

IgG4-Related Disease

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Continuing Education Activity

Immunoglobulin G4-related disease (IgG4-RD) is also known as IgG4-related systemic disease, hyper-IgG4 disease, IgG4-related autoimmune disease, IgG4-associated disease, IgG4-related sclerosing disease, and IgG4-syndrome. It is a multi-organ, fibro-inflammatory condition with tumefactive lesions of unknown etiology and characteristic histopathological features. Virtually any organ can be involved, but the most commonly involved organs are the pancreas, kidneys, orbital adnexal structures, salivary glands, and retroperitoneum. This activity describes the pathophysiology, evaluation, and management of immunoglobulin G4-related disease and highlights the role of the interprofessional team in enhancing care delivery for affected patients.

Objectives:

- Describe the causes of immunoglobulin G4-related disease (IgG4-RD).
- Describe the presentation of a patient with Immunoglobulin G4-related disease (IgG4-RD).
- Summarize the treatment options for immunoglobulin G4-related disease (IgG4-RD).
- Explain the importance of enhancing care coordination amongst interprofessional team members to improve outcomes for patients with immunoglobulin G4-related disease (IgG4-RD).

Introduction

IgG4-related disease (IgG4-RD) is known as an IgG4-related systemic disease, hyper-IgG4 disease, IgG4-related autoimmune disease, IgG4-associated disease, IgG4-related sclerosing disease, and IgG4-syndrome. It is a multi-organ, fibro-inflammatory condition with tumefactive lesions of unknown etiology and characteristic histopathological features. Virtually any organ can be involved, but the most commonly involved organs are the pancreas, kidneys, orbital adnexal structures, salivary glands, and retroperitoneum^[1]. The pathological hallmark of this disease is dense lymphoplasmacytic infiltrate with IgG4 positive plasma cells, storiform fibrosis, obliterative phlebitis, and a variable amount of eosinophils. Elevated levels of serum IgG4 is frequent. The pathology is very specific and looks similar in all organs. Because of this finding, it is considered to be analogous to systemic sarcoidosis. IgG4-RD affected patients are often misdiagnosed as having a malignancy since the lesions can mimic tumors, infections, or immune-mediated diseases^[2]. This is because of the lack of a systemic approach, and hence, this disease is underdiagnosed. These patients usually have a good recovery after being treated with systemic glucocorticosteroids. The response to steroids is so dramatic that it has been suggested as one diagnostic criterion for the disease.

Etiology

The etiology is unclear, it is thought to be related to genetic background, bacterial infection and molecular mimicry, and autoimmune disease.

Epidemiology

The exact prevalence of IgG4-related disease (IgG4-RD) is not known.

Pathophysiology

In 1961, Sarles et al. originally described IgG4-related disease in the pancreas based on a case of pancreatitis with hypergammaglobulinemia[3]. Yoshida et al. proposed the concept of autoimmune pancreatitis (AIP) in 1995, and in 2001, Hamano et al. noted increased serum levels of IgG4 in patients with AIP and made elevated IgG4 a diagnostic marker. Kamisawa, in 2003, noted multiple extra-pancreatic lesions in patients with AIP and identified this as a systemic disease. The nomenclature was proposed at the 2011 International IgG4-related Diseases Symposium in Boston. The term IgG4-related disease (IgG-RD) was proposed to include type I AIP and other systemic manifestations. Type II AIP was considered to represent a separate histopathological entity and was not included in this characterization.

There is not enough data to determine the true prevalence of IgG-4RD. Many medical disorders previously thought to be unique are now included in the spectrum of IgG4-RD. Most of the data come from Japan where the prevalence of autoimmune pancreatitis is 0.8 cases per 100,000 and accounts for 6 % of cases of chronic pancreatitis. In a clinic series by the Mayo Clinic, 11% of patients undergoing pancreatic resection for benign indications had AIP[2]. IgG-4 RD has predominance in older men, mostly in the 6th decade.

The disease can affect almost any organs. Hence the symptoms and signs are based on the affected organs, and the severity of the disease can vary. There are multiple organ involvements in 60% to 90% of patients. Commonly, the presentation is subacute due to the enlargement of the organs, and few are found incidentally during diagnostic imaging, laboratory work, i.e., Biochemistry and Immunopathology. IgG4-RD related tubulointerstitial nephritis may present with mass like lesions in radiological studies with acute or chronic renal failure. Allergy history is very common, with symptoms including atopy, bronchial **asthma**, and sinusitis in about 40% of cases. A single or multi-organ presentation may progress to include more organs and would need close follow up. The disease can affect almost any organs. Hence the symptoms and signs are based on the affected organs, and the severity of the disease can vary. The IgG4 RD responder index is a research tool that may be used in clinical practice to detect changes in disease activity and determine improvements or worsening in the affected organs.

Clinical Diagnosis

Diagnosis is based on clinical and histological features. There are two types of criteria available: (1) the Mayo Clinic HISORt criteria for the diagnosis of AIP and (2) the Japanese Comprehensive Clinical Diagnostic (CCD) criteria for IgG4-RD. Histopathology is the current "gold standard" for diagnosis.

The Mayo Clinic HISORt Criteria for the Diagnosis of AIP

Histopathology (one or both criteria required)

- Characteristic appearances within biopsy or resection material.*
- At least ten IgG4-positive plasma cells per high power field within areas of lymphoplasmacytic infiltrate.

Imaging and serology (3 criteria required)

- Diffusely enlarged pancreas with delayed and "rim" enhancement.
- Irregular pancreatic duct.
- Increased serum IgG4 concentration.

Response to steroid therapy (3 criteria required)

- Unexplained pancreatic disease after a full clinical workup – including the exclusion of cancer.
- Raised serum IgG4 concentration and/or extrapancreatic organ involvement with increased numbers of tissue IgG4-positive plasma cells.
- Resolution or marked improvement in disease with steroid therapy.

*This includes a lymphoplasmacytic infiltrate, "storiform" fibrosis, and obliterative phlebitis; the inflammatory cell infiltrate alone is not sufficient to meet this criterion.

[Reproduced from Culver E, Bateman General Principles of IgG4-related disease Diagnostic Histopathology 19:4, 2013 Elsevier]

The Japanese Comprehensive Clinical Diagnostic (CCD) Criteria for IgG-4RD

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs.
2. Hematological examination shows elevated serum IgG4 concentrations (greater than 135 mg/dL).
3. Histopathological examination shows:
 - Marked lymphocyte and plasmacytic infiltration and fibrosis.
 - Infiltration of IgG4 + plasma cells: ratio of IgG4 +/ IgG + cells greater than 40% and greater than 10 IgG4 + plasma cells/HPF.

Definite: 1 + 2 + 3 *Probable:* 1 + 3 *Possible:* 1 + 2

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However, it is vital to differentiate IgG4-RD from malignant tumors of each organ (e.g., cancer, lymphoma) and similar diseases (e.g., Sjogren syndrome, primary sclerosing cholangitis, Castleman disease, secondary retroperitoneal fibrosis, Wegener granulomatosis, sarcoidosis, Churg-Strauss syndrome) by additional histopathological examination. Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4-RD.

Laboratory Diagnosis

Elevated serum IgG 4 levels of more than 1.4 g/L is seen in 70% to 80% of patients. IgG4 elevation more than two times the upper limit of normal (normal 140 mg/dL) has 99% specificity for IgG4-RD[4]. Elevated IgG4 levels are nonspecific: five percent of persons without the disease can have elevated levels as well as 10% of patients with pancreatic-biliary malignancy, infectious, and inflammatory disorders. Multi-organ involvement has been associated with higher IgG4 concentration. Normal levels do not exclude the disease. Elevated total IgG and IgE, peripheral eosinophilia, ESR (Erythrocyte Sedimentation Rate), and CRP (C -reactive protein) have been reported but are nonspecific findings. Serum ANA (anti-nuclear antibody) titers are positive in almost 50% of cases and elevated RF (rheumatoid factor) in 20% of patients. Hypocomplementemia also has been reported and can be related to immune complex detected in the kidneys and pancreas of patients with the disease.

Radiological Diagnosis

Radiological images cannot differentiate between malignancy and benign disease in the affected organs.

Computed tomography and Magnetic resonance imaging

A combination of CT and MRI can identify the affected organs and monitor the disease activity, remission, or relapse. Patients with the following results have a high probability of autoimmune pancreatitis[5].

- A diffusely enlarged pancreas with delayed enhancement and borders
- No features in the presence or absence of a capsule-like rim in CT with contrast or
- MRI with more than twice the upper limit of IgG4 levels

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS)

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) can help obtain tissue samples for diagnosis. In case of renal lesions, they are commonly bilateral and multiple and involve the cortex. The radiological findings are classified as one of the following:

- Large, solitary masses
- Small, peripheral cortical nodules
- Round or wedge-shaped lesions
- Diffuse, patchy involvement

Histopathology

The three classic features are lymphoplasmacytic inflammation, fibrosis with a storiform pattern, and obliterative venulitis. Lymphoplasmacytic inflammation is dense with lymphoid aggregate and germinal center formation; eosinophilia may be prominent in the infiltrate. Lymphocytic venulitis is common. A storiform pattern is standard for this disease, and it marks a radiating pattern of closely packed fibroblasts (3). In addition to these, there may be keloid or hyaline patterns. Granulomas are uncommon, and the presentation makes the diagnosis unlikely. Obliterative venulitis is difficult to

identify using eosin and hematoxylin stains, and special connective tissue stains like elastin Van Gieson are useful. Individually these findings may be seen in any non-IgG4-RD disease, the presence of all the three components makes this diagnosis distinct. In a renal disease with tubulointerstitial nephritis, microscopy shows a plasma-cell-rich interstitial inflammatory cell infiltrate. The plasma cells in the lesions stain positively for IgG4.

Treatment

Corticosteroids

Corticosteroids are the mainstay of treatment. No randomized controlled studies for the treatment of IgG4-RD have been done to date. Some patients with AIP have had spontaneous remission with no treatment[6]. The urgency of treatment depends on the involvement of vital organs and the risk of organ damage. The major determinant of treatment responsiveness is the degree of fibrosis; patients who have long-standing fibrosis have low chances of cure. In patients with advanced organ dysfunctions like the presence of portal hypertension, cirrhosis, aortic dissection, irreversible fibrosis and encasement of vessels within mesentery and retroperitoneum, chronic salivary and lacrimal gland dysfunction, or orbital pseudo-tumors leading to vision loss, supportive management is advocated. Lymphadenopathy and pulmonary nodules may resolve spontaneously. Prompt improvement after starting glucocorticoid treatment is often interpreted as a useful diagnostic sign in patients with an unclear diagnosis. Such patients were noted to have relatively low serum IgG4 concentrations without the presence of obstructive jaundice or diabetes mellitus and showed focal rather than diffuse pancreatic swelling. The response is dramatic in those who have an early inflammatory disease in comparison to patients who predominantly have fibrosis. Most patients have a rapid but not sustained response to glucocorticoid. Clinical response is associated with radiological, biochemical, and serological improvement. The response is significant in early inflammation, and it reduces the time to remission and improves the exocrine function. The response usually starts in 2 to 4 weeks. At least a 3-month to a 6-month duration of treatment is usually recommended. Serum IgG4 levels come down but do not normalize. Persistent elevation of IgG4 has been associated with higher risk of disease relapse, but this is not consistent.

Prednisone

The two opinions regarding steroid dosages are from Japan and the Mayo Clinic in the United States. Seventeen referral centers in Japan suggested treating patients with prednisolone first. Specifically, 0.6 mg/kg per day for 2 to 4 weeks and tapered 3 to 6 months to a dose of 5 mg per day, and finally continued at a dose between 2.5 to 5 mg per day for up to 3 years[6][7][6]. At the Mayo Clinic, the guidance was to begin treatment with prednisone 40 mg per day and to maintain this dose for 4 weeks, then follow with a 7-week prednisone taper and reduce the dose of prednisone by 5 mg per week and stop, with the total duration 11 weeks. However, 50% of AIP patients relapsed within a median of 3 months. Relapse rates are between 10% to 53 % after treatment with steroids. The maintenance of glucocorticoids is associated with a lower relapse rate in comparison to complete cessation of steroid.

Biliary stenting

In addition to treatment with prednisone, many patients with AIP also undergo a biliary stenting procedure which is believed to shorten the time needed for symptomatic improvement[8]. Treatment with glucocorticoids is believed to shorten the time that biliary stents are needed. In patients with the

recurrent or refractory disease who are on steroid taper or discontinuation, second-line agents that can be tried include azathioprine (2 mg/kg per day), Mycophenolate mofetil (up to 2.5 g/day as tolerated), and methotrexate. However, no randomized control studies have been done to confirm their efficacy.

B-cell depletion

B-cell depletion using rituximab (1 g intravenously [IV] every 15 days for a total of 2 doses) is another mode of treatment. Patients undergoing B-cell depletion treatment show a rapid clinical response and lowering of serum IgG4 level. But the reduction of tissue IgG4 and Plasma cells are not significant. Targeted and often rapid reduction of serum IgG4 concentrations is possible through B-cell depletion, resulting in the relative preservation of other immunoglobulins and immunoglobulin subclass concentrations. This suggests that B-cell depletion achieves its effects, at least in part, by interfering with the repletion of short-lived plasma cells that are producing IgG4[9]. Once these IgG4-producing cells disappear, they are not repleted following the anti-CD20 therapy because the pool of circulating B cells has been depleted. Rituximab causes an even swifter, steeper decline in blood plasmablast concentrations. Bortezomib is a proteasome inhibitor with cytotoxicity against plasma cells which was approved for multiple myeloma, as per reports, it was effective in IgG4-related lung and orbital disease[4].

Differential Diagnosis

- Autoimmune pancreatitis
- Eosinophilia
- Hypereosinophilic syndromes
- Lymphadenopathy
- Multicentric Castleman disease
- Orbital disease
- Plasma cell neoplasm
- Polyclonal hypergammaglobulinemia
- Salivary and lacrimal gland enlargement

Enhancing Healthcare Team Outcomes

The diagnosis and management of IgG4 related disease is complex and best done with an interprofessional team including nurses. Because of the lack of controlled clinical trials, the treatment is based on anecdotal case reports and personal experience of the treating physician. Corticosteroids and other potent immunosuppressive agents are widely used to manage this disorder with varying success. Unfortunately, relapses are common.

References

1.

Wallace ZS, Stone JH. An update on IgG4-related disease. *Curr Opin Rheumatol*. 2015 Jan;27(1):83-90. [[PubMed](#)]

2.

Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med*. 2012 Feb 09;366(6):539-51. [[PubMed](#)]

3.

SARLES H, SARLES JC, MURATORE R, GUIEN C. Chronic inflammatory sclerosis of the pancreas--an autonomous pancreatic disease? *Am J Dig Dis*. 1961 Jul;6:688-98. [[PubMed](#)]

4.

Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Clain JE, Pearson RK, Pelaez-Luna M, Petersen BT, Vege SS, Farnell MB. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol*. 2007 Aug;102(8):1646-53. [[PubMed](#)]

5.

Kawa S, Ota M, Yoshizawa K, Horiuchi A, Hamano H, Ochi Y, Nakayama K, Tokutake Y, Katsuyama Y, Saito S, Hasebe O, Kiyosawa K. HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. *Gastroenterology*. 2002 May;122(5):1264-9. [[PubMed](#)]

6.

Khosroshahi A, Stone JH. Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol*. 2011 Jan;23(1):67-71. [[PubMed](#)]

7.

Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M., Research Committee for Intractable Pancreatic Disease and Japan Pancreas Society. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. *J Gastroenterol*. 2010 May;45(5):471-7. [[PubMed](#)]

8.

Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, Topazian MD, Clain JE, Pearson RK, Petersen BT, Vege SS, Lindor K, Farnell MB. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. *Gastroenterology*. 2008 Mar;134(3):706-15. [[PubMed](#)]

9.

Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. *Medicine (Baltimore)*. 2012 Jan;91(1):57-66.