University of Texas Southwestern Medical Center

A unifying condition: IgG4-Related Disease

Internal Medicine Grand Rounds

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This is to acknowledge that Kara Prescott, MD has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Prescott will be discussing off label uses in her presentation.

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Purpose and Overview:

IgG4-related disease is a newly recognized disease in the grand scheme of medical history. This newly documented disease exhibits how, over time, scientific growth allows for the discovery of new diseases in the place of old ones. In the case of IgG4-RD, multiple diseases which have been around for decades or even a century are now revealed as being part of a broader histopathological process. There have been purposeful measures taken to advance the disease as a whole over the last few years. This is a fascinating area which requires continued investigation while offering exciting growth and discovery.

Educational Objectives:

1) Review and discuss the definition and nomenclature of IgG-4 Related Disease as it relates to the International Symposium on IgG4-Related Disease in 2011.
2) Review and discuss the IgG4-Related Disease histopathology as it relates to the International Symposium on IgG4-Related Disease in 2011.
3) Review and discuss five of the IgG4-Related Disease entities.
4) Review and discuss the treatment of IgG4-Related Disease.

History

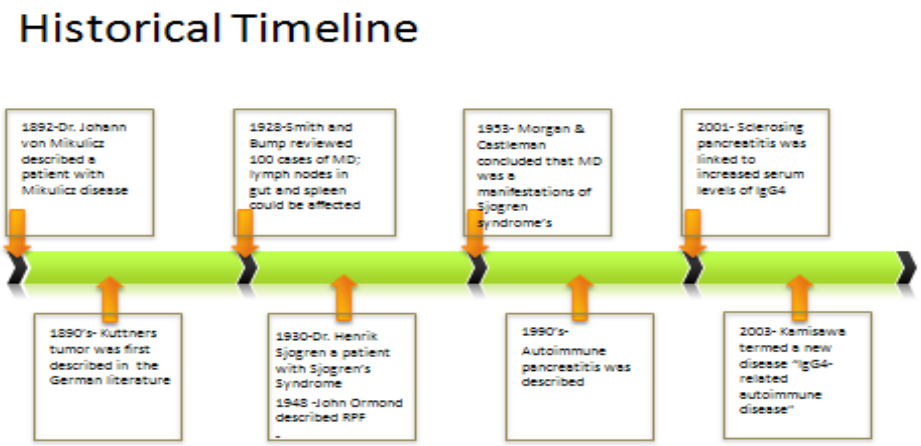
IgG4-related disease unifies multiple medical previously thought to be system diseases [1]. The are ones which have been some even for centuries; but part of a systemic disease characteristics [2]. This sarcoidosis that is a systemic manifestations are linked by and pathologic features is a novel term that (IgG4-RD) diagnoses which have been multiple different single organ diseases presented and discussed historically viewed as single entities, now they have been revealed as united by histopathological concept can be compared to disease in which diverse organ a unique histological appearance [1,2].

Occam's Razor

William of Occam - a 14th century English logician and Franciscan friar

Plurality should not be posited without necessity - pluralitas non est ponenda sine necessitate

Conditions which have been recognized since the 1800's are now found to be part of the IgG4-RD spectrum. In 1892, Dr. Johann von Mikulicz reported a patient with bilateral swelling of the lachrymal, parotid, and submandibular glands, with massive infiltration of these glands by mononuclear cells. In 1930, Dr. Henrik Sjogren described a woman with rheumatoid arthritis who had keratoconjunctivitis, sicca and severe swelling of the parotid glands; now known as Sjogren's syndrome. In 1953, Morgan and Castleman concluded that Mikulicz disease was a manifestation of Sjogren's syndrome [3]. Autoimmune pancreatitis (AIP) was first designated a disease in the 1990's [4]. Sclerosing pancreatitis was linked to elevated serum IgG4 elevations in 2001 by Hamano et al. [2]. In 2003, Kamisawa et al termed a new disease "IgG4-related autoimmune disease" to describe a patient with AIP, lesions of the bile duct, retroperitoneum and salivary glands [5].

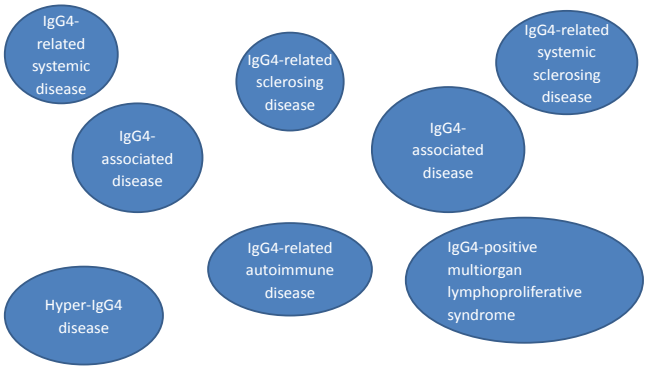


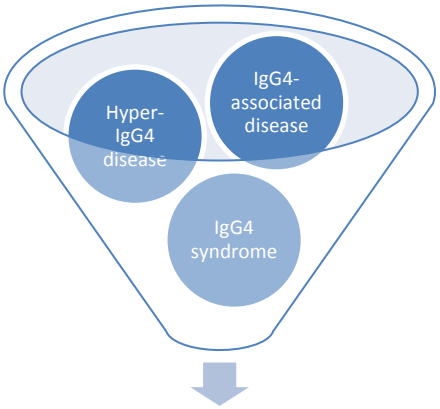
Definition & Nomenclature

IgG4-related disease is defined as, “a fibro-inflammatory condition characterized by a tendency for formation of tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, frequent, but not invariable elevations of serum IgG4 levels , and a swift initial response to glucocorticoids provided that tissue fibrosis has not supervened” [1]. Of note, now known to be synonymous with IgG4-RD is multifocal fibrosclerosis [6]. Multifocal fibrosclerosis was first described in the 1960’s. Multifocal fibrosclerosis is described as a simultaneous occurrence of inflammatory fibrotic pseudotumors. Examples include retroperitoneal fibrosis, thyroiditis, primary biliary cirrhosis, autoimmune pancreatitis and sialadenitis. These various organ manifestations have been found to be related by histopathologic features [7].

The International Symposium on IgG4-RD was held in Boston, MA, October 4-7, 2011. The symposium had 35 IgG4-RD experts from Japan, South Korea, Hong Kong, the United Kingdom, Germany, Italy, Holland, Canada, and the United States. These included clinicians, radiologists, pathologists and basic scientists [8]. A specific focus of this symposium was nomenclature. At the time, Japanese investigators had already reached a consensus on the name IgG4-RD, but at the 2011 meeting concerns were raised regarding using IgG4 in the disease name without qualifications because the role of IgG4 is still unresolved. The attendees of the symposium agreed to adopt the disease name IgG4-RD, however, in the interest of being able to “all speak the same language”. To be sure, it was noted that IgG4-RD refers to the increase in IgG4+ plasma cells within involved organs, not the frequency with which patients have an increased serum level [1]. The figure below demonstrates the multiple different names which were being used to refer to IgG4-RD [1].

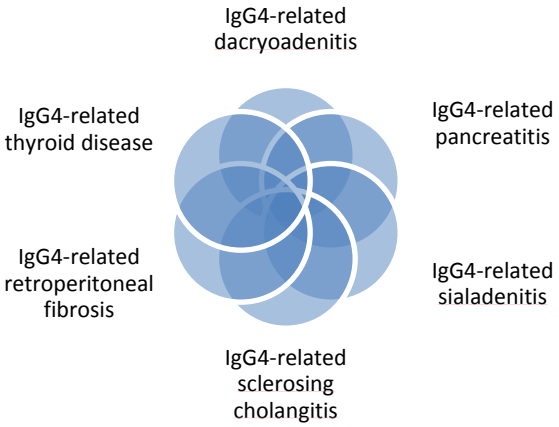
Different names employed to refer to IgG4-related disease





IgG4-Related Disease

International Symposium & Nomenclature



Preferred nomenclature for individual organ manifestations of IgG4-RD

As well, it has been proposed that in order to unify historic disease terms and improve clarity, new terms need to be applied to these conditions. For example, Kuttner's tumor would be IgG4-related submandibular gland disease. The table below lists preferred names for some of these historic conditions [9].

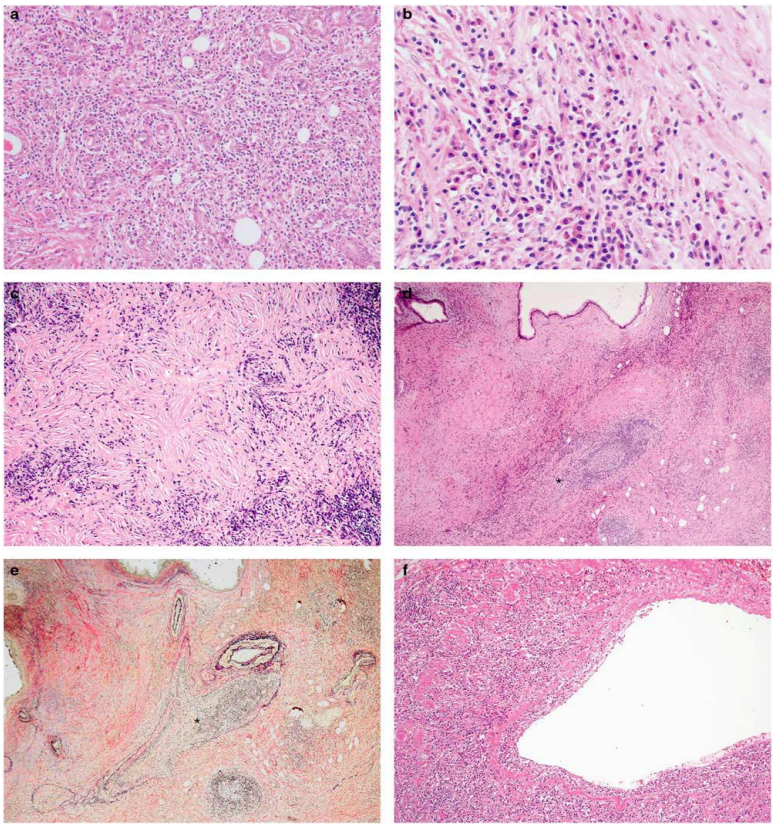
Historic Conditions	Preferred names for some of the historic conditions
Mikulicz disease	IgG4-related dacryoadenitis and sialadenitis
Kuttner's tumor	IgG4-related submandibular gland disease
Multifocal fibrosclerosis	IgG4-related disease
Ormond Disease	IgG4-related retroperitoneal fibrosis
Reidel's thyroiditis	IgG4-related thyroid disease

Histopathology

Another primary focus of the International Symposium was to provide practicing pathologists with a set of guidelines for the diagnosis of IgG4-RD. They specifically noted that one must also have careful correlation with the clinical scenario and imaging characteristics of a particular patient to arrive at a definitive diagnosis [8]. There were three major histopathological features designated to be associated with IgG4-RD. To be confident in the diagnosis it was determined that at least two of these three major features would need to be present. The three major features are 1) a dense lymphoplasmacytic infiltrate 2) fibrosis, arranged at least focally in a storiform pattern and 3) obliterative phlebitis [8].

A dense lymphoplasmacytic infiltrate is described as small lymphocytes throughout, intermingled with plasma cells. The lymphocytes are made up of mostly T-cells and some B-cells. Plasma cells are essential and may be in larger proportion to the T and B-cells [8]. Storiform fibrosis resembles the spokes of a cartwheel with spindle cells radiating from the center. Obliterative phlebitis is described as venous channels that are obliterated by a dense lymphoplasmacytic infiltrate. Partially obliterated veins with transmural inflammatory infiltrates can also be seen. The presence of arteritis does not exclude IgG4-RD; but arteries are less likely to be affected [8].

The figure below demonstrates these histopathological findings. The pictures depict the following: a) IgG4-sialadenitis – lymphocytes and plasma cells b) IgG4-sialadenitis – eosinophils c) IgG4-related orbital disease - storiform fibrosis – an irregularly whorled pattern d) IgG4-related pancreatitis – vein is completely obliterated by inflammation – obliterative phlebitis e) greater magnification of d f) vein with transmural inflammation; not obliterative [8].



a) lymphocytes and plasma cells
b) eosinophils
c) storiform fibrosis
d) obliterative phlebitis
e) greater magnification of d
f) vein with transmural inflammation; not obliterative

Features which have been noted to be inconsistent with IgG4-RD include: the presence of epithelioid cell granulomas (this excludes IgG4-RD), giant cells, and a prominent neutrophilic infiltrate. If there are neutrophils, necrosis and giant cells one should think of granulomatosis with polyangiitis (formerly Wegener's Granulomatosis) [8].

Diagnostic terminology has been proposed for IgG4-RD. The three categories are 1) histologically highly suggestive, 2) probable histological features, and 3) insufficient histopathological evidence [8].

Defining characteristics of each category is as follows:

1) Histologically highly suggestive of IgG4-related disease
    a. Two of the three major (lacrimal gland as an example of exception – may not have storiform fibrosis or obliterative phlebitis)
    b. Elevated IgG4 plasma cells in tissue (depends on organ involved)
    c. Aortic specimens need a ratio of 50% or higher; otherwise >40%; as giant cell arteritis, infectious aortitis and some atherosclerosis can have a ratio of close to 40%
2) Probable histological features of IgG4-RD (need further evidence to confirm the diagnosis)
    a. Lack the full histological spectrum or the immunohistochemical profile of IgG4-RD
    b. Examples

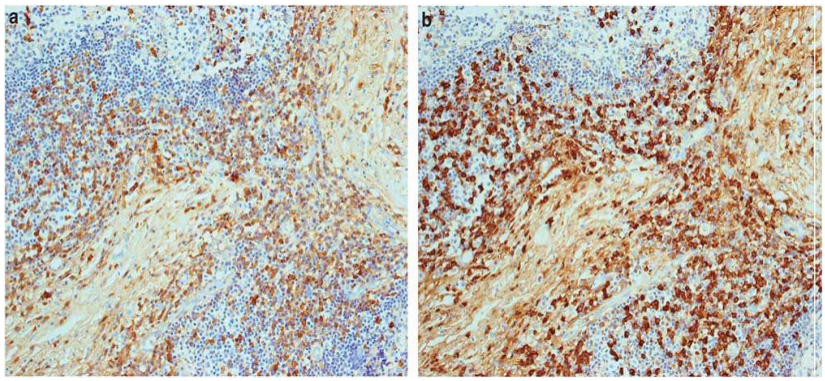
i. 1 histopathological feature (typically dense lymphoplasmacytic infilitrate) + required numbers of IgG4+ plasma cells
ii. Needle biopsies: the complete histopathology may not be evident on the biopsy specimen
iii. Meningeal and cutaneous disease – limited data

c. May also have:
i. Serum IgG4>135mg/dL – neither necessary nor sufficient for the diagnosis; 20-40% of patients will not have an elevated serum IgG. The serum IgG4 level may be approximately 25% higher than normal. Curiously, patients with multi-organ involvement tend to have higher serum levels of IgG4. Serum IgG4 levels cannot be depended on to reveal disease activity or response to treatment. Once again, it must be noted that the pathological findings in tissue must be reviewed for diagnosis.
ii. Other organ involvement by radiological or pathological examination

3) Insufficient histopathological evidence of IgG4-RD
a. Outside the two categories above, does not necessarily exclude may be sampling error, previous therapy, progression to fibrotic stage

Phlebitis without obliteration of the lumen and increased numbers of eosinophils are not sensitive or specific in isolation [8].

With above being said, there are some organ sites which may have varied histological changes and in these organs the diagnosis relies more on the IgG4+cells and ratio. A 50% or higher of IgG4-plasma cells to total IgG plasma cells is very suggestive of IgG4-RD [2]. IgG4 staining is essential, especially if there is not an elevated serum IgG4 concentration. This is felt to be a simple, highly reproducible test that provides strong confirmatory evidence for the diagnosis. The appropriate cutoff for the number of IgG4+ plasma cells varies depending on the organ involved due to the amount of fibrosis which may be present at the time; i.e. retroperitoneal fibrosis. The IgG4/total IgG ratio would be >40% in this case [8]. While elevated levels of IgG4 in serum and tissue supports the diagnosis of IgG4-RD, they are not a specific diagnostic marker [2]. In the literature it is cautioned to not rely on these levels for diagnosis because of the possibility of misdiagnosis and over-diagnosis of the disease [9]. The figure below depicts staining of IgG positive cells as in (a) and the majority from (a) are staining for IgG4 in (b)[8].



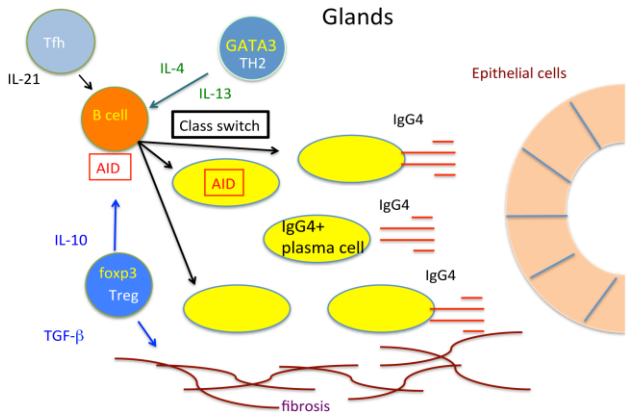
a) IgG positive cells
b) the majority from (a) are staining for IgG4

To note, there are diseases which have an elevated serum IgG4, but are not IgG4-RD. The differential diagnosis can be broad. Diseases in the differential are inflammatory conditions including primary sclerosing cholangitis, ANCA-associated vasculitis, rheumatoid arthritis, Rosai-Dorfman disease, and multicentric Castleman's disease. The key to distinguishing these other diseases from IgG4-RD is the lack of characteristic histopathologic features which define IgG4-RD [8].

Distinguishing IgG4-RD from lymphoma can be a bit more difficult as it has similar histopathologic features to IgG4-RD. Although, lymphomas are predominantly noted to have a B-cell infiltrate; whereas the IgG4-RD has a predominantly T-cell infiltrate [2]. Low grade B-cell lymphomas must be excluded, especially if the plasma cells demonstrate atypical features. These may include marginal zone lymphomas or follicular lymphomas [2]. Overall, in malignancies the plasma cell infiltration is patchy and the typical IgG4-RD histological features are not present [8].

Pathogenesis

The underlying mechanisms of the disease process are poorly understood. Autoimmune and allergic etiologies are thought to exist. Th2 and Treg cells are underlying the IgG4 production. Tsuboi and colleagues looked at labial salivary glands. Specifically, they found that Il-10, TGF-B, and AID (activation-induced cytidine deaminase) were over expressed in LSGs in patients with IgG4-RD. From this they proposed that these molecules may contribute to IgG4 class switching and fibrosis [10,11]. They looked at extracted RNA from labial salivary glands of 11 patients with IgG4-RD, 13 patients with SS and 3 healthy controls [11].



Th2 cytokines (IL-4 and IL-13) stimulate the production of IgG4 and IgE. Treg cytokines (IL-10 and TGF-B) contribute to IgG4-specific class switch

Clinical Presentation

The disease has been noted to be predominantly found in men over the age of 50. IgG4-RD typically has an indolent presentation without constitutional symptoms or elevations in acute phase reactants. There are many cases that are found incidentally on imaging. The course of the disease tends to depend on the organ involved. Disease may be confined to one organ or evolve into multi-organ involvement. In a minority of cases, it may spontaneously resolve, but most of the time it follows an indolent course progressing to organ damage. There are some examples of aggressive lesions as well [2].

Clinically, tumor like lesions and allergic symptoms are noted. These "tumors" tend to form in the orbital region, salivary glands, lung, kidney, lymph nodes, retroperitoneum, and others. Infiltrative lesions can also occur. Typically these are found in the meninges, skin and aorta. While lesions associated with IgG4-RD are not malignant and usually fairly indolent, they have been known to cause tissue destruction as evidenced by aortic aneurysms and dissections [9].

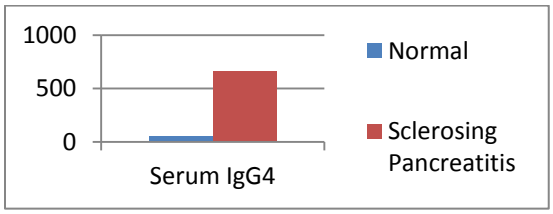
Allergic findings include: atopy, asthma, eczema, chronic sinusitis, and peripheral blood eosinophilia [2]. Allergic and atopic signs and symptoms can also be associated with the clinical presentation of IgG4-RD. Patients can have a long history of allergic rhinitis, sinusitis and asthma. As well, serum and tissue levels of eosinophils may be present [9].

Recommendations in regards to imaging for this disease include whole body examination to evaluate for systemic involvement. When evaluating response to treatment, morphologic and functional imaging can be helpful [4].

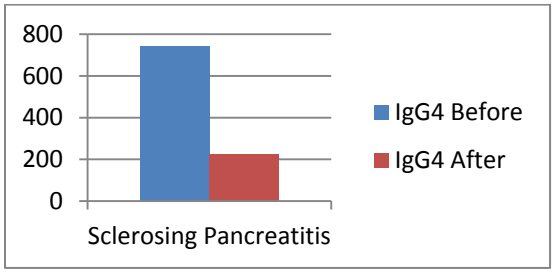
Overall, the course is indolent in nature for the majority with patients feeling well even when there is multi-organ involvement, but a minority of patients may have a stronger presentation with constitutional symptoms, fevers, and elevated acute phase reactants [9].

Autoimmune Pancreatitis Type 1

In the 1990's a subset of chronic pancreatitis was found to have an autoimmune etiology. Hamano et al in 2001 measured serum IgG4 concentrations in patients with sclerosing pancreatitis and normal subjects who were matched controls. Patients with sclerosing pancreatitis had significantly higher levels of serum IgG4. They also compared IgG and IgG4 in patients with sclerosing pancreatitis, pancreatic cancer, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis and sjogrens syndrome and found higher levels of serum IgG4 in sclerosing pancreatitis. Twelve of the patients with sclerosing pancreatitis were treated with glucocorticoids. Serum IgG4 levels decreased after 4 weeks of treatment [12].



Sclerosing pancreatitis had significantly higher levels of serum IgG4



Twelve of the patients with sclerosing pancreatitis were treated with glucocorticoids. Serum IgG4 levels decreased after 4 weeks of treatment

In 2003, a characteristic histopathologic finding was discovered – lymphoplasmacytic sclerosing pancreatitis [3]. There are two types of autoimmune pancreatitis (AIP); type 1 and type 2. Type 1 is thought to be IgG4-related pancreatitis. The clinical presentation seems to be one of older males with obstructive jaundice who have pancreatic and extrapancreatic manifestations responding to steroid therapy.

Recent studies have revealed two different types of AIP, type 1 and type 2. To look at type 2, resected pancreata of patients with chronic non-alcoholic pancreatitis were histologically reviewed by American and European pathologists and revealed a second AIP, termed type 2 AIP with GEL (granulocyte epithelieal lesion) or IgG4-unrelated idiopathic duct-centric pancreatitis (IDCP). A comparison of the two is noted in the table below [3].

Subtype of AIP	Type 1 AIP – IgG4-RD	Type 2 AIP – non-IgG4-RD
Prevalence	Asia>USA, Europe	Europe >USA>Asia
Age	High Age	Younger
Gender	Male>>Female	Male=Female
Symptoms	Often obstructive jaundice	Often obstructive jaundice
Pancreas Images	Swelling/diffuse	Swelling/diffuse
	Segmental/focal	Segmental/focal
	Mass-forming	Mass-forming
Serology	High serum IgG	Normal IgG
	High serum IgG4	Normal IgG4
	Autoantibodies (+)	Autoantibodies(-)
Other organ involvement	Sclerosing cholangitis	Unrelated other organ involvement
	Sclerosing sialadenitis	
	Retroperitoneal fibrosis	
Ulcerative colitis	Rare	Often
Steroid response	Responsive	Responsive
Relapse	High rate	Rare

Both entities have swelling of the pancreas, obstructive jaundice, and are steroid responsive. Type 1 IgG4-related AIP typically affects older males>females, rarely causes abdominal pain, have a high serum IgG4 concentration and associations with other organ involvement. Type 2 AIP affects males and females equally, has normal IgG4 levels, and is not associated with other organ involvement with the exception of ulcerative colitis which affects approximately 30% of patients with type 2 AIP [3]. Type 1 AIP is one of the entities which have organ specific clinical diagnostic criteria. These are summarized in the table below [3].

Clinical diagnostic criteria of autoimmune pancreatitis (2006)

1. **Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas on imaging modalities, such as abdominal ultrasound, computed tomography, and magnetic resonance imaging.**
2. **High-serum F-globulin, IgG, or IgG4 or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor.**
3. **Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells into the periductal area, with occasional lymphoid follicles in the pancreas.**

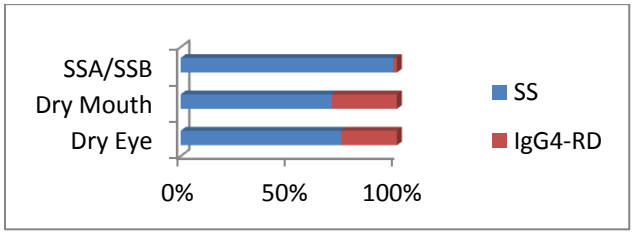
For diagnosis, criterion 1 must be present, together with criteria 2 and/or 3.
However, it is necessary to exclude malignant diseases such as pancreatic and biliary cancers.

Mikulicz Disease

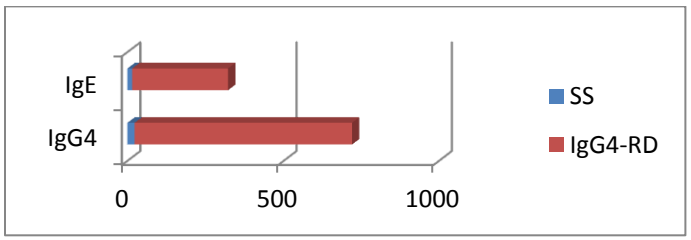
Mikulicz disease was first described by Dr. Johann von Mikulicz in 1892. He described a patient with a triad of swelling in the submandibular glands, lacrimal glands and parotid glands. Mikulicz disease was also felt to be a variant of Sjogren's syndrome [9]. In 1928, Smith and Bump reviewed 100 cases of MD and found MD was a disease of lymphoid tissue in the salivary and lacrimal glands and this

destroyed the glandular tissue. Other lymph nodes could also be affected as was found in the gut and spleen. Some cases were able to be followed over 12 years and were not found to transition to malignancy [13]. In 1930, Dr. Henrik Sjogren, an ophthalmologist, described a woman with Sjogren's syndrome. As described above in 1953, it was felt MD was a manifestation of Sjogren's syndrome. Yamamoto et al, reported MD to be associated with elevated IgG4 in 2004 [13]. Since this time, it has been proven through pathology that this is not Sjogren's syndrome and the term Mikulicz disease should be replaced with a more telling term, IgG4-related dacryoadenitis and sialadenitis [9].

Differences between Mikulicz disease and Sjogren's syndrome are found in gender, clinical presentations, complications, response to treatment and serum/tissue concentrations of IgG4-positive cells [3]. While MD affects women and men, SS has a female predominance. Xerostomia and xerophthalmia are relatively mild in MD. Steroid responsiveness is more robust in MD than in SS [3].



Patients with IgG4-RD had fewer sicca symptoms and SSA/SSB antibodies



Patients with IgG4-RD had higher levels of IgG4 and IgE

In a study comparing 61 patients with IgG4-RD and 31 patients who met both the Japanese and European SS criteria Masaki et al, found several differences as is illustrated in the chart above. Xerophthalmia, xerostomia, and arthralgias were less common in patients with IgG4-RD. SSA antibodies, SSB antibodies, rheumatoid factor and ANA were more common in the patients with SS. IgG4 and IgE were more common in patients with IgG4-RD than in patients with SS. Patients with IgG4-RD had a greater propensity for steroid responsiveness as compared to SS [3].

The differences extend to their histopathological features as well. Both conditions have lymphocytic infiltration of the glands. In IgG4-RD, the lymphocytes typically aggregate into lymphoid follicles, but do not infiltrate the salivary ducts. This may also explain the finding that IgG4-RD patients have less sicca symptoms (oral and ocular dryness) even though there can be marked swelling of the salivary glands. The other significant difference is found in the number of tissue IgG4+ plasma cells. IgG4-RD has a ratio of >40 of IgG4+ to total IgG + cells [3]. So, while the organ involvement is similar between the two diseases, the pathological characteristics are not. Organ specific diagnostic criteria for MD have also been defined.

Diagnostic criteria of IgG4+ Mikulicz's disease
1) Symmetrical swelling of at least 2 pairs of lachrymal, parotid, or submandibular glands for at least 3 months AND 2) Elevated serum IgG4 (>135mg/dl) OR 3) Histopathological features including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells>50%) with typical tissue fibrosis or sclerosis

Kuttner's Tumor

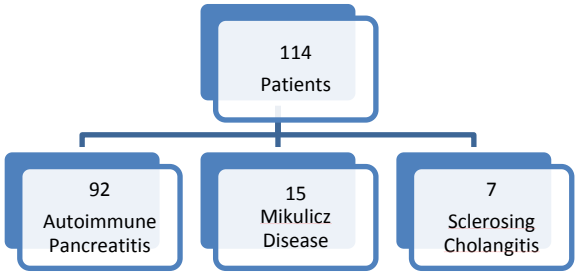
Kuttner's tumor was originally described in the German literature in the 1890's and it was described as tumorous swelling of the submandibular glands. It is now felt the term Kuttner's tumor should be reserved for submandibular disease caused by stones or infections [14]. If there is absence of stones and infections and there is bilateral submandibular swelling then likely it is associated IgG4-related sialadenitis [14]. Another distinction between the two is that Kuttner's tumor is unilateral; whereas the IgG4-related sialadenitis is typically bilateral [3].

Riedel's Thyroiditis

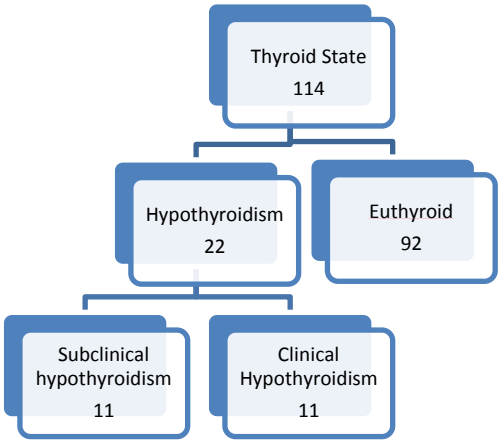
Bernhard Riedel first recognized Riedel's thyroiditis (RT) in 1883 [15]. In 1896, he published a description of two patients. They were found to have a hard goiter and tracheal compressive symptoms [4]. In 1897, he published a third case [15]. This goiter is described as a woody induration of the thyroid gland that can damage surrounding tissue by extending past the thyroid gland causing it to be fixed to adjacent structures [14,15]. As the disease progresses, fibrosis and sclerosis of the glandular tissue occurs [14]. The severe fibrosis and diffuse goiter seen in this disease has left some to question the association of Riedel's thyroiditis with IgG4-RD [15]. If biopsies are taken early in the disease course though, the hallmark histology may be seen; otherwise fibrosis is seen [14]. Of interest, Riedel's thyroiditis has also been associated with multifocal fibrosclerosis and thus has been proposed to be a part of IgG4-RD [14]. Given the rarity of the disease, it has been difficult to study in great detail. The Mayo clinic performed a review of 57,000 thyroidectomies between 1920 and 1984 and found only 37 cases of RT [15].

Watanabe T, et al, proposed IgG4-related thyroiditis as a new disease entity in their 2013 retrospective study. They looked at a total of 114 patients from 1992 to 2011 to evaluate for co-existence of thyroiditis, as seen in the table below [16]. Another study performed by the same group revealed hypothyroidism in 27% of patients with IgG4-related pancreatitis. Another group found 18%

and yet another with 14%. Overall, 14-28% of patients with AIP were found to have hypothyroidism. Noted was that the prevalence of hypothyroidism in the general population is 4.6% [16].



Watanabe et al reviewed 114 patients with an organ manifestation of IgG4-RD looking for thyroid disease.



Patients with elevated TSH levels were further classified into subclinical and clinical hypothyroidism.

Patients with elevated TSH levels were further classified into subclinical and clinical hypothyroidism. Patients with hypothyroidism did not have a goiter or destruction of surrounding tissues [16].

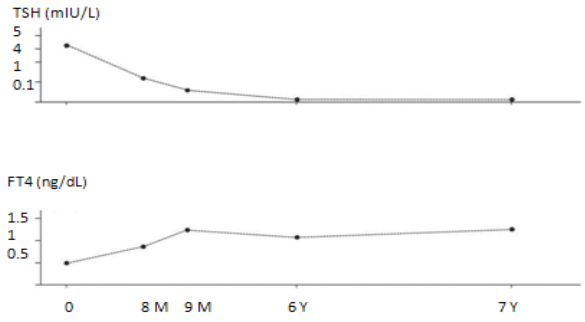
Watanabe and investigators looked at clinical and serological markers including FT3, FT4, TSH, and anti-thyroglobulin antibodies in these 114 patients with IgG4-RD. Elevated TSH levels were further classified into subclinical and clinical hypothyroidism as seen in the table below. Patients with hypothyroidism did not have a goiter or destruction of surrounding tissue [16]. Ten hypothyroid patients were treated with prednisolone, resulting in decreased TSH and increased FT4 levels over a period of time as seen in the graph below [16].

Thyroid State	Number of patients – total 114 patients
Hypothyroidism	22 (19%)
Subclinical hypothyroidism	11
Clinical hypothyroidism	11
Euthyroid	92

In a subset they assessed thyroid volume; CT scan of the thyroid was obtained in 20 euthyroid, 7 subclinical and 5 clinical hypothyroid patients. As a comparison, 24 normal control subjects >60 years of age were also evaluated with CT scan of the thyroid. Patients with hypothyroidism had a greater volume of thyroid as compared to the other thyroid states and control subjects [16].

Histological analysis had been done on one of the IgG4-RD patients who had thyroid tissue resected secondary to cancer. There was fibrosis and lymphocytic infiltration along with increased numbers of IgG4 plasma cells of the non-cancerous sample [16].

IgG4 levels were elevated in this study as in other forms of IgG4-RD. Imaging findings in this study were also indicative of IgG4-RD. The focal infiltration of lymphocytes and IgG4+plasma cells and atrophic loss of thyroid follicles were also consistent with IgG4-RD. As well, the hypothyroidism responded positively to steroids. It was noted that steroids do suppress TSH and could have been the cause of the lower TSH; but it was also noted that FT4 levels increased after steroid therapy lending credence to the conclusion that the steroids could have had an effect on the immune reactions [16].



The patients had an increase in FT4 after receiving glucocorticoids.

In a review of Hashimoto's thyroiditis, differences between Hashimoto's thyroiditis and IgG4-RD included: patients with IgG4-RD were older and predominantly male; there were not significant goiters; half of the IgG4-RD group had no thyroid antibodies; patients with IgG4-RD had a favorable response to steroids. As well, where Riedel's thyroiditis is characterized by invading surrounding tissue and structures, this was not found in the IgG4-related thyroiditis [15]. The authors concluded with the proposal of IgG4-related hypothyroidism as a new disease entity.

Whether Riedel's thyroiditis and Hashimoto's thyroiditis should be included in IgG4-RD remains to be determined [16].

Ormond's Disease

Ormond's disease is also known as retroperitoneal fibrosis (RPF) [6]. Albarran, a French urologist, in 1905 reported the first case of idiopathic RPF causing ureteral obstruction [17]. In 1948, the urologist Dr. John Ormond described a case of fibrous tissue encasing both ureters in a patient who had renal failure [6]. The incidence is estimated to be 1/1,000,000 person-years based on a Finnish study [18]. Imaging of these patients will reveal a soft tissue density which surrounds the abdominal aorta and/or iliac vessels causing renal failure. Idiopathic and secondary causes exist. Typically, infection and malignancy need to be ruled out as primary causes. In the past RPF has been associated with multifocal fibrosclerosis. In 2009, Zen et al reviewed 17 RPF patients. They looked at the histopathologic features and found that 10 of the cases had features consistent with IgG4-RD [19].

In a more recent study, Khosroshahi et al, identified and reviewed 23 cases of idiopathic RPF from Massachusetts General Hospital for characteristics related to IgG4-RD. Each of these cases had pathology blocks available for review. The slides were reviewed for lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis and tissue eosinophilia. The IgG4/total IgG ratio as well as the degree of IgG4+ plasma cells was also assessed. The cases were divided into two groups based on the IgG4/IgG ratio. There were 13 patients in the IgG4-related RPF group and 10 in the non-IgG4-related RPF group based on a cut off of >40%. Histopathological features were compared between the two groups [6].

	IgG4/Total IgG >40%	IgG4/Total IgG <40%	P
Histopathologic Features	**No. (%)**	**No. (%)**	
Storiform Fibrosis	12/13 (92)	3/10 (30)	0.006
Plasma Cell Infiltrate	12/13 (92)	3/10 (30)	0.006
Tissue Eosinophilia	10/13 (77)	0 (0)	0.0002
Phlebitis	4/13 (31)	0 (0)	0.1

T There were 13 patients in the IgG4-related RPF group and 10 in the non-IgG4-related RPF group based on a cut off of >40%. Histopathological features were compared between the two groups.

The mean age was 58 years old and 73% were male in the overall cohort. Clinical symptoms were similar in both groups with back and flank pain and lower extremity swelling. The masses were found to be periaortic and similar on imaging. Six of the IgG4-related RPF patients had manifestations other than RPF that was biopsy proven. There were none in the non-IgG4-RD group [6].

Overall, they found over half of the cases to be IgG4-related RPF. There was a significant correlation between the histopathologic findings (storiform fibrosis, lymphoplasmacytic infiltration, eosinophilia, elevated IgG4/total IgG ratios). Noted from this study is that the clinical, serological, and radiographic findings are typically not helpful in differentiating between idiopathic RPF and IgG4-related RPF [6].

Treatment

Treatment of IgG4-RD has not been evaluated with randomized trials. Glucocorticoids are the first line treatment [9]. It is reported that most patients should respond within a few weeks, but may take several months. Some authors recommend prednisone 40mg/day and taper over 2 months to off [9]. Others recommend prednisolone 0.6mg/kg/day for 2-4 weeks and then taper over 3-6 months to 5.0mg a day, and then continued at a dose between 2.5mg and 5.0mg per day for up to 3 years. Some have used this approach, but tapered the prednisone to off after an initial 3 months [2].

Consensus guidelines in Japan recommended 0.6mg/kg/day of prednisolone for 2-4 weeks, and then decrease by 5mg every 1-2 weeks until 2.5-5mg is reached. This should take 2-3 months. Consider continue the maintenance dose for 6-36 months. It has been noted that patients who were kept on a low maintenance dose of prednisolone were more likely to sustain remission (only 23% relapsed in one study).

Researchers at the Mayo Clinic described a steroid regimen. This was based on treating patients with cholangitis. The regimen is prednisone 40mg/day for 4 weeks, and then it decreases by 5 mg each week until off completely. The relapse rate with this regimen was 53% [20].

Some authors note azathioprine 2mg/kg/day or mycophenolate mofetil up to 2.5mg/kg/day for use in steroid dependent cases; others add in methotrexate as an option. Given the newness of the disease it is difficult to tell the true efficacy of these steroid sparing agents in this disease process [9].

Treatment with rituximab was first discussed in 2008. Rituximab seems to have promise as a therapy in patients who are steroid dependent or steroid resistant. In 2012, 10 patients who had IgG4-RD resistant to steroids and DMARDs were reported to respond to rituximab. While the cases seemed to respond to rituximab rapidly, there is still a question of how long the remission lasts. Rituximab does seem to have allowed patients to be able to taper steroids and/or DMARD therapy [21]. Patients have demonstrated a decrease in serum IgG4 levels associated with a prompt response of clinical and serological markers. Noted is that the serum IgG4 levels decrease with the IgG1, IgG2, and IgG3 levels remaining stable. There is an ongoing clinical trial investigating the efficacy of rituximab [9]. Less is known about the long term prognosis of patients treated with rituximab [21].

Bortezomib is a proteosome inhibitor that is toxic to plasma cells currently licensed for treatment of multiple myeloma and mantle cell lymphoma. It has been suggested as a treatment of IgG4-RD, but has not been studied [20].

It is important to consider the disease process in the case of treatment. IgG4-RD progresses from a lymphoplasmacytic inflammation to extensive fibrosis. The degree of fibrosis tends to determine how well the patient will respond to treatment [2]. Who should be treated? Symptomatic patient should be treated. Some cases should be treated urgently because without such treatment the disease process may lead to acute organ failure. Examples include: IgG4-sclerosing cholangitis, aortitis, pachymeningitis and some orbital pseudotumors [9]. Lacrimal gland swelling or other orbital pseudotumors with proptosis, pain secondary to submandibular gland or parotid gland swelling, renal involvement or kidney dysfunction, AIP, retroperitoneal fibrosis with flank pain or other involvement should likely be treated. Others, such as lymphadenopathy have a more indolent course and may be relatively asymptomatic [9].

Conclusions

In a broad sense IgG4-RD is still new. A consensus on nomenclature and histopathology has been accomplished, but there is still much work to be done. There are clinical diagnostic criteria for only two of the disease manifestations. More organ specific criteria are needed. Fortunately, treatment endeavors have begun to be organized. Currently, the Ministry of Health, Labor and Welfare Japan team is currently pursuing a “Prospective study for creating IgG4-related disease treatment guidelines” [3]. There are still many questions to be answered such as risk of malignancy, prognosis, and the actual role IgG4 plays in the pathogenesis overall.

IgG4-RD unites previously distinct and apparently disparate diseases. Studying a disease like IgG4-RD is intrinsically satisfying because it fulfills Occam's razor, a strongly held principle of parsimony in medicine that has stood the test of time.

References

1. Stone JH, Khosroshahi A, Deshpande V, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis & Rheumatism. 2012;64:10:3061-3067.
2. Stone JH, Zen Y, Deshpande V. Mechanisms of disease IgG4-related disease. N Engl J Med 2012; 366:539-51.
3. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22:1-14.
4. Horger M, Lamprescht H, Bares R, et al. Systemic IgG4-related sclerosing disease: spectrum of imaging findings and differential diagnosis. AJR. 2012;199:W276-282.
5. Hirabayashi K, Zamboni G. IgG4-related disease. Pathologica. 2012;104:43-55.
6. Khosroshahi A, Carruthers M, Stone JH, et al. Rethinking Ormond's Disease. Medicine. 2013;92:2:82-91.
7. Dahlgren M, Khosroshahi A, Nielsen GP, et al. Riedel's Thyroiditis and Multifocal Fibrosclerosis are part of the IgG4-related systemic disease spectrum. Arthritis Care and Research. 2010;62;9:1312-1318.
8. Deshpande V, Zen Y, Chan JKC, et al. Consensus statement on the pathology of IgG4-related disease. Mod Path 2012;25:1181-1192.
9. Stone JH. IgG4-related disease: nomenclature, clinical features, and treatment. Seminars in Diagnostic Pathology. 2012;29:177-190.
10. Koike T. IgG4-related disease:why high IgG4 and fibrosis? Arthritis Research & Therapy. 2013;15:103.
11. Tsuboi H, Matsuo N, Lizuka M, et al. Analysis of IgG4 class switch-related molecules in IgG4-related disease. Arthritis Res Ther 2012;14;R171.
12. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N ENGL J Med. 2001;344;10;732-738.
13. Yao Q, Wu G, Hoschar A. IgG4-related Mikulicz's disease is a multi-organ lymphoproliferative disease distinct from Sjogren's syndrome: a Caucasian patient and literature review. Clinical and Experimental Rheumatology. 2013; 31:289-294.
14. Khosroshahi A, Deshpande V, Stone JH. The clinical and pathological features of IgG4-related disease. Curr Rheumatol Rep. 2011;13:473-481.
15. Ahmed R, Al-Shaikh S, Akhtar M. Hashimoto thyroiditis: a century later. Adv Anat Pathol. 2012;19:3:181-186.
16. Watanabe T, Maruyama M, Ito T, et al. Clinical features of a new disease concept, IgG4-related thyroiditis. Scand J Rheumatol. 2013;iFirst article:1-6.
17. Stone JH. Aortitis, retroperitoneal fibrosis, and IgG4-related disease. La Presse Medicale. 2013;L45:622-625.
18. Fujimori N, Ito T, Igarashi H, et al. Retroperitoneal fibrosis associated with immunoglobulin G4-related disease. World Journal of Gastroenterology. 2013;19:1:35-41.

19. Zen Y, Kasashima S, Inoue D. Retroperitoneal and aortic manifestations of immunoglobulin G4-related disease. Seminars in Diagnostic Pathology. 2012;29:212-218.
20. Monach PA. IgG4-related disease: 2013 update. Current Treatment Options in Cardiovascular Medicine. 2013;15:214-223.
21. Murakami J, Matsui S, Ishizawa S, et al. Recurrence of IgG4-related disease following treatment of rituximab. Mod Rheumatol. 2012.