

IgG4-Related Disorder and Endocrine Diseases: A Review of the Literature

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Abstract

IgG4-related disorders (IgG4-RD) are a new entity of multi-organ disorders that share common fibro-inflammatory histopathologic characteristics and elevated IgG4 levels in serum and tissue. Autoimmune pancreatitis and Mikulicz syndrome are major entities, however many syndromes are part of IgG4-RD including eosinophilic angiocentric fibrosis, fibrosing mediastinitis, hypertrophic pachymeningitis, inflammatory pseudotumour, multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs), peri-aortitis and peri-arteritis, inflammatory aortic aneurysm, retroperitoneal fibrosis (Ormond's disease), Riedel's thyroiditis, and sclerosing mesenteritis.

In this review we detail the link between IgG4-RD and endocrine disorders and then examine the link between diabetes and IgG4-RD. We study the increased risk of IgG4-RD after using dulaglutide.

We concluded that IgG4-RD should be suspected in patients with progressive thyroiditis with mass effect and very high antibody titers. The relationship between IgG4-RD and diabetes is still controversial.

Keywords: IgG4; Thyroiditis; Pancreatitis; Diabetes mellitus; Hypophysitis

Abbreviations: IgG4-RD: IgG4 Related Disorders; AIP: Autoimmune Pancreatitis; MD: Mikulicz Disease; GLP-1: Glucagon Like Peptide 1

Introduction

In 2001, Hamano et al. [1] described elevated levels of IgG4 in the sera of patients presenting with autoimmune pancreatitis. A few years later, IgG4-positive cells were described in other organs of these patients, and the term IgG4-related disorders was suggested. This refers to an immune-mediated multi-organ group of disorders previously regarded as isolated single-organ diseases. The link between these diseases has been gradually established in view of the common fibro-inflammatory histopathologic characteristics and the elevation of IgG4 in the serum and tissues. Currently, IgG4-RD are described 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" [2].

Autoimmune pancreatitis (AIP) and the Mikulicz disease (MD) are major entities of IgG4-related disease. AIP is a form of chronic pancreatitis that presents with painless obstructive jaundice. Extra-pancreatic sclerosing manifestations were more frequent than previously thought in AIP patients. This could affect the bile duct, liver, gallbladder, retroperitoneum, salivary and lacrimal glands. Extensive IgG4 and plasma cell infiltration were also detected in the affected tissues [3]. Mikulicz disease (MD) presents with bilateral, painless, and symmetrical swelling of the lacrimal and salivary glands leading to dryness of the eyes and mouth—this presentation is easily confused with Sjogren's syndrome [4].

The diagnosis of IgG4-related disorder is based on typical histology makeup (dense lymphoplasmacytic infiltrates, storiform fibrosis, mild eosinophilic infiltration, and obliterative phlebitis), a high count of IgG4-positive plasma cells per high-power field (HPF), and high IgG4/

IgG ratio. However, non-histologic criteria for diagnosis of IgG4-related disease (IgG4-RD) have been proposed [5]. The following two criteria are the most established: IgG4 plasma level of >135 mg/dl and an IgG4/IgG plasma cell ratio of >40% with more than 10 IgG4-positive plasma cells per HPF. Stricter criteria for diagnosis were proposed by Deshpande et al. [6]. This group suggested that the critical histopathological features include a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis. The proposed terminology scheme for the diagnosis of IgG4-RD is based primarily on the morphological appearance on biopsy. The tissue IgG4 counts and IgG4:IgG ratios are secondary in importance. This means that the prominent IgG4+ plasma cells in the absence of one or more of the characteristic morphological features are usually not sufficient for diagnosis [6].

There are some histologic criteria that are inconsistent with IgG4-RD including the presence of epithelioid cell granulomas (this excludes IgG4-RD), giant cells, and a prominent neutrophilic infiltrate. The presence of neutrophils, necrosis and giant cells suggests granulomatosis with polyangiitis [6].

Based on these criteria, many other conditions are now considered to be part of the IgG4-RD including eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract), fibrosing mediastinitis, hypertrophic pachymeningitis, idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits,

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Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs), Küttner's tumor (affecting the submandibular glands), multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs), periaortitis and periarteritis, inflammatory aortic aneurysm, retroperitoneal fibrosis (Ormond's disease), Riedel's thyroiditis, and sclerosing mesenteritis. These disorders are usually seen in older males with atopic conditions. Many organs can be affected can result in a tumor effect especially in the lungs, orbits and pituitary gland [7,4].

There are no specific guidelines for treatment of IgG4-RD, however there is an agreement that all cases of symptomatic active IgG4-RD require treatment—some very urgently. The consensus states that glucocorticoids are the first line for all active untreated IgG4-RD unless there is a contraindication. Following successful induction, certain patients would benefit from maintenance therapy. Retreatment with steroids may be considered in patients who relapse off treatment following successful induction. Steroid-sparing agents should be considered following relapse [8].

There has been controversy regarding the initial use of combination steroids and steroid-sparing agents. This is because glucocorticoid monotherapy will ultimately fail to control the disease, and long-term glucocorticoid toxicities are a high risk to patients.

A response to treatment is often seen within 2-4 weeks and often sooner. The dose is tapered over 8 weeks once significant improvement is seen. In cases that are resistant to steroids rituximab (B cell depleting agent), azathioprine, mycophenolate are reasonable choices [9].

IgG4-RDs are associated with an increased risk of cancers including non-Hodgkin's lymphoma [10]. There are also cases of pancreatic cancer and salivary duct carcinoma, pulmonary adenocarcinoma, small cell carcinoma of the lung, and gastrointestinal clear cell sarcoma [11].

IgG4-related Disorders in Endocrine Practice

IgG4-related disorders and the thyroid

Riedel's thyroiditis is a part of IgG4-RD. In 2010, Dahlgren et al. [12], described three patients with Riedel's thyroiditis based on a fibro-inflammatory process. They found that the three patients had high IgG4/IgG ratios and very high levels of IgG4 per high power field. Li et al. [13] further studied the IgG4-related thyroiditis in a series of patients with Hashimoto's thyroiditis that underwent surgery. Staining for IgG4 was positive in histopathology sections in 19 patients. Positive patients were older, male, and had more progression and higher levels of circulating antithyroid antibodies.

Salook et al. [14] reported a patient who presented with an acute elevation in T4 and suppressed TSH associated with neck pain. The patient had already been diagnosed with Hashimoto's thyroiditis and was on a stable dose of thyroxine. Due to pressure symptoms, the patient underwent surgery and histopathology revealed extensive fibrotic processes, heavy plasmocytic infiltrates, and storiform fibrosis. This immunostained strongly for IgG and IgG4, and the IgG4/IgG ratio was over 80%. The serum IgG4 level was 737 mg/dl (normal, 3–201) with normal IgG1 and IgG3 levels and borderline IgG2 levels (805, normal 169–786 mg/dl). Thus, he was diagnosed with IgG4-related thyroiditis.

Considering thyroid diseases to be an IgG4-RD is still controversial; Pusztaszeri et al. described a patient with an expanding nodule that on histopathology showed features suggestive of IgG4-RD, however plasma IgG4 levels were normal [15]. Another study by Hamano et

al. [16] included patients with IgG4-RD and found high antithyroid antibodies in 41%, hypothyroidism in 21%, but none with Riedel's thyroiditis. Many other studies did not show any thyroid abnormalities [17-19].

Cameselle-Teijeiro et al. [20] studied a case of Riedel's thyroiditis in 2014 by applying both the classic criteria and the recent stricter criteria to diagnosis the IgG4-RD spectrum [6]. This suggested that Riedel's thyroiditis be included within the IgG4-RD spectrum.

Based on this data, we suggest that IgG4-RD should be considered in any patient with an aggressive form of thyroiditis including Hashimoto's thyroiditis. Suspected patients should be analyzed for a IgG4/IgG ratio with immunostaining when indicated.

IgG4-RD and the pituitary gland

There are many published cases of IgG4-RD affecting the pituitary gland. Almost all cases involved middle-aged or elderly men presenting with various degrees of hypopituitarism and diabetes insipidus and demonstrating a thickened pituitary stalk and/or pituitary mass. Pituitary swelling and the mass effect shrank remarkably in response to glucocorticoid therapy even at lower doses than that prescribed as a replacement for adrenocortical insufficiency. The presence of IgG4-related systemic disease and elevated serum IgG4 levels before glucocorticoid therapy were the main clues to a correct diagnosis of IgG4-related infundibulo-hypophysitis [21].

MRI shows a thickened pituitary stalk, swelling of the pituitary gland or mass formation. The pituitary stalk was markedly enhanced with gadolinium or had no enhancement in the pituitary gland. The "bright" signal seen in the posterior portion of the pituitary on T1-weighted imaging was absent in cases involving central diabetes insipidus and in several cases without clinical diabetes insipidus. Hypertrophic pachymeningitis and orbital lesions including pseudotumor formation were seen in a few cases. These MRI findings are not specific for IgG4-RD and can be seen in lymphocytic hypophysitis, sarcoidosis, tuberculosis and Wegener's granulomatosis [21].

To differentiate between lymphocytic hypophysitis (LYH) and IgG4-RD, the serum IgG4 level should be checked. Values >140 mg/dl indicate IgG4-RD. Moreover, LYH occurs more frequently in young females particularly during pregnancy or post-partum with a peak incidence between 30-40 years of age. The presence of an autoimmune disorder as well as anti-pituitary antibodies also suggests LYH [22-24].

There are no specific diagnostic criteria for IgG4-related hypophysitis, however Leporati et al. [25] suggested five criteria to diagnose IgG4-related hypophysitis. The first is mononuclear infiltration of the pituitary gland, which is rich in lymphocytes and plasma cells with more than 10 IgG4-positive cells per HPF. The second is a sellar mass and/or thickened pituitary stalk on pituitary MRI when pituitary histopathology is unavailable. The third is biopsy-proven IgG4-positive lesions in other organs. The fourth is increased serum IgG4 levels (>140 mg/dL), and the fifth is shrinkage of the pituitary mass and symptom improvement with steroids. Moreover, the authors suggested that the diagnosis is established when any of the following are fulfilled: criterion 1 alone or criterion 2 and 3 or criterion 2, 4, and 5. These criteria were proposed before the most recent guidelines and stricter criteria are applied to the diagnosis of IgG4-RD.

When serum IgG4 is high, systemic surveys to detect other organs should be considered using the gallium scintigraphy and/or FDG/PET [18]. Care should be taken when measuring serum IgG4 because there are many conditions that are associated with high IgG4 including

Wegener's granulomatosis, multicentric Castleman's disease, and idiopathic plasmacytic lymphadenopathy [26].

Treatment with prednisolone 30-50 mg per day resulted in significant improvement in all reported cases of hypophysitis except for one case that responded to an alternative treatment with azathioprine [7].

IgG4-RD and diabetes

To date, no data has linked diabetes with IgG4-RD; however we know that the immune system plays a role in the development of diabetes, and diabetes does affect the immune system to activate oxidative stress pathways. Moreover, some medications used for treatment of diabetes result in immune modulation

Auto-immune pancreatitis: Auto-immune pancreatitis (AIP) could be the link between diabetes and IgG4-RD. AIP is a chronic form of pancreatitis that results in painless jaundice, dark urine, and pale stool. It may also present with unexplained weight loss and extreme weakness. Systemic symptoms such as weight loss and fever are rare. Newly diagnosed type 2 diabetes malabsorption and pancreatic calcification and stones may be seen in some cases [18,28].

The first suggestion that pancreatitis could be related to an auto-immune process came from Sarles et al. [29] in 1961. However, the concept of auto-immune pancreatitis was introduced by Yoshida et al. [30] in 1995. The autoimmune association of AIP is based on association with other autoimmune disorders like sclerosing cholangitis, primary biliary cirrhosis, Sjogren's syndrome, and inflammatory bowel disease [31]. Autoantibodies commonly associated with AIP include antinuclear antibodies, rheumatoid factor, anticarbonic anhydrase II, and antilactoferrin [28].

There are two types of AIP—type 1 is IgG4-related and often affects males over 60 years of age; the male-to-female ratio is 4-7.5 :1 [32]. Patients might have associated sclerosing cholangitis, salivary gland involvement (sialadenitis), retroperitoneal fibrosis, or lung involvement. Type 2 AIP usually affects men or women over 40; 30% of them might have an associated inflammatory bowel disease [33].

Imaging studies show an enlarged pancreas—mostly the pancreatic head. The ERCP (endoscopic retrograde cholangiopancreatography) shows irregular narrowing of the pancreatic duct with or without stenosis of the common bile duct [34].

Many criteria have been developed to diagnose AIP and avoid surgery in cases that are steroid responsive [35]. These criteria include the Asian diagnostic criteria for auto-immune pancreatitis as well as the Mayo clinic diagnostic criteria (the HISORt criteria). There are four Asian criteria. Criterion I is a diffuse pancreatic parenchyma and segmental/focal enlargement of the gland occasionally with a mass or hypoattenuated rim. There may also be pancreato-biliary ducts with diffuse/segmental/focal duct narrowing often with stenosis of the bile duct. Criterion II is high levels of serum IgG or IgG4 or detection of antibodies. Criterion III is lymphocytic infiltration with fibrosis and abundant IgG4+ cells on pancreatic biopsy. Criterion IV is the presence of lymphocytic sclerosing pancreatitis in histopathology of resected pancreas including storiform fibrosis, lymphocytic infiltration, periductal inflammation, obliterative phlebitis, and numerous IgG4+ cells. One optional criterion is response to steroids. This suggests that these should be tried in patients to fulfill criterion I. The diagnosis of auto-immune pancreatitis is fulfilled if we have criterion I+II or criterion I + III or criterion I + II + III, or criterion IV alone [36].

The Mayo clinic's criteria are similar to the Asian criteria. Criterion H (histology) is periductal lymphocytic infiltrates, obliterative phlebitis, storiform fibrosis, lymphocytic infiltrates, storiform fibrosis, and abundant IgG4+ cells (> 10 HPF). Criterion I (imaging) is a diffusely enlarged gland with delayed rim enhancement and diffusely irregular attenuated pancreatic ducts. Criterion I also includes focal pancreatic mass enlargement, focal pancreatic duct stricture, pancreatic atrophy, pancreatic calcification, and pancreatitis. Criterion S (serology) includes elevated serum IgG4 (normal 8-140 mg/dl). Criterion O (other organ involvement) includes hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid lacrimal gland involvement, mediastinal lymphadenopathy, or retroperitoneal fibrosis. Criterion R (response to steroid therapy) includes resolution or marked improvement of pancreatic/extrapancreatic manifestations with steroid therapy. It is suggested that the diagnosis of AIP is fulfilled if we had criterion H or criteria I + S, or a strong clinical suspicion of AIP + criterion S and/or O + criterion R [36,37].

Anti-diabetes agents and IgG4-RD: As diabetes progresses, eventually one or perhaps more than one injectable drugs are added including insulin or glucagon like peptide-1 agonist (GLP-1). A recent concern in clinical practice is how to reduce the frequency of the injections to improve patient adherence and convenience.

The endogenously produced GLP-1 hormone is rapidly degraded by the dipeptidyl peptidase IV enzyme (DPP IV) or filtered through the kidneys. This usually only takes three minutes [38]. The current challenge is to protect synthetic GLP-1 from the DPP IV proteolytic effects to prolong the half-life of the drug. Increasing the molecular size of those agents protects them from being filtered via the kidney. Current examples of high molecular weight GLP-1 agonists include once daily liraglutide or albiglutide or dulaglutide or exenatide LAR once weekly. The extension of the GLP-1 activity was attained by adding albumin in case of albiglutide and immunoglobulin for dulaglutide. This provided a half-life of 90 hours with a steady-state trough of up to two weeks; dulaglutide is approved for once weekly injection [39-42].

Dulaglutide is GLP-1 composed of two identical disulfide-linked chemical chains. Each chain is formed with a human peptide analogue (GLP-1) covalently attached to an Fc fragment of a modified human immunoglobulin (IgG4). The attachment is via a linker peptide in each chain. The aim of this special biochemical engineering is to protect GLP-1 from deactivation by the DPP IV enzyme. This increases solubility, reduces renal clearance, and increases the pharmacodynamics duration [43-45].

Immunogenicity

Altered immune response is a major concern especially when new recombinant hormones are tested in clinical trials. One very effective weekly GLP-1 agonist is taspoglutide, which has been pulled from the market after reports of severe hypersensitivity reactions [46]; 35% of patients receiving exenatide had a low titer of anti-drug antibodies [47]. In liraglutide, 8.6% of LEAD trial patients had anti-drug antibodies [37]. The highest incidences of anti-drug antibodies were encountered in the duration trials of the exenatide once weekly (Bydureon) where it reached 43-54% in different trials [48-50].

In the albiglutide studies, only 2.5% developed antibodies, but these antibodies remained intact for only a short period [51]. This is not the case in dulaglutide. The peptide portion of dulaglutide was designed to be as high as 90% homologous to endogenous human GLP-1. Nonetheless, immunoadhesion of the Fc protein to an end organ molecule (receptors, an enzyme, or ligand) helps inhibit autoimmune

and inflammatory processes against it [43,52,53]. In the AWARD 1 trial—a multicenter trial comparing dulaglutide to exenatide—added pioglitazone and metformin (n=987); dulaglutide led to antibodies in 1.8% while the exenatide-treated group developed antibodies in 48% of the patients [53]. Another trial from Japan compared dulaglutide to placebo (dulaglutide group n= 108 showed zero incidences of antibodies over 12 weeks. This is, by far, considered a revolutionary addition to the GLP-1 agonist agents.

Conclusion

IgG4-RD are newly discovered disorders associated with storiform fibrosis, high serum levels of IgG4, and high IgG4/IgG ratios. Many endocrine disorders are related to IgG4 including Riedel's thyroiditis as well as some cases of Hashimoto's thyroiditis and hypophysitis with diabetes insipidus or panhypopituitarism. IgG4-RD should be suspected in patients with progressive thyroiditis with a mass effect and very high antibody titers.

Competing Interests

Authors declare that they have no competing interests.

Authors' Contributions

A B: came with the idea of the paper, shared in writing the IgG4-RD and endocrine disorders as well as the immune system and diabetes, edited and revised the manuscript.

G H: shared in writing the introduction edited and revised the manuscript.

E A: shared in writing Anti-diabetes agents and IgG4-RD, edited and revised the manuscript.

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