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Review Article

Immunoglobulin G4-Related Lesions in Autoimmune Diseases: Unusual Presentations at Atypical Sites—A Tale of 2 Cases with Literature Review

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) coexisting with clinically apparent autoimmune diseases, such as rheumatoid arthritis (RA) or antiphospholipid syndrome (APS), is a rarely documented combination in the scientific literature. In this case-based review, we present 2 intriguing cases with preexisting autoimmune diseases, namely, RA and primary APS, who exhibited coexistent IgG4-related lesions at unusual sites. The first case pertains to a patient with known RA who presented with an encasing mass in the esophagus leading to stricture, with histopathological diagnosis of IgG4-RD.The second patient, diagnosed with primary APS, experienced breathlessness, and imaging revealed a right atrial mass. Histopathological examination of the mass confirmed IgG4-RD. Notably, both patients demonstrated significant clinical improvement upon initiation of steroid therapy. Rheumatoid arthritis patients commonly exhibit elevated levels of IgG4 in their sera; however, RA with coexisting IgG4-RD is rarely reported in the literature. Similarly, APS with IgG4-related lesions is exceedingly rare. Although there are few case reports and series on esophageal and cardiac IgG4-RD, the occurrence of such unusual location of IgG4-related lesions in the context of known autoimmunity is presented here for the first time.

Keywords: IgG4-RD, cardiac IgG4-RD, esophageal IgG4-RD, RA, primary APS

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Introduction

Immunoglobulin G4-related disease (IgG4-RD), an evolving nomenclature, refers to a multisystem fibroinflammatory disease. It is characterized by significant infiltration of IgG4-positive plasma cells and lymphocytes. While the typical sites affected are the pancreas, salivary gland, and lacrimal gland, there have been reported cases of involvement in uncommon locations such as the heart and gastrointestinal system. The precise role of IgG4 in the disease's pathogenesis remains unclear, as many autoimmune diseases may exhibit predominantly elevated levels of the IgG4 subclass of IgGs, leading to the term IgG4-autoimmune disease overlap (IgG4-AID).[1]

In rheumatoid arthritis (RA), a prototypical autoimmune disease, elevated levels of IgG4 have been observed, suggesting its involvement in the disease's pathogenesis. However, the overlap between IgG4RD and clinically evident RA or antiphospholipid syndrome (APS) is rarely documented in the literature. In this report, we present 2 cases of known autoimmune diseases where patients presented with IgG4-related lesions affecting unusual sites. This article aims to discuss the clinical significance of extensive involvement of uncommon locations in IgG4RD and its potential overlap with other autoimmune diseases.

Case Presentation

Case 1: A 38-year-old female with a 10-year history of deforming inflammatory polyarthritis and a strongly positive rheumatoid factor presented to the Rheumatology Outpatient Department with painless progressive dysphagia. She had been diagnosed with RA and had intermittently used methotrexate and low-dose steroids. The dysphagia was insidious in onset and gradually progressive, more pronounced with solid food and did not present with any reflux symptoms. Upon examination, she exhibited bilateral supraclavicular fullness without superficial erythema or warmth. On palpation, there was no obvious lymphadenopathy in the neck, with tenderness in the right elbow, wrist, and metacarpophalangeal (MCP) joints with swelling. Upper gastrointestinal endoscopy revealed a stricture at 28 cm of the esophagus, impeding the passage

of the scope. Positron emission tomography (PET-CT) scan showed tumor-like infiltrating lesions in the posterior mediastinum, extending from the thoracic inlet, encasing the esophagus and azygos vein, and reaching the lung (Figure 1). A posterolateral thoracotomy was performed to excise the mass, and histopathological examination showed dense fibroinflammatory infiltrates with plasma cells and a few eosinophils, without any granuloma formation. Immunohistochemical staining revealed elevated IgG4:IgG ratio (25%) with an elevated serum IgG4 level (2.09 g/L, cut off 0.03-2.01 g/L). A diagnosis of possible IgG4-related disease (IgG4RD) was made. The patient experienced significant improvement of symptoms after initiating high-dose corticosteroid, and a follow-up PET-CT imaging after 2 years showed complete resolution of the mass with non-FDG avid fibrosis at the mid-esophagus.

Case 2: A 52-year-old female with a history of 5 consecutive first-trimester abortions, recurrent leg ulcers (biopsy showing evidence of thrombotic microangiopathy), left anterior tibial artery thrombosis with lupus anticoagulant and anticardiolipin antibody positivity, previously diagnosed with antiphospholipid syndrome (APS), had been under our care since 2003. In 2020, she was admitted with acute breathlessness, orthopnea, and bilateral lower limb edema. Transthoracic echocardiography revealed a mass-like lesion (1.5 × 2.3 cm) in the right atrium, prompting consideration of thrombus. Computer tomography (CT) of the chest showed an ill-defined lobulated enhancing lesion (Figure 2) involving the wall of the right atrium. Intraoperative findings via sternotomy approach showed a large circumferential polypoid mass originating from the right atrial wall, extending from the superior to inferior vena cava (SVC to IVC), occupying 90% of the right atrial cavity (Figure 3). Although complete excision of the mass was not possible, the biopsy revealed a fibroinflammatory reaction with lymphoplasmacytic infiltrates and dense fibrosis. Plasma cells stained positive for IgG4, with an IgG4:IgG ratio of 0.4 (40%) (Figure 4). Serum IgG4 levels were 145 mg/dL (<135 mg/dL). A diagnosis of IgG4RD was made, and the patient was initiated on corticosteroid treatment. Transthoracic echocardiography after 6 months showed resolution of the mass, and the patient remains asymptomatic till date.

Informed consent was taken from both the patients for publication purposes.

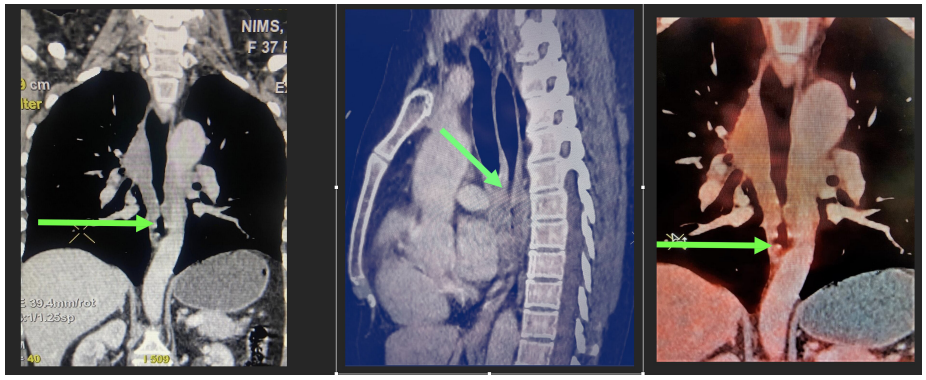

Figure 1. (A-C) Infiltrating tumor-like lesions in posterior mediastinum encasing esophagus and azygos vein causing esophageal stricture as shown in PET-CT (green arrows). PET-CT, positron emission tomography–computed tomography.

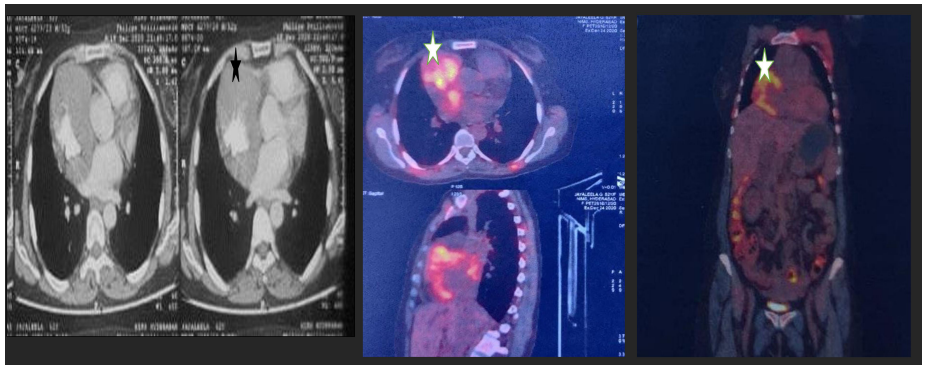

Figure 2. (A) CT pulmonary angiogram showed contrast-enhancing mass in right atrial wall with near circumferential wall thickening extending to supracardiac and supraortic recess (black asterisk). (B, C) 18 F-fluorodeoxyglucose (FDG)-PET image showed isolated metabolically active mass lesion in right atrium (white asterisk). PET, positron emission tomography.

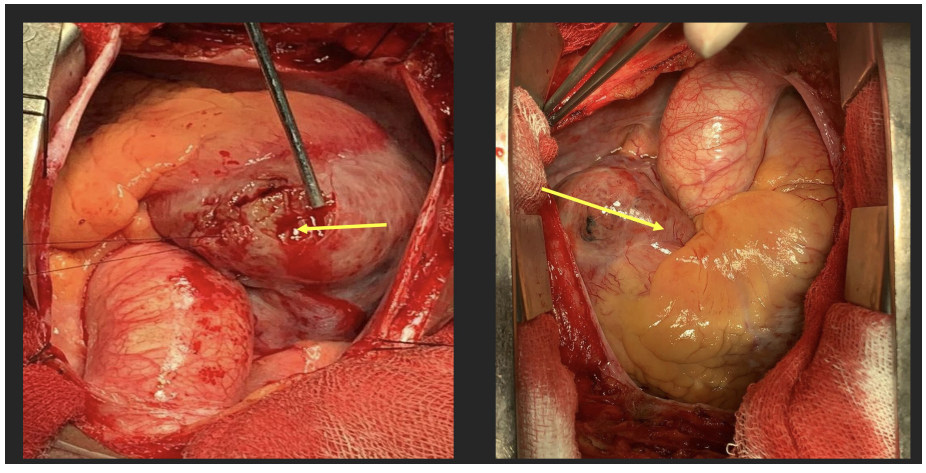

Figure 3. Intraoperative findings showed a large circumferential polypoid mass in right atrium extending from SVC to IVC occupying 90% of right atrial cavity (yellow arrow). IVC, inferior vena cava; SVC, superior vena cava.

Main Points

- Immunoglobulin G4-related disease (IgG4RD) coexists with autoimmune diseases, including rheumatoid arthritis and primary antiphospholipid syndrome.
- The occurrence of IgG4RD presenting as cardiac or esophageal masses has been rarely reported in the literature.
- Immunoglobulin G4, being a fascinating antibody, might play a role in the pathogenesis of autoimmune diseases or paradoxically, its overproduction as a protective mechanism against inflammation could lead to fibrosis or stricture in atypical locations.

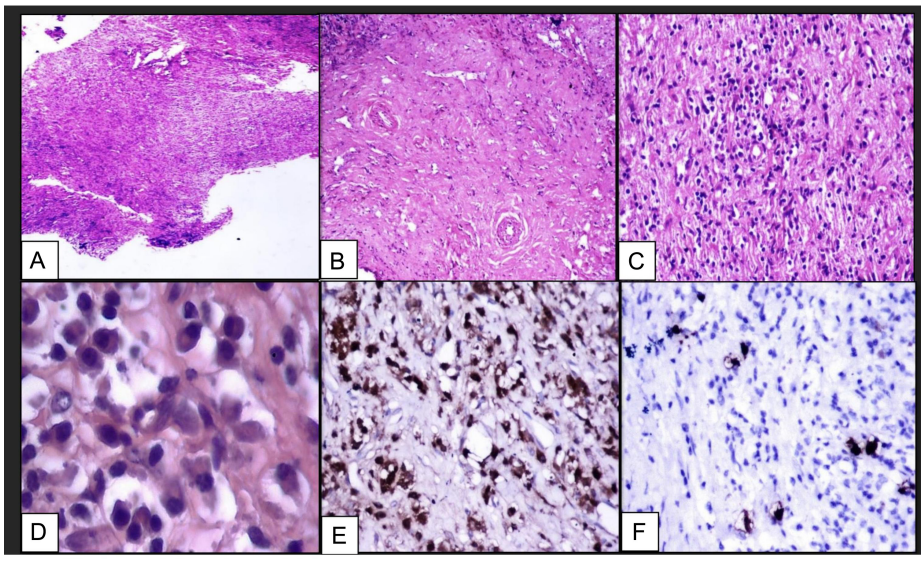

Figure 4. (A-F) Characteristic histopathological features of IgG4-related disease. (A) and (B) Dense collagenous fibrosis extending to myocardium (40×, 100×, black asterisk). (C) Extensive inflammatory infiltrates comprise of lymphocytes and plasma cells (200×, black asterisk). (D) Plasma cells with eccentrically placed nucleus and abundant cytoplasm (400×, black arrows). (E) Immunostaining with IgG (400×). (F) Immunostaining with IgG4 (400×) with ratio of IgG4 : IgG 0.4. IgG4, immunoglobulin G4.

Discussion

Immunoglobulin G4-related disease, a complex systemic fibroinflammatory disease, can manifest in various ways, primarily affecting salivary glands, pancreas, biliary tract, retroperitoneum, and orbit. As this syndrome is still evolving, its clinical presentations, underlying mechanisms, and treatment strategies pose intriguing questions and serve as potential areas of interest for researchers. Numerous autoimmune conditions such as myasthenia gravis, pemphigus, and thrombotic thrombocytopenic purpura exhibit autoantibodies predominantly belonging to the IgG4 subclass, referred to as IgG4-AID.[1] Furthermore, patients with IgG4RD often demonstrate elevated levels of rheumatoid factor in their serum. However, reports of IgG4 lesions in longstanding autoimmune diseases like RA or primary APS are rare in the literature. Only a limited number of case reports or series have described atypical locations of IgG4-RD, such as cardiac masses or esophageal strictures. In this context, both of our patients, who have chronic autoimmune conditions, presented with lesions consistent with IgG4RD in unusual locations. It is plausible to propose that systemic autoimmunity may have triggered the development of IgG4RD lesions at these atypical sites.

Search strategy (Figure 5): We conducted an extensive literature review from "PubMed" platform, "Scopus," "Google Scholar," "Web of Science," and "ScienceDirect" databases using the MeSH (Medical Subject Headings) terms like "IgG4RD with atypical site involvement," "IgG4-with autoimmune disease overlap," "Cardiac IgG4RD," "Oesophageal IgG4RD," "IgG4RD-RA overlap," and "IgG4RD-primary APS overlap." Relevant literature published in the English language up to 2022 were considered for review. In the available literature, there was only 1 reported case of primary APS and a limited number of cases related to secondary APS that exhibited IgG4-like lesions. However, no cases were reported of primary APS with a right atrial IgG4-related mass. Cases of chronic RA with IgG lesions were limited to a few case reports. There was no reported case of RA presenting as an esophageal IgG4-related lesion. We also tried to hypothesize the pathogenesis of such an association based on available literature.

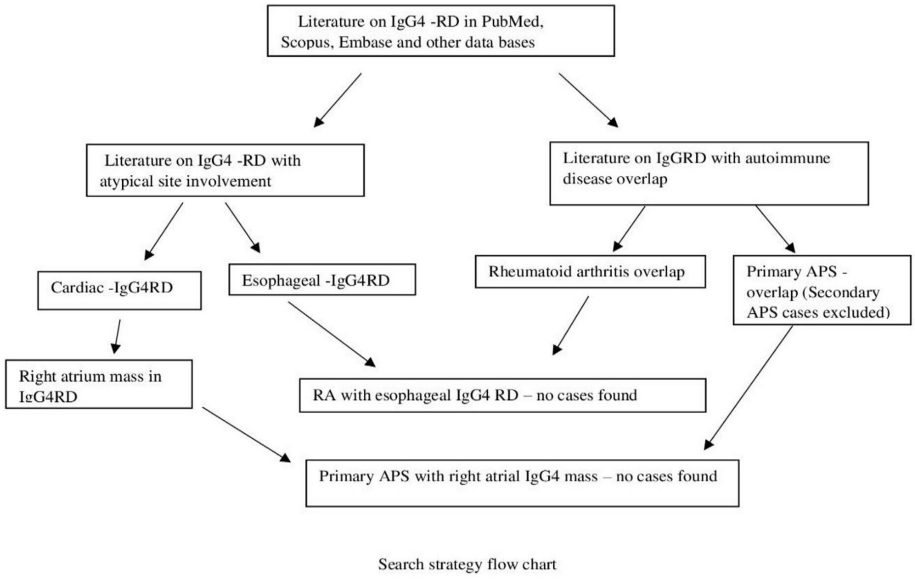

Figure 5. Search strategy.

Immunoglobulin G4-Related Disease with Autoimmune Overlap

Immunoglobulin G4 is a unique antibody that possesses both protective and pathogenic properties, setting it apart from other subclasses of immunoglobulin G. Its precise role in the development of IgG4-related disease (IgG4RD) remains unclear. Recently, autoantibodies of the IgG4 subclass have been identified, targeting carbonic anhydrase, plasminogen binding protein, and annexin A11 antigens in autoimmune pancreatitis, which serves as the prototype for IgG4RD.[2] Various autoimmune diseases, such as pemphigus and thrombotic thrombocytopenic purpura, exhibit a predominant presence of IgG4 subclass autoantibodies in the blood. There is now growing concern regarding the elevated levels of IgG4 autoantibodies in patients with RA.

One unique characteristic of IgG4 is its ability to mimic the activity of rheumatoid factor (RF) by interacting with other IgGs. While classical RFs act via the variable domain, IgG4 binds to the constant domain, but the implications of this variation in effect remain unclear.[3] Zack et al[4] demonstrated that in RA, RF IgGs are predominantly of the IgG4 class.

In a study by Lin et al,[5] it was discovered that RA patients had higher concentrations of IgG compared to healthy controls. Moreover, clinically active RA patients exhibited similar

concentrations of all IgG subclasses, leading to the hypothesis that persistent autoimmune stimulation during active RA contributes to IgG4 production.[1] Yu et al[6] reported elevated serum levels of IgG4 in 30.3% of 433 RA patients. Engelman et al[7] demonstrated a significant decrease in IgG4 anticyclic citrullinated peptide (CCP) antibody levels among treatment responders, irrespective of the type of treatment. Chen et al[8] reported a positive and significant correlation between elevated serum IgG4 levels and synovial IgG4-positive plasma cells. In their study of 136 RA patients, 46% exhibited elevated serum IgG4 levels, with higher IgG4 levels associated with increased erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), RF, and ACPA levels. Patients with high serum IgG4 levels displayed poor response to methotrexate and leflunomide treatments. Consequently, it was concluded that RA patients with elevated IgG4 levels may represent a distinct phenotype characterized by a more severe clinical course and poorer response to standard treatment. Blocking IL-6 with tocilizumab has been shown to reduce IgG4 ACPA antibodies, but not IgG1 ACPA antibodies, suggesting the potential influence of IL-6 on IgG4 anti-CCP antibody production in RA.[9]

Sakthiswary et al[10] recently conducted a systematic review comprising 19 studies that assessed serum IgG4 levels in RA. They demonstrated a positive correlation between elevated IgG4 levels and increased disease activity, as measured by the Disease Activity Score 28 based on erythrocyte sedimentation rate (DAS28-ESR), as well as inflammatory markers. Although the exact role of IgG4 in RA remains elusive, they hypothesized that interleukin 6 (IL-6), a cytokine with a potential role in RA pathogenesis, induces IgG4 production during active RA. They concluded that serum IgG4 exhibits diverse mechanisms of action in RA pathogenesis and its presence indicates a distinct subgroup of treatment-refractory RA patients. Despite these hypotheses, the topic continues to be a subject of debate.

Umekita et al[11] described a case of arthropathy characterized by the infiltration of IgG4-positive plasma cells in the synovium, without typical features of RA on imaging. Zatreh et al[12] reported a case of a 64-year-old man diagnosed with RA-associated interstitial lung disease, who presented with a lung nodule. Histopathological examination revealed a dense lymphoplasmacytic infiltrate and the presence of IgG4-positive plasma cells. Soliotis et al[13] reported 2 cases in their series, consisting of elderly males with seropositive RA, who presented with autoimmune pancreatitis and elevated serum IgG4 levels. Both patients showed an excellent response to steroid treatment. Martin Nares et al[14] described the case of a 36-year-old female with RA and chronic cough. Further investigation revealed bronchial stenosis, and histopathology from a tracheal biopsy specimen indicated a lymphoplasmacytic infiltrate and storiform fibrosis, suggesting IgG4RD.

The occurrence of IgG4RD in conjunction with primary APS is relatively rare. Fernandez et al[15] reported the case of a 58-year-old male with a diagnosis of APS based on thrombosis of the superior mesenteric vein, splenic vein, and strongly positive anticardiolipin, antibeta-2 glycoprotein antibodies, and lupus anticoagulant. Subsequently, the patient developed a pancreatic mass, which was excised, and its histology exhibited features of IgG4 disease with storiform fibrosis. His serum IgG4 level was 194 mg/dL (normal range: 1-135). Kawakami N et al[16] reported a case of IgG4-positive multiorgan lymphoproliferative syndrome (IgG4(+)-MOLPS) accompanied by antiphospholipid antibody syndrome (APS) in a 56-year-old Japanese man presenting with purpuric patches on his legs. Soliotos et al[13] included 2 cases in their series involving secondary APS with overlap of RA and lupus, where patients presented with autoimmune pancreatitis and interstitial nephritis, respectively. However, no other cases of APS overlapping with IgG4RD have been reported to date. Immunoglobulin G4 may induce tissue injury through complement-independent mechanisms in APS, possibly involving binding to platelets or endothelial cells, subsequent mediator release, and clotting.

Unusual Locations of Immunoglobulin G4-Related Disease

Immunoglobulin G4-related disease presenting as a cardiac mass is a rare occurrence. After conducting a thorough literature review, it was found that most cases of IgG4RD manifest as a tumor-like lesion surrounding the coronary arteries, within the right atrium, or around the valves, particularly the aortic or pulmonary valves. Nomura et al[17] reported a case of a 58-year-old male with cerebral infarction and atrial fibrillation. Computed tomography images of his heart revealed a mass in the right atrium and right atrioventricular groove, and histopathological analysis showed plasma cells and fibrosis with an IgG4:IgG ratio of 72.3%. Elevated serum IgG4 levels confirmed the diagnosis of IgG4RD.

Hajsadeghi M.D. et al[18] described a 45-year-old male with an infiltrating mass in the right atrioventricular groove, which was also biopsy-proven IgG4RD. This patient additionally had involvement of the retroperitoneum and pituitary gland. Maeda et al[19] presented the case of a 61-year-old Japanese man with IgG4-related autoimmune pancreatitis who developed a mass in the right atrium and another surrounding the left anterior descending coronary artery. Ikuko Matsumura et al[20] reported a 69-year-old male with a mass in the right atrium and septum, which was diagnosed as IgG4RD. Yano et al[21] described a patient with an intracavitary right atrial mass extending into the superior vena cava. Singh et al[22] and Ishida et al[23] presented cases of IgG4RD in the right ventricular outflow tract. In all these cases, the cardiac mass either presented as the sole manifestation of IgG4RD or was associated with other commonly involved organs such as the retroperitoneum, salivary gland, and eye.

Our case represents the first reported instance of an isolated cardiac IgG4 lesion in a known primary APS patient. Table 1[17-24] provides a detailed review of right atrial mass in IgG4RD. Macrophages in the valves or heart myocardium can be stimulated by pathogen-associated molecular patterns or damage-associated molecular patterns in the blood, leading to an abnormal immune response in IgG4-RD.

In IgG4RD, esophageal involvement can manifest as isolated or solitary lesions, either independently or in association with other autoimmune diseases such as Henoch–Schönlein purpura, idiopathic thrombocytopenic purpura, or primary Sjogren's syndrome. However, to date, no cases of esophageal IgG4 involvement have been reported in RA. Khan et al[25] reported in a review that dysphagia and weight loss were the most common symptoms in patients with esophageal IgG4-RD. Most patients presented with ulceration and stricture (66.66%) or mass-like lesions (22.22%), primarily affecting the distal and mid-esophagus.

Although an elevated level of serum IgG4 is less commonly reported in such conditions, all lesions were positive for IgG4 plasma cells. Yang et al[26] described a case with mass-like lesions in the cervical and lower esophagus, characterized by numerous lymphoplasmacytic infiltrates and IgG4+ plasma cells, which responded well to steroid therapy. It is important to consider IgG4-related esophageal disease in the differential diagnosis of patients with dysphagia presenting with esophageal stricture, ulcer, tumor, or unexplained

Table 1. A Detailed Review of Right Atrial Mass in IgG4RD

Case	Symptom	Location	Biopsy Finding	Other Organs
Song et al[24]	Syncope, sinus pause at exercise	RA superior vena cava to the right atrial septum	Proliferating IgG4-positive plasma cells and lymphocytes with surrounding sclerosis.	No
Yano et al[21]	Chest discomfort, proptosis	Intracavitary right atrial mass, extending into the superior vena cava.	Cardiomyocytes together with an area of massive replacement fibrosis, IgG4 : IgG ratio of more than 0.5	Eye, mediastinal lymph nodes
Maeda R[19]	Jaundice, fatigue	RA and a mass lesion surrounding the left anterior descending coronary artery.	Chronic inflammatory infiltration of IgG/IgG4-positive lymphocytes and plasma cells. The ratio of IgG4-positive cells to IgG-positive cells exceeded 40%, and IgG4-positive cells numbered >10/HPF	Pancreas
Matsumura I[20]	Palpitation, vertigo, low blood pressure	Right atrial tumor that infiltrated into the cardiac septum	Mature plasma cells, plasmacytoid cells, and small-to-medium-sized lymphocytes were found to have infiltrated diffusely, IgG4-positive plasma cells	Maxilla, lacrimal and salivary glands
Shokoufeh Hajsadeghi et al[18]	Fever of unknown origin	Right and left atria, right AV groove, tricuspid valve annulus	Edematous fibrosis, and infiltration of lymphocytes and plasma cells, IgG4 : total IgG ratio 43%	Retroperitoneum, aorta, pituitary
Shun Nomura[17]	Dysarthria, dysesthesia	Superior vena cava to the right atrial free wall, interatrial septum	Infiltration of lymphocytes and fibrotic tissues, IgG4-/IgG-positive cells 72.3%	None

IgG, immunoglobulin G; RA, right atrium; HPF, High power field.

esophagitis with strictures. Table 2[27-34] provides a detailed description of esophageal IgG4 involvement.

Pathogenesis of Immunoglobulin G4-Related Disease Autoimmunity

Immunoglobulin G4 is a fascinating subtype of immunoglobulin G that possesses unique characteristics. Recent advancements in molecular research and adoptive transfer models have shed light on both its role in disease pathology and immune protection. Unlike other subclasses of IgG, IgG4 contains serine at position 228 in the hinge region instead of proline, which allows for easy dissociation into 2 identical halves and facilitates the sharing of these halves with other antibodies. This phenomenon, known as Fab arm exchange (FAE), has raised the hypothesis that bispecific monovalent anti-inflammatory IgG4 plays a role in preventing immune complex deposition and subsequent autoimmunity.[1] However, the precise role of FAE in disease development or protection remains a topic of debate.

Table 2. A Detailed Description of Esophagal IgG4 in Different Case Reports or Series

Case	Symptom	Location	Biopsy Finding	Other Organs
Mori S et al[27]	Dysphagia, heartburn, vomiting, weight loss	Thoracic esophagus, esophageal stricture	Lymphoplasmacytic infiltration Scattered lymphoid follicles and eosinophils, IgG4 : IgG > 40%	No associated involvement, isolated IgG4
Lee H et al[28]	Dysphagia, weight loss	Mid-esophagus, ulceration, stricture	Dense lymphoplasmacytic infiltration Lymphoid follicles Stromal sclerosis	Isolated IgG4 lesion
Dumas-Campagna M et al[29]	Odynophagia, dysphagia	Distal esophagus, ulcer, stricture	Dense lymphoplasmacytic infiltration inflammatory fibrinous exudate with granulation tissue Few IgG4+ plasmacytic	PBC, PSS, Raynaud, asthma
Lopes et al[30]	Dysphagia, weight loss	Distal esophagus, tumor	Lymphoplasmacytic infiltration Venulitis	Isolated
Oh JH et al[31]	Progressive dysphagia	Cervical esophagus, massive stricture	Numerous plasma cells and eosinophils	-
Obiorah I—8 patients[32]	Dysphagia, GERD, epigastric pain	3—esophageal stricture, 1—erosion, 1—nodule, 1—unremarkable	All patients had higher lymphoplasmacytic infiltrate 3P—obliterative phlebitis	None = isolated IgG4+ lesion
Podboy J et al—29 patients[33]	Dysphagia	Fibrostenotic—mild or severe	10/29 patients had IgG4 staining positive, and 3 of them had dense IgG4 deposits	Esophageal lichen planus (nontypical IgG4+ lesion)
Zukerberg L et al—21 patients[34]	Food impaction, vomiting, asthma, eczema, allergic rhinitis, furrows, white patch	Eosinophilic esophagitis	16/21 patients showed intra-squamous extracellular IgG4 deposits	Eosinophilic esophagitis (nontypical IgG4+ lesion)

IgG4, immunoglobulin G4; PBC, Primary biliary cirrhosis; PSS, Primary sclerosing cholangitis; 3P, three patients.

In myasthenia gravis positive for muscle-specific tyrosine kinase (MuSK),[35] FAE actually enhances pathogenicity as monovalent IgG4 antibodies inhibit the binding of low-density lipoprotein receptor-related protein 4 (LRP4) to MuSK, directly disrupting synaptic transmission. On the other hand, in autoimmune nodopathy,[36] a variant of chronic inflammatory demyelinating polyneuropathy (CIDP), FAE occurs only in a small percentage of IgG4 molecules, while a significant number of monospecific bivalent pathogenic IgG4 antibodies in the serum lead to nodal destruction. Furthermore, recent studies propose that the Fc portion of IgG4 can bind to the Fc portion of other IgGs, primarily on solid support, forming a hexameric structure with high affinity for complement, thereby exacerbating the immune response.[37]

Although IgG4 does not interact with Fcγ receptor IIIb (FcGR3b) and lacks C1q-mediated action, it does exhibit affinity for FcGR1 and FcGR2, suggesting a potential role in immune pathogenesis.[1] Interestingly, in chronic inflammatory conditions such as RA, there is an overproduction of IgG4 as a protective mechanism against inflammation. Paradoxically, this excessive IgG4 production can contribute to abnormal fibrotic responses or strictures in atypical locations.[38] The association between IgG4-related lesions and autoimmune diseases, whether through a pathogenic or protective effect, remains an area of exploration with significant research potential.

Clinical heterogeneity is a fundamental characteristic of IgG4-related disease, akin to systemic lupus erythematosus (SLE) or antiphospholipid antibody syndromes. In SLE, the breakdown of B cell tolerance results in diverse clinical manifestations and the development of various autoantibodies.[2] Similarly, in IgG4-related disease, the self-antigens targeted by B cells are diverse, leading to a wide range of clinical phenotypes and autoantibody repertoires. While still in its early stages, efforts in autoantigen discovery and the identification of organ-specific antigen responses, along with the exploration of whether B and T cells are responding to the same self-antigen within individual patients, can provide valuable insights into the multifaceted aspects of autoimmune pathogenesis.

Our study presents 2 cases of known autoimmune diseases manifesting with IgG4-RD at atypical sites. While such coexistence is documented in the literature, a significant association between these 2 conditions has not been definitively established. Existing literature, combined with this case report, suggests that these clinically diverse entities might overlap. We emphasize that any direct relationship between IgG4-RD described in this context and the preexisting conditions cannot be conclusively asserted. However, further research is needed to clarify the role of autoimmune associations in IgG4-RD and to determine the specific contribution of IgG4 to the pathogenesis of autoimmunity.

Informed Consent: Informed consent was taken from both the patients for publication purposes.

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