

Review Article

IgG4-Related Disease: Insights into a Multisystem Inflammatory Disorder

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ABSTRACT

IgG4-related disease is a multisystem inflammatory disease characterized by the accumulation of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. Although it is often referred to as a disease of the pancreas, salivary glands, and kidneys, it occurs with the involvement of almost any organ, which makes the diagnosis very difficult. The reason is not well understood, but an abnormal immune response, particularly that involving helper T cells, regulatory T cells, and B cells, plays an important role. The diagnosis is usually made based on clinical, laboratory, and histopathological lines. Serum IgG4 levels are minimally supportive when determining a diagnosis, never definitively so, but for the most part. The traditional management starts with glucocorticoids, which have been proven to alleviate the condition; however, flare-ups occur frequently. Consequently, steroid-sparing agents like rituximab are becoming increasingly employed to treat the disease over the long term. This review highlights the contemporary aspects of research by relating IgG4-RD in the areas of epidemiology, underlying mechanisms, natural history, clinical factors, diagnostic difficulties, and therapeutic strategies. The ongoing research provides better insights on the possibility of other targeted therapies and standardized guidelines that would help improve the care of patients. The elucidation of this disorder is vital for the early diagnosis and treatment of patients to avert irreversible organ damage and improve the outcome.

Key words: Storiform fibrosis, IgG4-related disease, Rituximab, Obliterative phlebitis, Autoimmune pancreatitis

Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory disease associated with elevated serum IgG4 levels, infiltration of IgG4+ plasma cells, and severe fibrosis in the affected tissues [1]. IgG4-related disease is usually characterized by storiform fibrosis, and hyperplastic ectopic germinal center formation, which mimics many other diseases [2]. The most frequent localizations include the pancreas and salivary glands [3]. Other common manifestations are observed in tubulointerstitial nephritis, dacryoadenitis, and peri aortitis. IgG4-RD has been found to affect the pancreas, bile duct, lacrimal glands, salivary glands, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, skin, and the breast. Therefore, IgG4-RD includes a wide variety of diseases, including Mikulicz's disease (MD) [4, 5]. In the last decade, several pathophysiological mechanisms, potentially responsible for developing IgG4-RD, have been described. B cells and plasmablasts play an important role in IgG4-RD, secreting autoantibodies or acting as antigen-presenting cells in the expansion of pathogenic T cells [6].

Presently, the pathophysiological mechanisms underlying IgG4-RD have not yet been fully established. Diagnosis of

IgG4-RD is based on a set of clinical, serological, and pathological criteria, and the histological picture is critical for diagnosis [6]. The epidemiology of the disease is unclear; however, it often affects predominantly male individuals starting in their middle years [7]. Elevated serum IgG4 levels, while suggestive, are not definitive on their own [8]. Hallmarks of the diseases are a lymphoplasmacytic infiltrate enriched with IgG4 plasma cells, a storiform pattern of fibrosis, and obliterative phlebitis [9]. The goal of disease management in patients with IgG4-related disease is to reduce inflammation, maintain disease remission, and preserve organ function while minimizing the adverse effects of treatment. Watchful waiting is appropriate in a minority of patients [10]. Steroids are the first-line therapy but Rituximab may be used as steroid-sparing treatment [11].

Azathioprine, 6-mercaptopurine, Cyclophosphamide, Mycophenolic acid, and Methotrexate have also been used as steroid-sparing agents [11]. This literature review aims to provide a comprehensive overview of IgG4-RD, including its pathophysiology, clinical manifestations, diagnostic challenges, and treatment options. By synthesizing current

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knowledge, this review seeks to enhance understanding and inform clinical practice in managing this complex and multifaceted disorder.

Epidemiology

Although the disease has been described worldwide, the true epidemiology of IgG4-RD remains unknown due to a lack of research, the disease usually presents in the sixth or seventh decade of life, with a median age of diagnosis of 59 to 68 years [3]. IgG4-RD has been increasingly recognized over the last 20 years and described in patients of diverse racial and ethnic backgrounds [12]. The male-to-female ratio ranges from 1.6:1 for head and neck involvement and ranges from 4:1 for other sites [13]. In the occupational context of blue-collar workers, exposure to mineral dust, vapors, gases, fumes, and asbestos has been linked to an increased risk of developing IgG4-RD in the biliary tract and pancreas [14] [15]. In general, IgG4-RD is still an underdiagnosed condition, and more epidemiological research is required to fully comprehend its global distribution and implications.

Pathology

Histopathology is a key diagnostic tool to study the IgG4-related disease. The three central pathology features include lymphoplasmacytic infiltration, obliterative phlebitis, and storiform fibrosis [8], [16]. The gold standard for the diagnosis of IgG4-RD, regardless of the organs involved, is the identification of typical histopathologic features [17]. Storiform fibrosis is a histological pattern characterized by irregular, loosely arranged whorls on low-power light microscopy, akin to a straw blanket [8]. In Obliterative phlebitis, the venous channels are obliterated by a dense lymphoplasmacytic infiltrate. Lymphocytes and plasma cells are seen both within the wall of the venous channel and within the lumen. Partially obliterated veins with transmural inflammatory [18]. Infiltrates are also consistent with the diagnosis of IgG4-related disease. For the diagnosis of IgG4-RD, immunohistochemistry is crucial. Increased IgG4-positive plasma cells in tissue samples are the hallmark finding; an IgG4/IgG ratio of more than 40% and a recommended threshold of more than 10 IgG4-positive cells per high-power field (HPF) are the standard criteria [19].

To differentiate IgG4-RD from disorders with comparable presentations, such as lymphoma or other autoimmune diseases, these results must be interpreted alongside clinical and further histopathological features. IgG4-RD may affect several organ systems, such as the kidneys, salivary glands, and pancreas, resulting in a variety of clinical presentations [20]. Renal disease has been associated with IgG4-related sclerosing disease, usually in the form of plasma cell-rich tubulointerstitial nephritis (TIN) and Tubular basement membrane immune complex deposits [21]. The most common initial involved organ was the submandibular gland (26.3%) followed by the pancreas (20.4%), lacrimal gland (20.1%), and retroperitoneum

(9.1%) in IgG4-RD patients [22]. Submandibular glands are more frequently affected; intense tissue fibrosis seems to be a common feature of biopsies obtained from submandibular glands and obliterative phlebitis is present in almost one-third of patients with submandibular involvement [6]. In the pancreas, autoimmune pancreatitis is the condition associated with the presence of periductal lymphoplasmacytic infiltrate and fibrosis is prominent [23]. Riedel thyroiditis (RT) is a rare form of chronic thyroiditis, characterized by inflammatory proliferative fibrosis which involves the thyroid parenchyma and surrounding tissue structures [24]. Recognition and diagnosis through histological and immunostaining techniques are essential for effective management and to prevent irreversible organ damage [8].

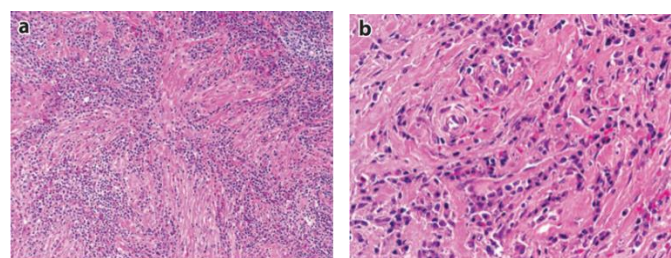


Figure 1

Histopathological Characteristics of Immunoglobulin G4-Related Disease (IgG4-RD). (a) The storiform pattern of fibrosis. (b) A high-power view of the image showing dense fibrosis within which lymphocytes, plasma cells, and occasionally eosinophils are embedded [8].

Pathogenesis

A complex interaction of immune responses plays a role in its pathogenesis. Interleukins 4, 5, 10, 13 and transforming growth factor β (TGF- β) are overexpressed through an immune reaction in which type 2 helper T (Th2) cells predominate, followed by activation of regulatory T (Treg) cells [5]. These cytokines contribute to eosinophilia, elevated serum IgG4 and IgE concentrations, and progression of fibrosis that are characteristic of IgG4-related disease [20]. IL-21 produced by macrophages has been reported to control the functional activity of effector follicular helper T (Tfh) cells and to promote their formation of ectopic GCs, which are often seen in lesions of IgG4-RD [19]. Also, Tfh-subsets of cells may play a crucial role in the differentiation of B cells into IgG4-producing plasmablasts, leading to abnormal IgG4 production and irreversible tissue damage [25].

CD4⁺ cytotoxic T lymphocytes (CD4⁺ CTLs) in IgG4-RD tissues secrete profibrotic cytokines including interleukin (IL)-1 β , transforming growth factor β 1 (TGF- β 1), and interferon γ (IFN- γ) as well as cytolytic molecules such as perforin and granzymes A and B [26]. Due to the anti-inflammatory properties of IgG4, IgG4-releasing plasmablasts represent a regulatory response to inflammatory stimuli. Despite increased serum IgG4 levels and tissue IgG4+plasma cells, which are

characteristic of IgG4-RD, abnormal T cell activity is considered as the principal immune defect [27]. Higher susceptibility to IgG4-RD has been linked to genetic factors, specifically HLA class II alleles like HLA-DRB1 and HLA-DQB1, indicating a hereditary component. Some theories propose that infections or environmental antigens might trigger molecular mimicry, leading to an autoimmune response in individuals who are genetically predisposed [3], [28]. B cell-depletion therapy is a highly effective treatment for IgG4- RD, confirming the importance of B cells in the pathophysiology of this disease [29].

Clinical Manifestation

IgG4-related disease (IgG4-RD) can manifest through a wide range of clinical presentations, and its diverse syndromes often cloud the overall clinical picture, frequently resulting in missed or delayed diagnoses [7]. Fevers and hectic presentations are unusual but fatigue commonly accompanies IgG4-related disease [16]. The presentation of IgG4-related disease is typically subacute. Traditionally, IgG4-related pancreatitis is regarded as the most frequent manifestation of IgG4-RD [4]. Many individuals with IgG4-RD exhibit characteristics of atopic conditions, they may experience respiratory symptoms similar to asthma, such as coughing, wheezing, and shortness of breath [3]. The allergic phenomena that occur in a large subset of patients with IgG4-RD—allergic rhinitis, nasal polyps, chronic sinusitis, nasal obstruction, and rhinorrhea—often manifest most prominently in the ear, nose, and throat region [8].

In IgG4-related sialadenitis (IgG4-RS), swelling of the lacrimal and salivary glands is typically bilateral, though not always, and painless, usually lasting more than 3 months. The submandibular glands are most commonly affected, but the parotid, sublingual, and labial salivary glands can also be involved. Xerostomia occurs in 30% of patients, though less frequently than in Sjögren’s syndrome (SSj). Differentiating IgG4-RD from SSj can be challenging, as these conditions often share similar features [6]. IgG4-related tubulointerstitial nephritis (IgG4-TIN) is the most prevalent renal manifestation of IgG4-related disease. However, other conditions such as IgA nephropathy, membranoproliferative glomerulonephritis, and minimal change disease have also been reported. The characteristic histopathological features include plasma cell-rich tubulointerstitial nephritis with fibrosis and a notable presence of infiltrating eosinophils [9].

The vascular wall affected by IgG4-RD is susceptible to aneurysm formation and occasionally to dissection or perforation [11]. IgG4-related retroperitoneal fibrosis (IgG4-RPF) is a rare form of IgG4-RD, the diagnosis of which often relies on radiological technology [7]. The thyroid gland enlargement caused by Riedel’s thyroiditis can lead to neck pain, dyspnea, dysphagia, and dysphonia [8]. Many RPF series suggest that IgG4-RD is responsible for 40% of idiopathic RPF cases [11]. Thickening of the bronchovascular bundle, best

shown by CT, is a characteristic lesion in the lung [16]. Destructive bone lesions that mimic granulomatous polyangiitis (formerly Wegener’s granulomatosis) or tumors in the sinuses, head, and middle-ear spaces have been reported [8]. Conditions previously thought to be unrelated are now recognized as part of the IgG4-related disease spectrum, as shown in Table 1.

Table – 1: Conditions that are considered unrelated that are now recognized as part of IGg4 Related Spectrum

Affected Organ(s) or Tissue (s)	Condition
Mediastinum	Fibrosing Mediastinitis
Aorta	Inflammatory Aortic Aneurysm
Thyroid	Riedel’s Thyroiditis
Pancreas	Sclerosing Pancreatitis
Dura Mater	Hypertrophic pachymeningitis
Mesentery	Sclerosing Mesenteritis
Salivary and Lacrimal Glands	Mikulicz’s Syndrome
Submandibular Glands	Küttner’s tumor
Retroperitoneum	Retroperitoneal Fibrosis (Ormond’s Disease)
Orbits, upper respiratory tract	Eosinophilic Angiocentric Fibrosis
Skin	Pseudolymphoma
Pituitary Gland	Hypophysitis
Peripheral Nerve	Perineural mass
Stomach	Chronic Gastritis or Ulcer
Pleura	Nodular Pleuritis

Diagnosis

The diagnosis of IgG4-RD primarily relies on the documentation of certain characteristic histopathologic features and only secondarily on the presence of an elevated IgG4 concentration in blood or tissue [4]. Evidence suggests that the ratio of IgG4 to total IgG in serum may be more useful for diagnosis than IgG4 concentration alone [6]. Serological findings in IgG4-RD are mostly non-specific. ESR may be moderately elevated, while CRP is typically normal, except for slight increases in cases like retroperitoneal or aortic involvement [30]. Abdominal CT and magnetic resonance imaging (MRI) are the most frequently utilized diagnostic radiological technologies [7]. Multiple hypodense lesions are the most common observation in IGG4-related kidney disease [9]. Typical histopathological features include storiform fibrosis, dense lymphoplasmacytic infiltrates, and obliterative phlebitis. Serum IgG4 level is neither a specific nor a sensitive

marker for IgG4-RD, but high values have been found to correlate with the severity and recurrence of disease [27]. Eosinophils are present in at least 50% of IgG4-RD lesions and might be the histological picture in those cases of orbital or upper respiratory tract involvement [28]. Notably, 18F-fluorodeoxyglucose-PET only reveals metabolically active sites, and unfortunately, not all active lesions are detectable [11]. Cholangiogram features that are characteristic of IgG4-SC include long (over one-third the length of strictures in the bile duct) and multifocal strictures, mild upstream dilatation and proximal biliary disease in conjunction with diffuse pancreatic swelling, with a thin, diffusely-narrowed pancreatic duct [15].

Treatment

The goal of disease management in patients with IgG4-related disease is to reduce inflammation, maintain disease remission, and preserve organ function while minimizing the adverse effects of treatment. Successful remission induction is defined as the resolution of symptoms related to active disease and normalization (or substantial improvement) of most biochemical and radiological abnormalities [10]. Most clinical manifestations of IgG4-related disease respond to glucocorticoids. These agents are the first-line, standard-of-care approach for most patients [16]. but disease flares are common [20]. When relapse predictors like multi-organ involvement, elevated baseline IgG4 and IgE, or peripheral eosinophilia are present, Disease-modifying antirheumatic drugs (DMARDs) may be added to the initial steroid therapy to boost remission chances. Drugs like azathioprine, mycophenolate mofetil, methotrexate, leflunomide, tacrolimus, ciclosporin A, iguratimod, and cyclophosphamide have been used with glucocorticoids. However, evidence supporting their added benefit is limited, mostly based on retrospective studies [10, 11, 13, 30].

However, more research is needed to confirm whether DMARDs alone can effectively induce remission and to determine the ideal situations where they could be used as an alternative to glucocorticoids. This is crucial, as access to advanced therapies and biologics often depends on geographical, economic, and social factors, impacting treatment availability for many patients [14]. An international consensus of experts on disease management concluded that urgent treatment is appropriate in biliary disease, even when asymptomatic, to prevent infectious cholangitis and permanent fibrosis that might complicate untreated disease [15]. Further studies are needed to provide reliable and standardized guidelines for the long-term management of IgG4-RD.

Future prospects

There is growing recognition that the role of innate immunity in IgG4-RD may have been underexplored. Future research will be crucial in understanding whether IgG4 antibodies actively contribute to the disease or are simple bystanders. Additionally,

investigating potential antigenic triggers that could initiate the disease and unraveling the complex interactions between B and T cells—particularly how they lead to tissue fibrosis—are essential. Uncovering these mechanisms could open new avenues for developing more precise and effective therapies, ultimately transforming the way we manage IgG4-RD and improving patient outcomes. The focus is gradually moving away from the use of glucocorticoids and nonbiologic DMARDs, towards more precise therapies. These new treatment options can be thoughtfully selected and tailored to each patient's unique clinical presentation, allowing for a more personalized and rational approach to managing the disease.

CONCLUSION

IgG4-related diseases represent a challenging clinical entity due to their variable presentation and multisystem involvement. Early and accurate diagnosis is critical to prevent irreversible organ damage. While glucocorticoids remain the cornerstone of treatment, there is an increasing shift towards more precise, B-cell-targeted therapies like rituximab. Understanding the underlying immune mechanisms, particularly the role of T and B cell interactions, is essential for developing effective and personalized treatments. Future research should prioritize identifying antigenic triggers, refining diagnostic criteria, and exploring novel therapeutic agents that minimize side effects and elevate long-term outcomes. A multidisciplinary approach is crucial to optimize patient care and address the diverse manifestations of this enigmatic disorder.

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