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IgG4-Related Disease: The Importance of Early Diagnosis in Clinical Practice

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Abstract

Background: IgG4-related disease (IgG4-RD) is a chronic immune-related fibroinflammatory disease characterized by multiorgan involvement and a highly heterogeneous clinical presentation, often mimicking malignant, infectious, or autoimmune conditions. These features contribute to frequent diagnostic delays and can lead to irreversible organ damage.

Aim: To summarize the current evidence on the pathogenesis, clinical manifestations, diagnostic approach, and treatment of IgG4-RD, with particular emphasis on the importance of early diagnosis in clinical practice.

Material and Methods: A review of medical literature published between 2015 and 2025 was conducted using major bibliographic databases, including PubMed. The search covered articles released within this period and employed the following keywords and their combinations: “IgG4-related disease”, “IgG4-RD”, “autoimmune pancreatitis”, “retroperitoneal fibrosis”, “IgG4-related kidney disease”.

Results: IgG4-RD most commonly affects the salivary and lacrimal glands, pancreas, bile ducts, kidneys, and retroperitoneal space. Delayed diagnosis of the disease is associated with progression of fibroinflammatory changes and permanent organ dysfunction. Glucocorticoids remain first-line therapy, while immunosuppressive drugs and rituximab are effective options in case of recurrence or resistance to treatment. Data from clinical cohorts indicate that the lack of early immunosuppression significantly increases the risk of organ failure.

Conclusions: IgG4-RD should be routinely considered in the differential diagnosis of unexplained mass lesions or chronic inflammatory and fibrotic disorders. Early diagnosis and prompt initiation of immunosuppressive therapy are crucial for preventing irreversible organ damage and improving patient outcomes.

Keywords: IgG4-related disease, clinical manifestations, early diagnosis, differential diagnosis, immunosuppression, organ fibrosis

1. Introduction

IgG4-related disease (IgG4-RD) is a chronic idiopathic disorder characterized by tissue infiltration with T and B lymphocytes as well as IgG4-producing plasma cells. This leads to progressive fibrosis and impairment of organ function [1,2].

The clinical presentation is highly heterogeneous, and almost any organ may be involved [3]. For this reason, IgG4-RD is frequently misdiagnosed as a malignant, infectious, or autoimmune condition, such as Sjögren's syndrome or systemic vasculitis, which may lead to delayed diagnosis and inappropriate treatment [4].

Diagnosis is based on a comprehensive clinical assessment supported by laboratory testing, imaging studies, and histopathological evaluation [5].

Glucocorticoids remain the first-line therapy for IgG4-RD, while immunosuppressive and biologic agents are used in cases of disease relapse or resistance to standard treatment [4,6].

The aim of this study is to present the current state of knowledge regarding the pathogenesis, clinical manifestations, diagnosis, and treatment of IgG4-RD, with particular emphasis on the importance of early recognition of the disease.

2. Epidemiology

IgG4-RD is classified as a rare disease; however, the number of diagnosed cases has been steadily increasing. The actual prevalence remains difficult to estimate due to the heterogeneous clinical presentation of the disease [7]. In the latest population-based study from Slovenia, the annual incidence was estimated at approximately 5 cases per 1,000,000 people per year. The median age at diagnosis was 64 years, and the disease was more common in men than in women, with a male-to-female ratio of 2.9:1 [8].

3. Pathogenesis of IgG4-RD

The pathogenesis of IgG4-RD involves a complex dysregulation of the immune system. The disease process involves the interactions among T and B lymphocytes, plasma cells, fibroblasts, and cytokines, leading to the development of fibrosis and inflammatory infiltrates rich in IgG4-positive cells within affected organs. CD4-positive cytotoxic T lymphocytes are believed to play a key role in the pathogenesis of IgG4-RD [9,10]. These cells produce proinflammatory cytokines, including transforming growth factor-β (TGF-β) and interferon-γ (IFN-γ), which promote inflammation and fibrogenesis. Follicular helper T cells (Tfh) also play a significant role by facilitating B-cell differentiation into plasma cells and memory cells. Pathological activation of B lymphocytes leads to increased production of IgG4-positive plasma cells, which represent a characteristic feature of IgG4-RD inflammatory infiltrates [11].

Despite significant progress in understanding the disease mechanisms, IgG4-RD is considered to result from the interplay of many factors, including chronic antigenic stimulation, dysregulation of innate immunity, and abnormal activation of T and B lymphocytes, but no single causal factor has been definitively identified [12].

4. Clinical presentation and organ involvement in IgG4-RD

IgG4-RD is characterized by a chronic fibroinflammatory infiltration which may involve various organs and tissues, leading to an extremely diverse clinical picture. The clinical features of the disease often mimic other conditions, such as cancer, autoimmune or inflammatory disorders [7]. In many patients, the disease develops gradually, and the first symptoms are non-specific and often include chronic fatigue, discomfort in affected structures and gradually progressive complaints resulting from enlargement and dysfunction of the involved organs [7,13]. The disease often affects more than one organ and its course may differ among individual patients, further complicating accurate diagnosis. The organs most commonly involved include the salivary and lacrimal glands, pancreas, kidneys, respiratory and urinary systems, as well as retroperitoneal space and mediastinum. In contrast, involvement of the thyroid gland, pituitary gland, central nervous system and spleen is observed much less frequently [14,15].

4.1 Salivary and lacrimal glands

Involvement of the salivary and lacrimal glands in IgG4-RD most commonly presents as chronic, painless, bilateral enlargement persisting for more than three months and occurring in approximately 57.1-72.7% of patients, making it one of the most frequent organ manifestations of the disease. The submandibular glands are most often affected, but the disease process may also involve the parotid, sublingual glands and lacrimal glands. Salivary secretion usually remains normal or is only mildly reduced, resulting in no obvious dryness syndrome, which is an important feature distinguishing IgG4-RD from Sjögren's syndrome. The diagnosis is supported by elevated serum IgG4 concentrations and characteristic histopathological findings, including chronic inflammation of the glands with IgG4-positive plasma cell-rich infiltrates [15–17].

4.2 Pancreas and bile ducts

One of the organ manifestations of IgG4-RD is pancreatic involvement, which occur in approximately 25.5% of patients, most commonly in the form of autoimmune pancreatitis type 1 (AIP-1) [15]. The disease is characterized by periods of exacerbation and remission that may progress to chronic pancreatitis. Clinically, it manifests primarily as recurrent obstructive jaundice resulting either from compression of the common bile duct by an enlarged pancreas or from direct infiltration of the bile duct wall by lymphocytes and plasma cells. In addition, symptoms of exocrine and endocrine pancreatic insufficiency are observed, including the development of diabetes, abdominal pain and progressive weight loss. The diagnosis is based on the coexistence of typical clinical symptoms, elevated serum IgG4 levels, characteristic imaging changes, and histopathological confirmation of lymphoplasmacytic infiltrates with a predominance of IgG4-positive plasma cells and fibrosis.

On computed tomography, the typical appearance of AIP-1 includes diffuse pancreatic enlargement with delayed contrast enhancement, commonly described as “sausage-shaped pancreas” [18,19]. IgG4-related sclerosing cholangitis may also occur during the course of the disease and is observed approximately 88% of patients with AIP-1. Clinically, it manifests as cholestasis and the presence of bile duct strictures, most often involving the intrapancreatic segment of the common bile duct. The clinical and radiological features may mimic primary sclerosing cholangitis or biliary tract malignancies, which significantly complicates differential diagnosis [19]. Long-term, preferably lifelong, follow-up of patients with AIP-1 is recommended due to the increased risk of pancreatic tumors [18].

4.3 Retroperitoneal fibrosis

Retroperitoneal fibrosis (RPF) is a rare disorder characterized by the proliferation of fibrous tissue in the retroperitoneal space. It is estimated that IgG4-RD accounts for approximately 25% of all cases of idiopathic RPF [15]. The fibrotic process may lead to compression of the ureters, development of hydronephrosis, and abdominal and back pain radiating to the groin or lateral thigh. The changes may also surround major abdominal vessels, including the aorta and inferior vena cava, which may result in deep vein thrombosis of the lower extremities, intermittent claudication, or intestinal ischemia. The prognosis of IgG4-RD-associated RPF is generally favorable due to a good response to glucocorticoid therapy. However, untreated fibrosis may lead to progressive ureteral obstruction and renal failure. In most cases, steroid therapy results in clinical improvement, while surgical treatment remains an effective alternative in cases refractory to pharmacological therapy. Ureterolysis, which involves surgical release of the ureters from surrounding fibrotic tissue, is reserved for patients with recurrent disease or no improvement despite pharmacological treatment [20,21].

4.4 Kidneys

The most well-characterized renal manifestation of IgG4-RD is tubulointerstitial nephritis (IgG4-TIN), which is observed in approximately 23.7% of patients [15]. It rarely occurs as an isolated organ involvement and usually coexists with extrarenal manifestations of the disease [22]. IgG4-TIN is typically characterized by mild proteinuria and variable degrees of renal dysfunction, which may present as either acute kidney injury or chronic kidney disease. Characteristic laboratory findings include normal C-reactive protein levels, absence of leukocyte casts in the urine sediment, elevated serum IgG4 concentrations, and low-density renal lesions on computed tomography imaging. Histopathological examination is crucial for diagnosis and reveals characteristic fibrosis and dense lymphoplasmacytic infiltrates with a predominance of IgG4-positive plasma cells. Unlike other manifestations of IgG4-RD, IgG4-TIN is frequently accompanied by decreased serum complement levels C3 and/or C4 [22,23].

5. Diagnosis of IgG4-RD

The heterogeneous organ involvement and non-specific clinical presentation make the diagnosis of IgG4-RD a complex process requiring careful differentiation from other diseases. Accurate diagnosis is based on a comprehensive clinical assessment, with laboratory test results, imaging studies, and histopathological evaluation [5,7,13].

5.1 American College of Rheumatology (ACR) / European Alliance of Associations for Rheumatology (EULAR) classification criteria for IgG4-RD

The diagnostic process utilizes the classification criteria developed by the ACR and EULAR [5]. The diagnostic process consists of three stages: confirmation of typical organ involvement, assessment of exclusion criteria, and final scoring [5,7]. These criteria are auxiliary in nature and are not intended for direct clinical diagnosis. Failure to meet all classification criteria in a patient with clinically suspected IgG4-RD should not delay initiation of treatment [5,13].

5.1.1 Stage 1

The first stage of the IgG4-RD diagnostic process involves confirming involvement of one of the organs typically affected by the disease, including the salivary glands, lacrimal glands, orbits, pancreas, bile ducts, kidneys, retroperitoneal space, aorta, meninges, lungs and thyroid gland [5,13,14]. These changes most often manifest as organ enlargement or tumor-like masses. In certain locations, they may also include biliary strictures, thickening or dilatation of the aortic wall, and thickening of the bronchovascular bundles in the lungs [5,14].

5.1.2 Stage 2

The second stage of the diagnostic process involves evaluation of clinical, serological, radiological, and histopathological features suggesting other diseases, such as cancer, infectious diseases or autoimmune disorders, which may lead to misinterpretation of the clinical picture as IgG4-RD (Table 1) [5,12].

Table 1. Selected ACR/EULAR exclusion criteria for IgG4-related disease [5]

Category	Exclusion criteria
Clinical	• Recurrent fever (>38°C) in the absence of signs of infection • Lack of response to treatment with glucocorticoids at a dose of ≥40 mg/day of prednisone for 4 weeks
Serologic	• Leukopenia and thrombocytopenia without alternative explanation • Peripheral eosinophilia>3000/mm³ • Positive antineutrophil cytoplasmic antibody (ANCA) • Presence of antibodies: anti-Ro, anti-La, anti–double-stranded DNA (dsDNA), anti-RNP, anti-Sm, antisynthetase antibodies (e.g., anti-Jo-1), anti–topoisomerase III (Scl-70), and anti–phospholipase A2 receptor antibodies (anti-PLA2R) • Cryoglobulinemia
Radiologic	• Findings suggestive of malignancy or infection • Rapid progression of lesions within 4-6 weeks • Multifocal osteosclerotic lesions of the long bones • Splenomegaly >14 cm with no identifiable alternative cause
Pathologic	• Cellular infiltrates with features of malignancy • Positive markers of inflammatory myofibroblastic tumor • Extensive neutrophilic infiltrates or neutrophilic abscesses • Necrotizing vasculitis • Prominent necrosis • Primary granulomatous inflammation • Pathologic features of a macrophage/histiocytic disorder
Specific disease exclusions	• Multicentric Castleman's disease • Crohn’s disease (in cases of suspected IgG4-RD involving the pancreas and bile ducts) • Ulcerative colitis (in cases of suspected IgG4-RD involving the pancreas and bile ducts) • Hashimoto’s thyroiditis (in cases of suspected IgG4-RD involving the thyroid gland)

Stage 3

The third stage of the diagnostic process involves a point-based evaluation of the ACR/EULAR classification features. The classification criteria for IgG4-RD are fulfilled when typical organ involvement has been confirmed (Stage 1), no exclusion criteria are found (Stage 2) and the total score is ≥20 points [5,7]. The classification includes eight domains of inclusion criteria relating to clinical, laboratory, radiological, and histopathological data (Table 2), within each domain, only the higest-scoring item is counted [5].

Table 2. Classification criteria IgG4-RD [5]

Histopathology	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
Immunostaining	0-16
Serum IgG4 concentration	
Normal or not checked	0
Greater than normal but <2 × the upper limit of normal	+4
2–5× the upper limit of normal	+6
>5× the upper limit of normal	+11
Bilateral involvement of the lacrimal and salivary glands	
No involvement	0
One set of glands involved	+6
Involvement of ≥2 glands	+14
Chest	
No involvement	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in the thorax	+10
Pancreas and bile ducts	
No involvement	0
Diffuse pancreatic enlargement	+8
Diffuse pancreatic enlargement with a capsule-like rim showing decreased enhancement	+11

Pancreatic and biliary involvement	+19
Kidney	
No involvement	0
Decreased complement levels (C3 and/or C4)	+6
Thickening of the renal pelvis wall / soft-tissue lesions	+8
Bilateral low-attenuation cortical lesions	+10
Retroperitoneum	
No involvement	0
Diffuse abdominal aortic wall thickening	+4
Periaortic soft tissue below the renal arteries or iliac vessels	+8

Biopsy of the affected organ remains the gold standard for confirmation of the diagnosis, especially in cases with an ambiguous clinical presentation or those not fully meeting classification criteria [7,24]. Imaging studies, particularly computed tomography and magnetic resonance imaging, play an important role not only in diagnosing typical locations of disease, but also in assessing disease extent and monitoring response to treatment [25]. It should also be emphasized that normal serum IgG4 levels do not exclude the diagnosis of IgG4-RD, so this parameter should always be interpreted in conjunction with the full clinical picture [7,26]. A comprehensive diagnostic approach is essential to avoid misclassification of IgG4-RD as another disease entity.

6. Treatment of IgG4-RD

The therapeutic process of IgG4-RD aims to achieve rapid control of disease activity, reduce fibrosis and prevent disease relapse and organ complications of the disease. Treatment selection should be individualized based on the patient's clinical status and disease activity [5,7,11].

6.1 Glucocorticoids and immunosuppressive therapy

Glucocorticosteroids are the primary treatment for IgG4-RD. In most patients, rapid response to treatment is observed, manifested by clinical improvement, reduction of organ involvement on imaging studies and gradual normalization of serum IgG4 levels [7,27]. Disease relapse after dose reduction or discontinuation of glucocorticoids is observed in approximately 30-60% of patients, often requiring maintenance treatment [28]. In order to reduce the toxicity of glucocorticosteroids, combination therapy with azathioprine, mycophenolate mofetil, methotrexate, leflunomide, tacrolimus and cyclophosphamide is increasingly used [29].

Combined treatment with glucocorticoids and immunosuppressive drugs is associated with a decreased relapse rate of IgG4-RD, estimated at approximately 25-30% [30].

6.2 Rituximab

Rituximab, an anti-CD20 monoclonal antibody that reduces the number of B lymphocytes, represents an effective therapeutic option for IgG4-RD, especially in patients with relapsing disease or those who are unable to tolerate long-term glucocorticosteroid therapy [31]. In a study by Ebbo et al., including 33 patients with IgG4-RD, high efficacy of rituximab was demonstrated, with a clinical response achieved in 93.5% of patients. At the same time, a significant recurrence rate of 42% was reported. Retreatment with rituximab was effective in all patients who experienced relapse and maintenance therapy was associated with a temporary prolongation of the disease-free period [32].

6.3 Novel therapeutic strategies

As understanding of IgG4-RD pathogenesis expands, current research focuses on the development of novel immunomodulatory therapies, including biological drugs and small molecule inhibitors targeting cytokine activity, T-cell costimulation, and the Janus kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signaling pathways [9,11,31]. The most promising strategies include efgartigimod -a neonatal Fc receptor antagonist, abatacept - a T-cell costimulation inhibitor, dupilumab - a monoclonal antibody blocking the Th2 immune response, tocilizumab - a monoclonal antibody directed against interleukin 6, as well as tofacitinib and baricitinib - JAK pathway inhibitors [9,11,31]. Currently, their use in IgG4-RD remains at the clinical trial stage and requires further evaluation of efficacy and safety [11,26,31].

7. Importance of early diagnosis

IgG4-RD is a multisystem disorder characterized by a highly heterogeneous clinical presentation. Incorrect or delayed diagnosis promotes progression of the inflammatory-fibrotic process, which may lead to permanent organ damage and significant worsening of patient prognosis [33]. An example of the consequences of delayed diagnosis is the case report published by Tawhari et al., in which lack of response to glucocorticosteroid therapy was due to the late onset of severe IgG4-RD. The patient presented with extensive tubulointerstitial infiltrates accompanied by massive interstitial fibrosis, leading to progression to end-stage renal failure, the need for chronic dialysis, and the development of thromboembolic complications [34].

The importance of early initiation of immunosuppressive treatment is confirmed by data on patients with IgG4-RD involving the kidneys and retroperitoneal space. Progressive renal failure was observed in 28.6% of patients who did not receive immunosuppressive treatment or received only a minimal dose of the drug. Among these patients, two developed end-stage renal failure and one required kidney transplantation [35]. These results clearly indicate that early and accurate diagnosis and rapid initiation of immunosuppressive treatment are key factors in halting disease progression and preserving organ function.

8. Conclusions

IgG4-RD represents a diagnostic challenge due to its nonspecific and multisystem clinical presentation. Delayed diagnosis and progression of fibrotic changes may result in permanent damage to the affected organs. In clinical practice, IgG4-RD should be considered in the differential diagnosis of patients with unexplained tumor-like lesions, chronic inflammatory processes or fibrotic changes of atypical localization. Early diagnosis and rapid initiation of immunosuppressive therapy are crucial for halting disease progression and improving patient outcomes.

Disclosure

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