with a homogeneous internal architecture, enhancement patterns, and bone remodeling without destruction.[30,35]

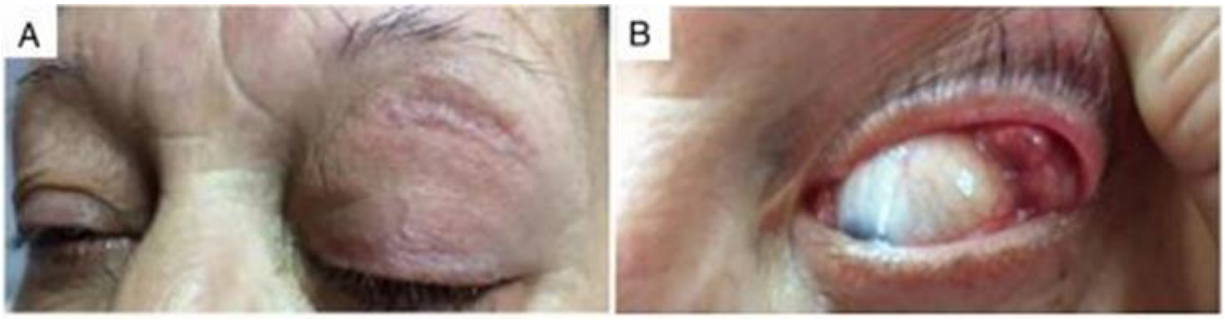

Figure 2. A. Left Palpebral tumefaction. B. Left dacryoadenitis. Reprinted with permission from Flores Balverdi. IgG4-related orbital disease. 2018; 93:494-6.[36]

Mikulicz's disease/ IgG4 related sialodenitis

Over the last century, it has been recognized as Mikulicz's disease; it was recently recognized as the classic IgG4-RD. Sialodenitis associated with IgG4 is marked by submandibular and parotid gland enlargement. Unlike in Sjgren's syndrome, where parotid gland enlargement is predominant, submandibular gland enlargement is more prominent in IgG4-related sialodenitis. On T2WI MRI, well-defined, iso/hypopointense lesions with uniform enhancement and no vascular occlusion or compression symptoms are seen.[37,38]

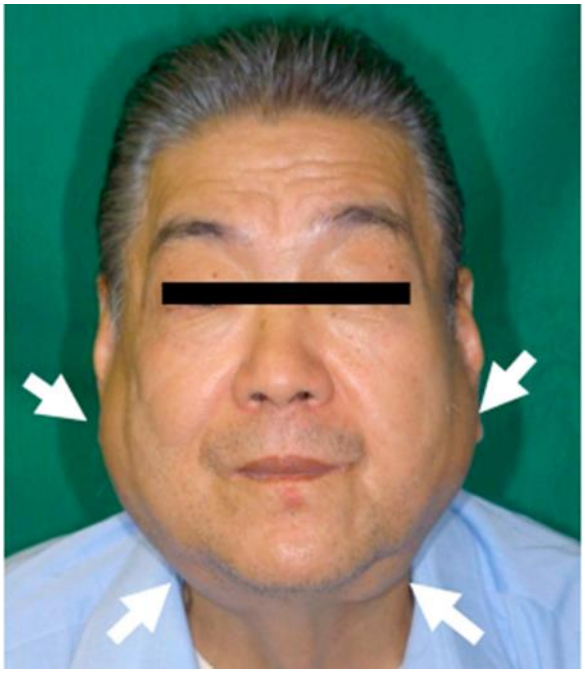

Figure 3. Painless swelling of both sides of the lower jaw is remarkable and the parotid glands area is also swollen at relapse. Reprinted with permission from Tomoko Sugiyama. Relapsed IgG4-related dacryoadenitis and sialodenitis, so called Mikulicz's disease: A case report. 2013; 25:368-73.[39]

IgG4 related kidney disease and membranous nephropathy

Tubulointerstitial nephritis is the most frequent renal manifestation of IgG4RD, accounting for about 80% of all cases. It is believed that another organ is involved in the majority of instances of IgG4-related kidney illness. With varied degrees of proteinuria, creatinine increases can develop at different rates, ranging from slow to fast. When IgG4-associated kidney disease is present, the pathologic results are consistent with membranous glomerulonephritis, which presents clinically as nephrotic syndrome. However, this is only true in a small proportion (7 percent) of cases. It is important to distinguish between autoimmune illnesses caused by IgG4 and those caused by idiopathic autoimmune diseases. On radiographic examination, diffuse bilateral renal hypertrophy can be seen in a significant amount of cases. Another radiologic finding that is more common in the cortical zone is the presence of several bilateral lesions on the same side. Idiopathic membranous nephropathy is another type of kidney disease that might present itself. Membranous nephropathy is the most common glomerular lesion in individuals with IgG4-RD, accounting for 7 percent to 10 percent of all patients with the condition in any given year.[40,41]

IgG4 related aortitis, periaortitis, and periarteritis

In contrast to Takayasu's arteritis, which affected the aortic branch, IgG4-related aortitis typically does not affect this branch. Aneurysms and dissections are the consequence of aortitis produced by IgG4 antibodies. The presence of a coronary artery involvement in this case is unusual. Aortitis linked with IgG4 is commonly observed in combination with other symptoms of Ormond's disease, such as retroperitoneal fibrosis associated with IgG4, abdominal aortitis associated with IgG4, and perianeurysmal fibrosis associated with IgG4. There are several common clinical manifestations,

including discomfort in the back, flanks, lower abdomen, or thighs that is not clearly localized; leg edema; and hydronephrosis (water retention) owing to ureteral compression. Aortic/arterial regions, which contain connective tissue around the abdominal aorta or its initial branches, are commonly implicated, as are periureteral areas, and a plaque-like mass involving the retroperitoneum, which is involved in a small percentage of cases. Another example included a patient who experienced edema in one leg alone. An increased blood IgG4 level, as well as constriction of the iliac vein by a soft tissue mass around the iliac artery, indicate IgG4-related periarteritis, as shown by computed tomography (CT).[2, 42,38]

IgG4-related pulmonary disease

IgG4 related lung disease can present in several manifestations, including interstitial lung disease, sarcoidosis, mass, or small airway involvement such as bronchiolitis. Pulmonary vascular involvement has also been reported ACR/recent EULAR's criteria for igG4-RD included peribronchovascular and septal thickening or paravertebral band-like soft tissue on imaging. Imaging has developed into one of the diagnostic modalities for lung and chest involvement in igG4-RD.[43,44, 45]

2. Conclusion

Numerous pathomechanisms have been proposed and studied in order to deduce the precise pathogenesis of IgG4-RD, and additional research is required. Despite the fact that the histopathologic findings are identical, IgG4-RD manifests itself in a variety of ways clinically, with the most notable being tumefactive lesions in any organ and compression/mass effects on surrounding tissues. Other clinical alterations, however, are found in patients with hypothesized pathomechanisms such as renal illness, lymphoproliferative diseases, and changes in the composition of blood cells. Lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis are histologic features of IgG4-RD. Clinicians continue to face difficulties with clinical diagnosis, laboratory findings, radiologic characterization, and molecular studies of IgG4-RD.

3. References

1. Zwerina J. IgG4-related disease : current challenges and future prospects. 2016; 189–99.
2. Stone JH, Pillai S. IgG4-Related Disease. In: Gary S. Firestrein, MD, Ralph C.Budd, MD, Sherine E.Gabriel, MD, MSc, IAIN B. McINNES, PhD, FRCP, FRSE, FMedSci, James R. O'Dell M, editor. Kelley & Firestein's Textbook of Rheumatology. 10th ed. Philadelphia: Elsevier; 2017; 2026–36.
3. Ryu JH, Horie R, Sekiguchi H, Peikert T, Yi ES. Spectrum of disorders associated with elevated serum IgG4 levels encountered in clinical practice. International Journal of Rheumatology. 2012; 2012(June).
4. Atallah PC, Shea R, Waldrop MD. The Many-Faced God : IgG4-Related Disease- a Clinical Review. 2003.
5. Uchida K, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-related disease in Japan based on nationwide survey in 2009. International Journal of Rheumatology. 2012; 2012.
6. Inoue D, Yoshida K, Yoneda N, Ozaki K, Matsubara T, Nagai K, et al. IgG4-related disease: Dataset of 235 consecutive patients. Medicine (United States). 2015; 94(15): 1–8.
7. Weindorf SC, Frederiksen JK. IgG4-Related Disease: A Reminder for Practicing Pathologists. Archives of Pathology & Laboratory Medicine. 2017; 141(11): 1476–83.
8. Yamamoto M, Takahashi H. IgG4-Related Disease in Organs Other than the Hepatobiliary-Pancreatic System. Seminars

in Liver Disease. 2016; 36(3): 274–82.
9. Wallace ZS, Zhang Y, Perugino CA, Naden R, Choi HK, Stone JH. Clinical phenotypes of IgG4-related disease: An analysis of two international cross-sectional cohorts. Annals of the Rheumatic Diseases. 2019; 78(3): 406–12.
10. Karim F, Loeffen J, Bramer W, Westenberg L, Verdijk R, van Hagen M, et al. IgG4-related disease: A systematic review of this unrecognized disease in pediatrics. Pediatric Rheumatology. 2016; 14(1).
11. Umehara H, Nakajima A, Nakamura T, Kawanami T, Tanaka M, Dong L, et al. IgG4-related disease and its pathogenesis-cross-talk between innate and acquired immunity. International Immunology. 2014; 26(11): 585–95.
12. Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: From structure to effector functions. Frontiers in Immunology. 2014; 5(OCT): 1–17.
13. Nirula A, Glaser SM, Kalled SL, Taylora FR. What is IgG4? A review of the biology of a unique immunoglobulin subtype. Current Opinion in Rheumatology. 2011 Jan; 23(1): 119–24.
14. Deshpande V, Zen Y, Chan JKC, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Modern Pathology. 2012; 25(9): 1181–92.
15. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-relateddisease (IgG4RD): General concept and details. Modern Rheumatology. 2012; 22(1): 1–14.
16. Koike T. IgG4-related disease: Why high IgG4 and fibrosis? Arthritis Research and Therapy. 2013; 15(1): 1–2.
17. Oguchi T, Ota M, Ito T, Hamano H, Arakura N, Katsuyama Y, et al. Investigation of Susceptibility Genes Triggering Lachrymal/Salivary Gland Lesion Complications in Japanese Patients with Type 1 Autoimmune Pancreatitis. Rakonczay Z, editor. PLoS ONE. 2015; 10(5): e0127078.
18. Sebastian A, Donizy P, Wiland P. IgG4-Related Disease and the Spectrum of Mimics in Rheumatology. In: Maślińska M, editor. Chronic Autoimmune Epithelitis - Sjogren's Syndrome and Other Autoimmune Diseases of the Exocrine Glands [Internet]. IntechOpen; 2019 [cited 2021 Jul 28]. Available from: https://www.intechopen.com/books/chronic-autoimmune-epithelitis-sjogren-s-syndrome-and-other-autoimmune-diseases-of-the-exocrine-glands/igg4-related-disease-and-the-spectrum-of-mimics-in-rheumatology
19. Stone JH. IgG4-related disease: pathophysiologic insights drive emerging treatment approaches. Clinical and experimental rheumatology. 2016; 34(4): 66–8.
20. Wallace ZS, Deshpande V, Mattoo H, Mahajan VS, Kulikova M, Pillai S, et al. IgG4-Related Disease: Baseline clinical and laboratory features in 125 patients with biopsy-proven disease HHS Public Access. Arthritis Rheumatol. 2015; 67(9): 2466–75.
21. Kamekura R, Takahashi H, Ichimiya S. New insights into IgG4-related disease: emerging new CD4+ T-cell subsets. Current opinion in rheumatology. 2019; 31(1): 9–15.
22. Newman JH, Shaver A, Sheehan JH, Mallal S, Stone JH, Pillai S, et al. IgG4-related disease: Association with a rare gene variant expressed in cytotoxic T cells. Molecular Genetics and Genomic Medicine. 2019; 7(6): 1–8.
23. Maehara T, Moriyama M, Nakamura S. Pathogenesis of IgG4-related disease: a critical review. Odontology. 2019 Apr; 107(2):

127–32.

24. Akiyama M, Suzuki K, Yasuoka H, Kaneko Y, Yamaoka K, Takeuchi T. Follicular helper T cells in the pathogenesis of IgG4-related disease. Rheumatology. 2018 Feb 1; 57(2): 236–45.
25. Culver EL, Smit WL, Evans C, Sadler R, Cargill T, Makuch M, et al. No evidence to support a role for Helicobacter pylori infection and plasminogen binding protein in autoimmune pancreatitis and IgG4-related disease in a UK cohort. Pancreatology. 2017; 17(3): 395–402.
26. Della-Torre E, Lanzillotta M, Doglioni C. Immunology of IgG4-related disease. Clinical and Experimental Immunology. 2015; 181(2): 191–206.
27. Miura N, Uemura Y, Suzuki N, Suga N, Maeda K, Yamaguchi S, et al. An IgA1-lambda-type monoclonal immunoglobulin deposition disease associated with membranous features in a patient with chronic hepatitis C viral infection and rectal cancer. Clinical and Experimental Nephrology. 2010; 14(1): 90–3.
28. Hamada S, Masamune A, Nabeshima T, Shimosegawa T. Differences in Gut Microbiota Profiles between Autoimmune Pancreatitis and Chronic Pancreatitis. Tohoku J Exp Med. 2018; 244(2): 113–7.
29. Weindorf SC, Frederiksen JK. IgG4-related disease: A reminder for practicing pathologists. Archives of Pathology and Laboratory Medicine. 2017; 141(11): 1476–83.
30. Stone JH, Brito-Zerón P, Bosch X, Ramos-Casals M. Diagnostic Approach to the Complexity of IgG4-Related Disease. Mayo Clinic Proceedings. 2015; 90(7): 927–39.
31. Wallace ZS, Naden RP, Chari S, Choi H, Della-Torre E, Dicaire JF, et al. The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease. Arthritis and Rheumatology. 2020; 72(1): 7–19.
32. Takahashi H, Yamamoto M, Suzuki C, Naishiro Y, Shinomura Y, Imai K. The birthday of a new syndrome: IgG4-related diseases constitute a clinical entity. Autoimmunity Reviews. 2010; 9(9): 591–4.
33. Okazaki K, Yanagawa M, Mitsuyama T, Uchida K. Recent advances in the concept and pathogenesis of IgG4-related disease in the hepato-bilio-pancreatic system. Gut and Liver. 2014; 8(5): 462–70.
34. Kleger A, Seufferlein T, Wagner M, Tannapfel A, Hoffmann TK, Mayerle J. IgG4-Related Autoimmune Diseases. Deutsches Aerzteblatt Online. 2015.
35. Song YS, Choung HK, Park SW, Kim JH, Khwarg SI, Jeon YK. Ocular adnexal IgG4-related disease: CT and MRI findings. British Journal of Ophthalmology. 2013; 97(4): 412–8.
36. Flores Balverdi J, Baenas DF, Riscanevo NC, Sánchez AV, Figueroa Rosales R, Alvarellos A. Enfermedad orbitaria relacionada con Ig-G4. Archivos de la Sociedad Española de Oftalmología. 2018; 93(10): 494–6.
37. Katsura M, Mori H, Kunimatsu A, Sasaki H, Abe O, MacHida T, et al. Radiological features of IgG4-related disease in the head, neck, and brain. Neuroradiology. 2012; 54(8): 873–82.
38. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. The Lancet. 2015; 385(9976): 1460–71.
39. Sugiyama T, Jinbu Y, Matsumoto K, Itoh H, Noguchi T, Kusama M. Relapsed IgG4-related dacryoadenitis and sialoadenitis, so called Mikulicz's disease: A case report. Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology. 2013; 25(4):368–

73.
40. Ma XY, Xu HP, Sun JY, Gedara YSS, Sun FY. Idiopathic membranous nephropathy in a patient diagnosed with IgG4-related disease: A case report. Medicine. 2020; 99(42): e22817.
41. Cortazar FB, Stone JH. IgG4-related disease and the kidney. Nature Reviews Nephrology. 2015; 11(10): 599–609.
42. Koda R, Tsuchida M, Iino N, Murata M, Inui K, Nakagawa Y, et al. IgG4-related periarteritis successfully diagnosed by an alternative prostate biopsy. Internal Medicine. 2019; 58(16): 2401–6.
43. Zhou Y, Shao L, Ruan W, Jin J, Xu H, Ying K, et al. Pulmonary vascular involvement of IgG4-related disease: Case series with a PRISMA-compliant systemic review. Medicine (United States). 2019; 98(6).
44. Chen C-F, Chu K-A, Tseng Y-C, Wu C-C, Lai R-S. IgG4-related lung disease presenting as interstitial lung disease with bronchiolitis: A case report. Medicine. 2017; 96(49): e9140.
45. Matsui S. IgG4-related respiratory disease. Modern Rheumatology. 2019 Mar 4; 29(2): 251–6.