



# IgG4-related disease; a newly recognized entity with expanding spectrum

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## Abstract

IgG4-related disease (IgG4RD) represents a newly recognized group of diseases affecting a wide spectrum of organs and systems of the human body. The disease has certain characteristic gross, morphologic, immunohistochemical and serological features. Its accurate diagnosis is important for optimal treatment and prognostication. There is a strong need for clinicopathological correlation to arrive at the correct diagnosis of this condition. Strict criteria must be used for identifying unusual cases of the disease in unusual locations.

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## Introduction

In today's rapidly advancing field of medicine, the emergence of novel diseases never ceases. Among such recently discovered rare entities is IgG4-related disease (IgG4RD) (1). A family of multi-systemic autoimmune diseases involves the vast parts of the human body, such as: the pancreas, kidneys, salivary glands, lungs, thyroid gland, biliary tree, mastoid bone, eyes, meninges, otorhinological organs, blood vessels, skin and the retroperitoneum (1-16). It is distinguished by the presence of IgG4 positive cells in body tissues and elevated serum levels of IgG and IgG4 along with a raised serum IgE and/or peripheral eosinophilia (1). This disease was first recognized in the pancreas in the form of autoimmune pancreatitis type 1 (1,2).

The disease has a characteristic histological appearance, being described by the presence of dense lymphoplasmacytic infiltrate, fibrosis and obliterative phlebitis (9). Having a male predominance, it occurs more commonly in the middle aged to elderly age group (1). Like most autoimmune disorders, IgG4RD also shows a dramatic response to corticosteroids that serve as the first line therapy in this disease (1,5). However, therapy with steroids should be continued even after remission since there remains the possibility of relapse. This feature was highlighted by Andrew et al on ophthalmic IgG4RD, where in most cases repeated corticosteroid

## Key point

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injections were needed to avoid relapses (15). Pancreatic form of the disease can coexist with other organ involvement (12). Fan et al presented a patient diagnosed with IgG4-related autoimmune pancreatitis having submandibular gland involvement (12). Laboratory results revealed increased IgG4 levels and the patient was ultimately diagnosed with IgG4-related autoimmune pancreatitis (AIP) and was started on prednisone (12). The patient showed improvement, however once the drug was stopped, he presented with submandibular gland enlargement (12). At which point prednisone was restarted and then continued, due to which the patient again showed marked response (12). Around 7.2% of IgG4RD have no pancreatic involvement (16).

Around 17% of the patients with IgG4RD having extra-pancreatic form of the disease, presenting with IgG4-related kidney disease, an autoimmune systemic disease characterized by any degree of kidney involvement by IgG4 positive plasma cells (1,10,16). This highlights the importance of renal biopsy in diagnosing and confirming the disease (4).



IgG4-related kidney disease mostly manifests as tubulointerstitial nephritis (TIN); however this is not its sole renal involvement (1). It can also involve the glomeruli and present as membranous glomerulonephritis (GN), IgA nephropathy and as mesangioproliferative immune complex-mediated GN (1). On immunofluorescence, deposits of immune complexes rich in IgG4 are seen within the tubular basement membranes (1). IgG4-related kidney disease can also mimic acute renal insufficiency (10).

The involvement of the submandibular gland in IgG4RD occurs with the presentation of chronic sclerosing sialadenitis (9). IgG4RD's manifestation in blood vessels is seen as arteritis and two separate studies, one conducted by Siddiquee et al and the other by Tran et al showed the involvement of the aorta and the coronary arteries by the disease (11,14). In the setting of aortitis, the disease tends to occur mainly in the distal aorta on the background of chronic infectious aortitis and atherosclerosis (11).

Rosai-Dorfman disease, a rare disorder itself, has been further distinguished by its association with IgG4RD (3). The histopathology is significant for the concurrent presence of both histiocytes and IgG4 positive plasma cells (3). IgG4-related retroperitoneal fibrosis is a rare disease, the etiology of which remains unknown (5). The disease is characterized by the typical features of IgG4RD, that is, raised serum IgG4 levels, tissue infiltration with IgG4 positive cells and fibrosis; however, in addition to this, there is also the presence of a retroperitoneal mass (5). The retroperitoneal mass can be found encompassing the abdominal aorta, iliac arteries, the inferior vena cava and even the ureters (5).

A relationship between IgG4RD and mastoiditis has also been seen (7). Therefore, it is noteworthy that IgG4RD be considered in the setting of otological symptoms. The association between the two entities has been reported in a study carried out by Barnado and Cunningham, in which they discussed a 43-year old female who presented with the complains of right-sided ear fullness and otorrhea. The patient had been initially treated for mastoiditis with antibiotics and steroids. However, failure of recovery prompted a second diagnosis which was refractory inflammatory pseudotumor. The following treatment consisted of several mastoidectomies, more steroids as well as radiation therapy. The patient again failed to recover and instead developed mastoiditis in the contralateral ear which was accompanied by headache and right sided facial paresthesia, indicating the involvement of the central nervous system, which lead to the reexamination of the mastoid tissue and a significant elevation in the number of IgG4 positive cells was noted. Thus, IgG4RD was confirmed, and treatment with Rituximab was started. Patient showed clinical and radiographic improvement (7).

Cutaneous forms of the disease have also been reported, although it is very rare and of unknown etiology (8). The cutaneous manifestations of IgG4RD are more commonly a secondary rather than a primary involvement (8). Muscardin et al in their study described a rare case of primary

pseudo-lymphomatous IgG4RD in a male who came with a history of sclerosing erythematous nodules involving his scalp (8). Histological examination of these nodules revealed a mixed lymphoplasmacytic infiltrate within fibrosclerotic tissue (8) and were surrounded by a significant number IgG4 positive cells, whereas the serum IgG4 levels were normal (8).

## Conclusion

IgG4RD represents a newly recognized group of disorders having in common certain morphological and serological features. There is a need for further studies on this group of diseases to understand its full spectrum, pathogenesis and ultimately treatment.

## Authors' contribution

All authors contributed equally to the work.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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