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IgG4-Related Disease: Comprehensive Overview of Pathogenesis, Clinical Manifestations, and Diagnostic Challenges.

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Abstract

Introduction

IgG4-related disease (IgG4-RD) is a progressive and potentially life-threatening condition characterized by immune system activation and tissue fibrosis, affecting various organs such as the pancreas, kidneys, and lungs. Initially recognized in 2003, it often presents as mass-like lesions, which can mimic tumors. Despite advancements in understanding its pathology, epidemiological data are limited, and many patients remain undiagnosed due to unfamiliarity with the disease.

Aim of the study

The aim of this article was to summarize the latest knowledge on the diagnosis and clinical manifestations of IgG4-related disease.

Materials and methods

This review is based on articles from the PubMed and Google Scholar databases, covering the years 2007-2024, using the keywords: IgG4-related disease; autoimmune pancreatitis; retroperitoneal fibrosis; classification criteria.

Results

The disease's complex pathogenesis involves B and T cell activity, with genetic and environmental factors contributing. While effective treatments, like B cell depletion, exist, the disease's broad clinical manifestations and multi-organ involvement require a multidisciplinary approach for proper diagnosis and management.

Conclusion
Diagnosing IgG4-RD is challenging due to its varied symptoms, often mimicking other diseases. Key findings include high IgG4 levels and specific histopathological features. Further research is needed to understand its genetic factors, pathogenesis, and epidemiology.

Keywords: IgG4-related disease; autoimmune pancreatitis; retroperitoneal fibrosis; classification criteria.

Introduction

IgG4-related disease (IgG4-RD) is a slowly progressive condition that can be highly destructive and, in some cases, life-threatening. It is characterized by persistent immune system activation and the development of tissue fibrosis. IgG4-RD was initially recognized in 2003 when it was discovered that conditions previously considered unrelated—such as type I autoimmune pancreatitis (AIP), sclerosing cholangitis, retroperitoneal fibrosis, hypertrophic pachymeningitis, Mikulicz's disease, and Riedel's thyroiditis—could co-occur in some patients and exhibited similar histological characteristics [1]. IgG4-RD frequently manifests with organ enlargement that can resemble a tumor, affecting a wide range of organs including the lacrimal glands, orbits, major salivary glands, pancreas, bile ducts, retroperitoneum, lungs, kidneys, aorta, pachymeninges, and thyroid gland. This tendency to form mass-like lesions can present in various forms, such as dacryoadenitis, soft tissue expansion in the retroperitoneum surrounding the abdominal aorta, or diffuse pancreatic enlargement, which might be mistaken for pancreatic adenocarcinoma. When multiple organs are involved in this characteristic pattern, it strongly suggests a diagnosis of IgG4-RD [2]. Affected tissues are distinguished by dense infiltrations of polyclonal lymphoplasmacytic cells, with a high concentration of IgG4-positive plasma cells embedded within a fibrotic matrix, often arranged in a storiform pattern. Additional features typically include obliterative phlebitis and tissue eosinophilia. Approximately two-thirds of patients present with elevated serum IgG4 levels; however, the remaining one-third may have normal IgG4 levels, even when classic clinical and histological characteristics are present before treatment begins [3,4].

Although IgG4-RD was first recognized as a distinct systemic disease nearly two decades ago, a significant number of patients likely remain undiagnosed due to ongoing unfamiliarity with the condition. The Japanese Ministry of Health, Labour, and Welfare estimates the incidence of IgG4-RD to be between 0.28 and 1.08 cases per 100,000 people, with 336 to 1,300 new diagnoses each year [1]. However, comprehensive epidemiological studies on the incidence and prevalence of IgG4-RD are still lacking.

Similarly, research into the genetic factors contributing to IgG4-RD is in its early stages. Despite these gaps, there have been significant advancements in the study of IgG4-RD. These include establishing a consensus on disease nomenclature and histopathological features, the development and validation of the IgG4-RD Responder Index, and detailed phenotyping of the humoral immune response in patients. Other key discoveries include the identification of potential causal autoantigens, the role of T follicular helper (TFH) cells in IgG4 class-switching, and the recognition of a CD4+ effector T cell subset likely involved in disease promotion.

Additionally, B cell depletion has been identified as a highly effective therapy, and classification criteria for IgG4-RD have been developed and endorsed by both the ACR and EULAR [5, 37].

Pathogenesis and epidemiology

The pathogenesis of IgG4-related disease (IgG4-RD) remains only partially understood. The absence of infectious triggers, the clinical manifestations, and the generally favorable response to glucocorticoids or other immunosuppressive treatments all point towards an immune-mediated origin [1]. Although a few antigens capable of initiating an immune response have been discovered, these are mostly linked to particular disease manifestations, highlighting the diverse clinical presentations [2].

IgG4-related disease most commonly affects middle-aged and older adults, with a notable variation in the male-to-female ratio depending on the site of organ involvement. For head and neck manifestations, the male-to-female ratio is approximately 1.6:1, while for other organs, the ratio can be as high as 4:1, indicating a significantly higher prevalence in men [6]. A Dutch study focusing on patients with IgG4-related cholangitis and pancreatitis identified occupational exposure to solvents, oils, as well as industrial and metal dusts as potential risk factors [7]. Additionally, research has uncovered a link between retroperitoneal fibrosis (RPF) and factors such as smoking and asbestos exposure [8].

Genetically, there are currently no well-defined associations that apply to IgG4-RD as a whole. Nevertheless, research indicates that genetic factors may contribute to susceptibility to IgG4-RD or its specific manifestations. Notably, variants within the HLA and non-HLA regions have been identified as potential risk factors. For example, patients with RPF have shown a genome-wide significant association with the HLA-DRB1*03 allele, suggesting a possible genetic predisposition in certain subtypes of the disease [7].

T and B cells play a significant role in the immune mechanisms that lead to tissue damage and fibrosis. Nonetheless, the role of IgG4 in the disease's pathogenesis is still under debate. This is partly because IgG4 typically has anti-inflammatory properties and only weakly activates the complement system. However, there is emerging evidence suggesting that environmental factors may also play a role in the development of IgG4-RD. Elevated IgG4 levels are not unique to IgG4-related disease, as they can also be observed in various other inflammatory, allergic, and neoplastic conditions. Thus, increased IgG4 levels are thought to indicate a broader abnormal inflammatory response, possibly serving as a secondary phenomenon rather than a primary cause of the disease [4].

Both B and T cells are recognized as key players in the pathogenesis of IgG4-RD, although their precise roles are yet to be fully elucidated. The centrality of B cells in the disease process is highlighted by the efficacy of rituximab (RTX), an anti-CD20 antibody, in treating IgG4-RD [9]. B cells, driven by still unidentified antigens, proliferate and differentiate into IgG4-producing plasmablasts and plasma cells. These plasmablasts, which are rare in healthy individuals, are significantly elevated in patients with active IgG4-RD, and their numbers decrease following RTX therapy, indicating their involvement in the disease [10]. T cells have also been implicated in the pathogenesis of IgG4-RD.

Biopsies from affected patients reveal high levels of cytokines associated with regulatory T cells and Th2 cells, such as IL-4, IL-10, IL-13, and TGF-β. These cytokines likely promote fibrosis and induce immunoglobulin class switching to IgG4 production [11]. Furthermore, the recent discovery of CD4+ cytotoxic T cells in IgG4-RD provides new insights into the disease's pathophysiology. A clonally expanded population of these cytotoxic T lymphocytes has been found in both the peripheral blood and tissue lesions of patients, suggesting that these cells play a pathogenic role [12]. Additionally, T follicular helper (Tfh) cells, which typically reside in germinal centers and assist in B cell differentiation and expansion, are increased in the peripheral blood and affected tissues of IgG4-RD patients. The Tfh response likely contributes to the formation of germinal centers within lymph nodes and affected organs, as well as the production of cytokines that drive IgG4 class-switching [13]. Finally, fibrocytes—circulating precursors of mature tissue fibroblasts—may infiltrate target tissues under the influence of Th2 cytokines and chemokines like CXCL12, contributing to the fibrosis characteristic of IgG4-RD. These complex interactions between various immune cells and cytokines underscore the multifaceted nature of IgG4-RD pathogenesis [14].

Histopathology

Diagnosing IgG4-RD can be difficult, as clinical assessments, lab tests, and imaging often fall short. Because of this, biopsy is the key to confirming the diagnosis [10]. There are four main pathological features of IgG4-RD: dense polyclonal lymphoplasmacytic infiltrates rich in IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis, and mild-to-moderate tissue eosinophilia [15].

Storiform fibrosis is a whorled pattern of fibrosis resembling a woven mat. This fibrosis is accompanied by a dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells and CD4+ T cells, with moderate numbers of eosinophils also present. Obliterative phlebitis, which destroys the walls and lumens of veins, is another characteristic finding in some patients, with elastin staining often needed to visualize these changes. The inflammation of veins, and less commonly arteries, leading to partial or complete occlusion of small- to medium-sized vessels by an infiltrate of lymphocytes and plasma cells. This occlusion does not result in necrotizing vasculitis and rarely damages the vessel walls. In certain organs like the lung and pancreas, obliterative arteritis may also occur, but necrosis is rarely seen [16]. Additionally, mild tissue eosinophilia is common in IgG4-RD. In rare cases, such as eosinophilic angiocentric fibrosis or eosinophilic cholangitis, eosinophils are the dominant cells in the histological appearance.

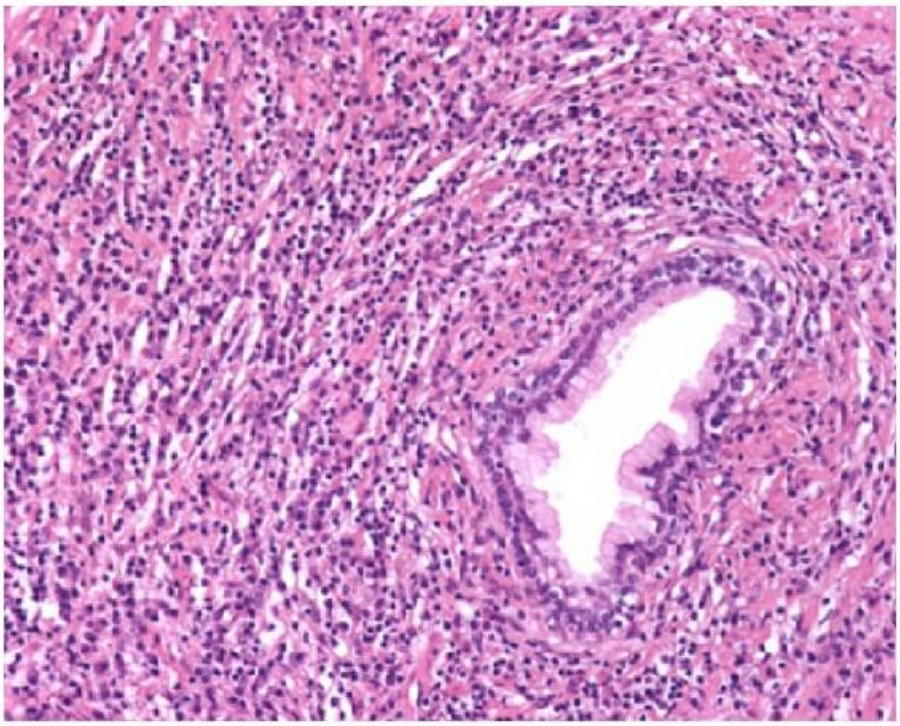

Figure 1. IgG4-related prostatitis. A prostatic gland is surrounded by a dense inflammatory infiltrate with numerous plasma cells. Prostatic vessels showed obliterative phlebitis (H&E, 200x). [17]

The accumulation of IgG4+ plasma cells at disease sites indicates chronic activation of the immune system in IgG4-RD. High numbers of these cells and a high IgG4+ plasma cell ratio support a diagnosis of IgG4-RD. However, the threshold for the number of IgG4+ cells per high-power field varies depending on the organ and biopsy method, with surgical biopsies generally yielding more cells than non-surgical ones. For example, in retroperitoneal biopsies, as few as 10 IgG4+ plasma cells per high-power field may be sufficient for diagnosis, especially if the IgG4+ ratio is high. Increased IgG4+ plasma cells must be interpreted cautiously, particularly in less specific sites like the nasal cavity, sinuses, and lymph nodes. Numerous other diseases, such as ANCA-associated vasculitis, can also show elevated IgG4+ cells. Thus, IgG4-RD diagnosis should not rely solely on immunostaining; it requires a comprehensive evaluation combining clinical, serological, radiological, and histopathological data [2].

Clinical manifestations

IgG4-RD presents with an extraordinarily diverse range of clinical manifestations, making it a complex disease to diagnose and manage. The variability in symptoms is largely due to the fact that the disease can affect multiple organs, with 60-90% of patients experiencing multi-organ involvement. The specific clinical manifestations largely depend on the organs that are involved, adding to the complexity of the disease [18]. For instance, patients may present with symptoms ranging from mild discomfort to severe organ dysfunction, depending on the extent and location of the disease.

In many cases, the first clue to IgG4-RD comes from the presence of tumefactive lesions, which are abnormal growths or swellings that can affect one or more organs. These lesions are often detected during a physical examination when there is noticeable swelling in areas such as the salivary or lacrimal glands, lymph nodes, or thyroid gland. For instance, salivary gland swelling or lacrimal gland enlargement can be visible signs prompting further investigation. Thyroid enlargement, another common finding, may lead to a suspicion of IgG4-RD, especially if the patient has other systemic symptoms [19]. When fever does occur, it typically suggests an alternative diagnosis. Weight loss is another symptom that may be observed, particularly in patients with exocrine pancreatic insufficiency due to IgG4-related autoimmune pancreatitis (AIP). In such cases, the weight loss is often a result of malabsorption syndrome, where the pancreas fails to produce enough digestive enzymes, leading to poor nutrient absorption and subsequent weight loss. Lymphadenopathy, or the swelling of lymph nodes, is a frequent finding in IgG4-RD and can be one of the earliest signs of the disease. It may occur in isolation or alongside other manifestations of IgG4-RD, and the affected lymph nodes are typically painless. Additionally, approximately 40% of patients with IgG4-RD have a history of asthma or allergic conditions, such as allergic rhinitis or eczema. This association with allergic disorders suggests a link between IgG4-RD and a predisposition to atopic conditions, which might provide insight into the underlying immunological mechanisms of the disease [20].

In addition to physical examination findings, imaging studies play a crucial role in identifying and assessing the extent of organ involvement. Radiological imaging can reveal the presence of these tumefactive lesions in various internal organs that may not be easily detectable through physical examination alone. For example, imaging might uncover pancreatic involvement, retroperitoneal fibrosis, or lung nodules, all of which can be associated with IgG4-RD. The identification of such lesions through imaging not only aids in diagnosis but also helps in determining the severity and extent of the disease [10,19].

The broad spectrum of clinical presentations in IgG4-RD underscores the importance of a thorough and multidisciplinary approach to diagnosis and treatment. Given the potential for multiple organ involvement and the variable nature of symptoms, healthcare providers must consider IgG4-RD in the differential diagnosis when patients present with unexplained tumefactive lesions or multi-organ dysfunction. Early recognition and appropriate management are crucial in preventing irreversible organ damage and improving patient outcomes [10].

Head and Neck

IgG4-RD has a notable tendency to target glandular tissues, with the major salivary glands (such as the submandibular and parotid glands) and lacrimal glands frequently being the most affected. This manifestation typically involves painless, symmetric swelling of the lacrimal, parotid, and/or submandibular glands. Historically, this presentation was often labeled as Mikulicz disease—a term still found in medical literature—though it is now recognized as one of the hallmark presentations of IgG4-RD [21]. Patients may experience sicca symptoms, such as dry eyes and dry mouth, due to the involvement of these glands, but these symptoms are generally milder than those seen in Sjögren syndrome, a condition that is often mistaken for IgG4-RD in such cases [4].

In addition to glandular involvement, IgG4-RD frequently manifests in the head and neck region through a variety of orbital and ocular conditions. These include uveitis, orbital pseudotumor, and chronic rhinosinusitis. Though less common, the disease can also lead to more severe complications such as bony destruction of the sinuses or nasal bridge, a presentation that can mimic granulomatosis with polyangiitis. This broad spectrum of head and neck manifestations underscores the need for careful differential diagnosis to distinguish IgG4-RD from other conditions with overlapping features [22].

Recent studies have confirmed that Riedel thyroiditis, also referred to as fibrosing thyroiditis, is indeed a manifestation of IgG4-related disease (IgG4-RD) [23, 24]. This rare and severe form of autoimmune thyroid disorder is characterized by a striking enlargement and significant hardening of the thyroid gland. The thyroid often becomes so enlarged—referred to as thyromegaly—that it compresses adjacent structures like the trachea or esophagus, leading to symptoms such as difficulty breathing (dyspnea), trouble swallowing (dysphagia), or changes in voice, specifically hoarseness. This compression of local structures is a hallmark of the disease's aggressive nature. Interestingly, the thyroid function in patients with Riedel thyroiditis can vary widely; some may experience an overactive thyroid (hyperthyroidism), an underactive thyroid (hypothyroidism), or they might maintain normal thyroid function (euthyroidism) despite the physical changes in the gland. This variability in thyroid function further complicates the clinical management and underscores the unique challenges presented by Riedel thyroiditis as a component of IgG4-RD [24].

Chest

IgG4-related disease exhibits a diverse array of thoracic manifestations, reflecting its broad clinical spectrum. Lung involvement in IgG4-related disease occurs in approximately 10–30% of cases. There are four main pulmonary syndromes associated with this condition: inflammatory pseudotumor, central airway disease, localized or diffuse interstitial pneumonia, and pleuritis. Symptoms often include cough, hemoptysis, dyspnea, and pleural effusion. Radiological findings can be similar to those of other lung diseases and may present as solid nodular lesions, ground-glass opacities, alveolar interstitial patterns, bronchovascular bundle thickening, and pleural nodular thickening [10].

In addition to these, pleural involvement is frequently observed, presenting as chronic or recurrent pleural effusions along with notable pleural thickening [25]. These effusions are typically exudative, although there have been cases of chylous effusions described as well [26]. Pericardial involvement is also a significant feature of IgG4-RD, often resulting in pericardial effusions, pericardial thickening, and constrictive pericarditis. An increasingly recognized aspect of the disease is coronary arteritis, which can lead to severe complications such as large coronary aneurysms or acute coronary syndrome [27]. This broad spectrum of thoracic manifestations underscores the complexity of diagnosing and managing IgG4-RD, necessitating careful evaluation to distinguish it from other conditions with similar presentations. Mediastinal involvement, although less common, can occur and is known as fibrosing mediastinitis. This condition can be severe, potentially compressing crucial mediastinal structures and leading to significant organ dysfunction that poses challenging treatment issues [28].

Pancreas and the biliary tree

The pancreas is the organ most commonly affected by IgG4-related disease, with involvement reported in 20–60% of cases across various studies. Patients with pancreatic involvement typically present with symptoms such as jaundice, itching (pruritus), abdominal pain, fatty stools (steatorrhea), and newly diagnosed diabetes mellitus. Imaging studies of the pancreas often reveal diffuse or segmental enlargement of the organ, along with a loss of its normal lobular structure and a characteristic diffuse narrowing of the pancreatic duct [29].

Autoimmune pancreatitis (AIP), a key manifestation of pancreatic involvement in IgG4-RD, is frequently associated with IgG4-related sclerosing cholangitis. This condition, which occurs in about 20% of patients with systemic IgG4-RD, leads to inflammation and scarring of the bile ducts. If left untreated, it can progress to severe liver damage, potentially resulting in end-stage liver disease. Fortunately, both AIP and sclerosing cholangitis typically respond well to corticosteroid therapy.

IgG4-related cholecystitis, involving the gallbladder, is a rarer manifestation of the disease. It is often detected incidentally during imaging studies, where thickening of the gallbladder wall is observed. In many cases, cholecystitis is only identified after the gallbladder has been surgically removed, usually due to suspicions of gallbladder cancer [10, 30].

Retroperitoneum

Retroperitoneal fibrosis is one of the most prevalent manifestations of IgG4-related disease, especially in non-Asian populations [20]. A significant manifestation of IgG4-related disease (IgG4-RD) that is not restricted to a single organ but rather involves an entire body region is retroperitoneal fibrosis (RPF) or periaortitis. Historically, many cases previously labeled as idiopathic RPF, also known as Ormond's disease, are now understood to likely represent IgG4-RD [29].

Studies suggest that based on pathological or serological criteria, 20%–50% of all cases of retroperitoneal fibrosis can be attributed to IgG4-RD. Typically, this condition presents as a periaortic or peri-iliac mass, which can extend laterally, leading to medial deviation or obstruction of the ureters or other structures. This obstruction can result in acute or chronic kidney injury if left untreated [31]. Pressure on the veins or lymphatic vessels can cause lower-extremity edema, manifesting as swelling in the legs [32]. In addition to the more common periaortic involvement, there have been rare instances where ureteral obstruction occurs due to primary ureteral IgG4-related pseudotumors, even in the absence of periaortic retroperitoneal fibrosis [33].

Kidney

Renal involvement in IgG4-related disease (IgG4-RD) occurs with varying frequency, reported in 7% to 24% of cases across different studies [10]. IgG4-related tubulointerstitial nephritis (IgG4-TIN), although less common than retroperitoneal fibrosis, is the most frequent form of parenchymal kidney involvement in IgG4-related disease. This condition is generally marked by mild proteinuria and varying degrees of kidney impairment, which can be either acute or chronic [3].

Radiologically, IgG4-related tubulointerstitial nephritis often presents with bilateral nodular or wedge-shaped lesions that show low contrast enhancement on computed tomography and T2-weighted magnetic resonance imaging. Kidney biopsy remains the gold standard for diagnosing this condition [34]. Histopathological examination of kidney biopsies reveals severe tubular atrophy, storiform fibrosis, and a diffuse inflammatory infiltrate rich in plasma cells and eosinophils. Immunohistochemistry for IgG4 confirms the presence of IgG4-positive plasma cells within the tubulointerstitium [35].

A key serological indicator of IgG4-TIN is an elevated serum IgG4 level, typically observed alongside increased serum IgE, eosinophilia, and hypergammaglobulinemia. Moreover, more than half of the patients with active IgG4-TIN exhibit reduced levels of complement fractions, with recent studies highlighting a strong association between extremely low C3 levels and renal involvement in IgG4-RD [36].

In addition to TIN, IgG4-RD can manifest as a variety of glomerular lesions. Approximately 30 cases of membranous nephropathy associated with IgG4-related disease have been reported [37]. The primary clinical manifestation in these cases is nephrotic syndrome. Kidney biopsies often reveal that membranous nephropathy coexists with IgG4-related tubulo-interstitial nephritis in about two-thirds of patients. Typically, IgG4 subclass deposits are predominant in the glomerular basement membrane. In roughly half of these cases, kidney involvement occurs alongside other IgG4-related conditions such as autoimmune pancreatitis, dacryoadenitis, or sialadenitis. In the remaining cases, IgG4-related disease often precedes membranous nephropathy by several years. Most patients with IgG4-related membranous nephropathy test negative for antiphospholipase A2 receptor antibodies, though rare cases show positivity either on immunostaining or in serum. Unlike IgG4-related tubulo-interstitial nephritis, where glucocorticoids alone might be effective, membranous nephropathy often requires additional immunosuppressive therapies, as glucocorticoids alone may be insufficient [3,37].

Diagnosis

IgG4-related disease (IgG4-RD) is identified through a combination of clinical, radiological, and histopathological evaluations rather than relying solely on elevated serum IgG4 levels, which lack both sensitivity and specificity. The characteristic histopathological features of IgG4-RD can also be found in several other conditions, some of which share similar clinical presentations, making diagnosis challenging. Therefore, a thorough and integrated approach is essential to accurately diagnose IgG4-RD, considering all relevant clinical contexts.

In 2019, classification criteria for IgG4-RD were established and jointly endorsed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) [37]. According to these criteria, the first requirement for classification is the involvement of a typical organ associated with IgG4-RD, which must be evident through clinical, radiological, or histopathological findings. This serves as the initial entry point for diagnosis. Organs commonly affected by IgG4-RD include the lacrimal glands, major salivary glands, orbits, lungs, pancreas, biliary system, kidneys, retroperitoneum, aorta, paravertebral soft tissues, meninges, and the thyroid gland.

Once involvement of a typical organ is confirmed, it is crucial to rule out other conditions by applying specific exclusion criteria.

These criteria are divided into clinical, serological, radiological, and pathological categories. If any of these exclusion criteria are present—such as the presence of fever, specific autoantibodies like proteinase-3, rapid radiological changes, or evidence of granulomatous inflammation or necrosis on histopathology—the diagnosis of IgG4-RD should be reconsidered, and alternative diagnoses must be explored [37].

Table 1. Inclusion criteria definitions for IgG-4 related disease, ACR/EULAR, 2019 [37].

Immunostaining	IgG+ cells can be identified using either IgG staining or CD138 staining.
Head and neck gland involvement	A "set" of glands refers to both lacrimal glands or both submandibular glands, etc. If a gland has been surgically removed for the purpose of diagnosis, it can be considered to have been involved if confirmed by pathology. Involvement of the lacrimal glands and the major salivary glands in IgG4-related disease is bilateral (but can be asymmetric). Involvement of the glands can be determined either by clinical examination or by a radiology study (e.g., positron emission tomography scan or computed tomography scan).
Chest	Peribronchovascular and septal thickening in the lung must be determined by a cross-sectional imaging study of the chest. The paravertebral band-like soft tissue in the thorax is usually right-sided, located between T8 and T11, and does not encase the aorta.
Pancreas and biliary tree	Diffuse pancreas enlargement usually encompasses more than two-thirds of the pancreas. The type of biliary involvement that is highly consistent with IgG4-related sclerosing cholangitis involves the proximal biliary tract (i.e., intrahepatic and extrapancreatic portions of the extrahepatic bile ducts). The bile duct walls often have smooth thickening.
Kidney	Hypocomplementemia pertains to low serum levels of C3, C4, or both. Renal pelvic wall thickening can be either unilateral or bilateral, usually without severe stenosis or luminal irregularity. Low-density areas in both renal cortices can be seen only on contrast-enhanced computed tomography and are usually patchy or round-shaped in appearance.
Retroperitoneum	The location of IgG4-related retroperitoneal fibrosis or periaortitis is typically circumferential or on the anterolateral sides of the aorta. The segment of aorta involved tends to be the infrarenal aorta, often extending to include the iliac vessels.

Table 2. Exclusion criteria definitions for IgG-4 related disease, ACR/EULAR, 2019 [37].

Clinical	
Fever	Documented, recurrent temperature >38°C, with fever being a prominent part of the patient's overall presentation with the underlying disease, in the absence of any clinical features of infection.
No objective response to glucocorticoids	If the patient has been treated with prednisone at a minimum of 40 mg/day (~0.6 mg/kg/day) for a period of 4 weeks, it is assumed that the patient has not demonstrated an objective clinical response. An objective response includes unequivocal improvement of the clinical lesions, biochemical abnormalities, or radiologic findings. There are 2 additional points to consider with regard to glucocorticoid response: Improvement only in the serum IgG4 concentration should not be regarded as a clinical response without improvement in other aspects of the disease. Some forms of IgG4-related disease (IgG4-RD) associated with advanced fibrosis, e.g., some cases of retroperitoneal fibrosis or sclerosing mesenteritis, may not demonstrate obvious radiologic responses to glucocorticoids.
Serologic	
Leukopenia and thrombocytopenia without alternative explanation	Reduction in the total white blood cell count and platelet count to levels below those normal for the reference laboratory, having no apparent explanation except for the underlying disease. Reductions in both the white blood cell count and platelet count are unusual in IgG4-RD but are typical of, for example, myelodysplastic syndromes, hematopoietic malignancies, and autoimmune conditions within the systemic lupus erythematosus spectrum.
Peripheral eosinophilia	To a concentration of >3,000 mm
Positive antineutrophil cytoplasmic antibody (ANCA)	Enzyme-linked immunosorbent assay results positive for ANCA targeted against proteinase 3 or myeloperoxidase.
Positive antibodies	Ro, La, double-stranded DNA, RNP, or Sm antibodies positive in titers greater than normal suggest an alternative diagnosis. Other autoantibody associated with high specificity for another immune-mediated condition that is a reasonable explanation for the patient's presentation. Such specific autoantibodies include antisynthetase antibodies (e.g., anti–Jo-1), anti–topoisomerase III (Scl-70), and anti–phospholipase A receptor antibodies. This does not include autoantibodies of low specificity such as rheumatoid

Table 2. Exclusion criteria definitions for IgG-4 related disease, ACR/EULAR, 2019 [37].

	factor, antinuclear antibodies, antimitochondrial antibodies, anti–smooth muscle antibodies, and antiphospholipid antibodies.
Cryoglobulinemia	Cryoglobulinemia (type I, II, or III) occurring in a clinical context that provides a reasonable explanation for the patient's presentation.
Radiologic	
Known radiologic findings suspicious for malignancy or infection that have not been investigated sufficiently	Such radiologic findings include mass lesions that have not been evaluated thoroughly, necrosis, cavitation, hypervascular or exophytic mass, bulky or matted lymphadenopathy, loculated abdominopelvic fluid collection, among others.
Rapid radiologic progression	Defined as significant worsening within a 4–6- week interval.
Long bone abnormalities consistent with Erdheim-Chester disease	Multifocal osteosclerotic lesions of the long bones, usually associated with bilateral diaphyseal involvement.
Splenomegaly	>14 cm in the absence of alternative explanation (e.g., portal hypertension).
Pathologic	
Cellular infiltrates suspicious for malignancy that have not been investigated sufficiently	A high likelihood of malignancy may be suggested by cellular atypia, a monotypic nature of immunohistochemistry findings, or light chain restriction on in situ hybridization studies. If malignancy is suspected, this must be excluded by appropriate studies before inclusion.
Markers consistent with inflammatory myofibroblastic tumor	Known positivity for a marker suggestive of inflammatory myofibroblastic tumor, e.g., anaplastic lymphoma kinase 1 or ROS, a receptor tyrosine kinase that is encoded by the gene ROS1.

Table 2. Exclusion criteria definitions for IgG-4 related disease, ACR/EULAR, 2019 [37].

Prominent neutrophilic inflammation	Neutrophilic infiltrates are unusual in IgG4-RD, with the exception of occasional examples in the lung or near mucosal sites. Extensive neutrophilic infiltrates or neutrophilic abscesses strongly indicate the possibility of a non–IgG4-RD diagnosis.
Necrotizing vasculitis	Although vascular injury (e.g., obliterative phlebitis or arteritis) is a hallmark of IgG4-RD, the presence of fibrinoid necrosis within blood vessel walls provides strong evidence against IgG4-RD.
Prominent necrosis	Small foci of necrosis may rarely be present around the luminal surface of ductal organs, but zonal necrosis with no alternative explanation (e.g., stenting) provides strong evidence against IgG4- RD.
Primary granulomatous inflammation	Inflammation rich in epithelioid histiocytes, including multinucleated giant cell formation and granuloma formation, is highly atypical of IgG4-RD.
Pathologic features of a macrophage/histiocytic disorder	Example: known S100-positive macrophages demonstrating emperipolesis, a pathologic feature of Rosai-Dorfman disease.
Specific disease exclusions	
Known diagnoses of the following diseases are exclusion criteria	- Multicentric Castleman's disease; - Crohn's disease (if pancreatobiliary disease is present); - Ulcerative colitis (if pancreatobiliary disease is present); - Hashimoto thyroiditis (if the thyroid is the only proposed disease manifestation). Patients with IgG4-RD can certainly have Hashimoto thyroiditis separately from IgG4-RD, but Hashimoto thyroiditis is part of the IgG4-RD spectrum.

Conclusions

IgG4-related disease (IgG4-RD) is a multifaceted and systemic condition that presents significant diagnostic and therapeutic challenges due to its diverse clinical manifestations and its potential to affect multiple organs. Since its identification in 2003, considerable advancements have been made in understanding its pathology, particularly the roles of immune system components like B and T cells. Histopathological evaluation remains crucial for diagnosis, with key features including storiform fibrosis, dense lymphoplasmacytic infiltrates, and obliterative phlebitis.

Despite progress, much remains unknown about the precise pathogenesis and epidemiology of IgG4-RD, with gaps in understanding the genetic factors and immune mechanisms involved. B cell depletion therapies, such as rituximab, have shown promise, highlighting the central role of B cells in the disease. However, the variable clinical presentations—from head and neck involvement to thoracic, pancreatic, renal, and retroperitoneal manifestations—demand a multidisciplinary approach to management. Early recognition and treatment are essential to prevent irreversible organ damage. As research continues to evolve, a deeper understanding of IgG4-RD will likely lead to more effective strategies for diagnosis and management, ultimately improving patient outcomes.

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