

Pulmonary vascular involvement of IgG4-related disease

Case series with a PRISMA-compliant systemic review

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Abstract

Background: Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized, immune-mediated chronic fibrotic inflammation that can involve almost all organs, causing tumefaction and dysfunction. Its presence in pulmonary circulation is underestimated and has not yet been investigated.

Objectives: We describe a representative IgG4-RD patient with pulmonary artery stenosis and pulmonary embolism, leading to reversible pulmonary hypertension. Literature review of IgG4-RD with pulmonary circulation involvement was conducted.

Data sources: References for this review were identified through searches via PubMed, EBSCO, and Web of Science for published articles before November 2016.

Results: There were 15 published cases of IgG4-RD with pulmonary vascular involvement, 3 with pulmonary arteritis, 2 with pulmonary artery aneurysm, 3 with pulmonary artery stenosis, 1 with obliterative phlebitis, and 1 with pulmonary embolism. Possible immunity and inflammation mechanisms were summarized.

Conclusions: IgG4-RD with pulmonary vascular involvement is rare. Echocardiogram and contrast-enhanced chest CT are helpful to screen the disease. Clinical manifestations were found from asymptomatic to dyspnea or even syncope. And nearly all cases had more than 1 organ affected, with significantly increased serum IgG4 levels. PET/CT aided in identifying affected organs and determining candidate biopsy sites. More awareness is urged to evaluate the pulmonary vascular manifestations of this disease.

Abbreviations: HPF = high power field, CTPA = computed tomographic pulmonary angiography, G/GM = 1,3-β-D-glucan/galactomannan tests, IFN = interferon, IgG4-RD = Immunoglobulin G4-related disease, IL = interleukin, MRI = magnetic resonance imaging, RVSP = right ventricular systolic pressure, TGF = transforming growth factor.

Keywords: IgG4-related disease, pulmonary arteritis, pulmonary circulation, pulmonary embolism, pulmonary hypertension

1. Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated chronic fibrotic inflammation first described in 2001.^[1] It can affect virtually any organ synchronously or metachronously, causing tumefaction and dysfunction, mimicking many malignant, infec-

tious, and inflammatory disorders.^[2] The pancreas, salivary gland, and lymph node are among the most involved organs. Its clinical presentations in lung have been reported and reviewed. Interstitial pneumonia accounts for about 4% of all reported articles with more than 10 cases.^[3] Characteristic histopathological changes include a lymphoplasmacytic infiltrate and “storiform” fibrosis, with a preponderance of IgG4-positive plasma cells.^[4] Obliterative phlebitis has been recognized as a microscopic vascular change of IgG4-RD since 2003.^[5] Subsequently, medium and large vessel involvements were reported in IgG4-RD, mostly in the form of coronary periarteritis, splenic aneurysm, inflammatory abdominal aortic aneurysm, and inflammatory thoracic aortic aneurysm. Such vascular lesions, complicated with sudden cardiac attack or aortic dissection, often resulted in high mortality and numerous morbidities.^[6–10] However, the involvement of pulmonary circulation is rare and has yet to be investigated. Here, with the patient’s informed consent and an ethic approve from Sir Run Run Shaw Hospital committee, we reported 1 case of IgG4-RD with uncommon pulmonary vascular manifestations and provided a comprehensive review of its clinical features. Furthermore, the literature pertaining to IgG4-RD with pulmonary vascular involvement was reviewed.

1.1. Representative patient with IgG4-RD pulmonary vascular manifestations

A 54-year-old bank employee presented with shortness of breath on exertion and fatigue for 2 months. He denied cough, chest pain, hemoptysis, and fever, with a chest CT scan suggesting

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bronchitis. However, he responded poorly to 10 days of antibiotics and mucolytics and was subsequently referred to our hospital. His temperature was 36.6°C, with a pulse at 98 beats per minute, respiratory rate at 20 times per minute, and blood pressure of 142/84mmHg. He was alert without cyanosis, and there was no sign of jugular venous distention. Superficial lymph nodes were not palpable, and clear sounds were heard in both lungs. His heart rate was regular with no murmur audible, and his abdomen was soft without tenderness. No palpable hepatosplenomegaly was found, and no edema or varicose veins were present on either leg. Complete blood count (CBC) and blood chemistry were within normal ranges except for high level of IgG (45.3g/L[†]), and CRP (43.2mg/L). Arterial blood gas analysis (ABG) showed FiO₂ of 33%, PO₂ of 127.8mmHg, PCO₂ of 39.2mmHg, and P/F of 387; antinuclear antibody (ANA) was 1:100 (nucleolus type). Anticentromere antibody showed weak positive, while anti-neutrophil cytoplasmic antibody (ANCA), anticardiolipin antibody, rheumatic factor (RF), angiotensin-converting enzyme (ACE), T-SPOT, and 1,3-β-D-glucan/galactomannan tests (G/GM) tests were negative. His pulmonary function test was normal, and an echocardiogram suggested an intraluminal mass in the pulmonary artery, with an EF of 72% and right ventricular systolic pressure (RVSP) of 35mmHg (Fig. 1). Emergent computed tomographic pulmonary angiography (CTPA) showed a periaortic mass with pulmonary artery

stenosis and left branch occlusion (Fig. 2A and C). A wedge-shaped lesion was present in the left lower lobe (Fig. 2E).

Anticoagulation with low-weight molecular heparin was administered; a second-day scintigraphy suggested pulmonary embolism in the left lung and right S5 segment (Fig. 3D). A chest magnetic resonance imaging (MRI) suspected malignancy (Fig. 3A and B), and a PET/CT was ordered to evaluate the extent of disease and guide further biopsy. FDG-avid lesions were found in the periaortic areas, extending to the intraluminal pulmonary artery (Fig. 4). CT-guided needle biopsy was carried out, while pathological results showed lymph node tissue, and was thus inconclusive. The second CT-guided needle biopsy came back with fibrosis and lipid tissues, with dominant lymphocyte infiltration; mediastinal fibrosis was suspected. Stainings for fungus and tuberculosis DNA test were negative, and the patient's serum IgG4 test presented as 6.44g/L. He underwent angiogram and following thoracoscopy (Fig. 3C). His mean pulmonary arterial pressure was 30mmHg. Surgical periaortic specimens confirmed periaortitis associated with IgG4-RD. The left lower lobe pathology showed infarction with necrosis (Fig. 5); systemic methylprednisolone was administered and tapered afterwards according to the international IgG4-RD expert consensus. The patient's symptoms then improved, with serum IgG4 level decreasing back to normal range. After half a year, CTPA showed normalization of all areas in the pulmonary artery

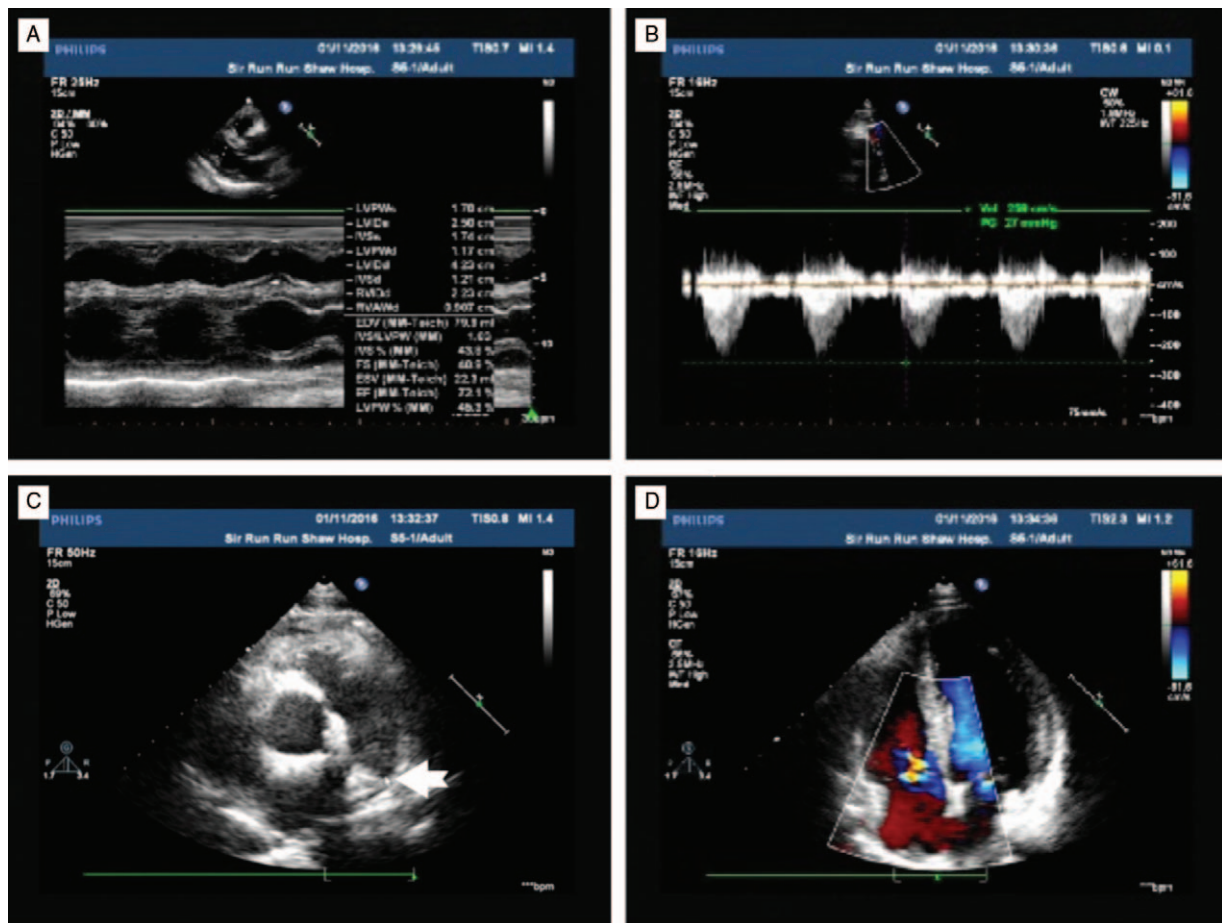


Figure 1. A) Normal size and function of the heart, with mild dilated ascending aorta (internal diameter 39.5 mm). B) The blood flow of pulmonary artery, it showed Vmax=2.74m/s, RVSP=35mmHg. C) An intraluminal pulmonary artery mass, sized 15.6×18.2mm (arrow). D) mild regurgitations of the tricuspid valve and the mitral valve.

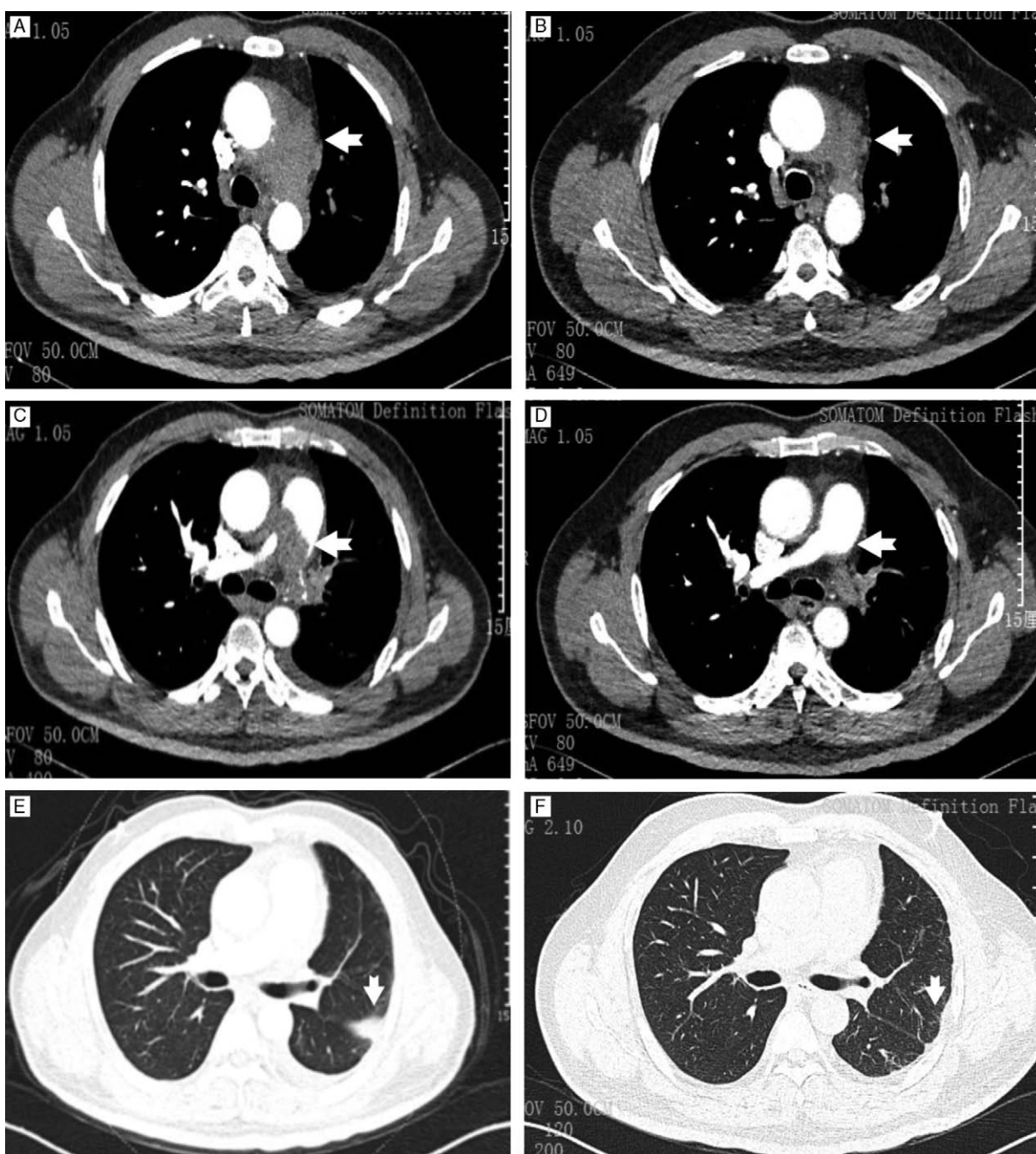


Figure 2. A) Periaortic mass found on CTPA (arrow). B) Periaortic mass partially resolved after 6 months of steroid therapy (arrow). C) Intraluminal pulmonary artery mass mimics pulmonary embolism or intima sarcoma with complete obstruction of the left pulmonary artery (arrow). D) Resolution of intraluminal pulmonary artery mass aside from the left pulmonary artery after 6 months of steroid therapy (arrow). E) Wedge-shaped lesion with patchy ground-glass changes in the left lung (arrow). F) Resolution of left lung lesions after 6 months of systemic steroid therapy (arrow). CTPA = computed tomographic pulmonary angiography.

aside from the left pulmonary branch (Fig. 2B, D, and F). His echocardiogram showed RVSP of 26mmHg.

2. Materials and methods

2.1. Search strategy and selection criteria

References for this review were identified through searches via PubMed, EBSCO, and Web of Science for published articles before November 2016 by use of the terms “Mikulicz’s syndrome”, “Küttner’s tumor”, “Riedel’s thyroiditis”, “Multi-

focal fibrosclerosis”, “Inflammatory pseudotumor”, “Mediastinal fibrosis”, “Retroperitoneal fibrosis”, “Periaortitis and periarteritis”, “Inflammatory aortic aneurysm” and “IgG4-related” and “pulmonary arteritis”, “pulmonary embolism”, “pulmonary aneurysm”, “pulmonary artery”, and “pulmonary hypertension”. Articles in English, French, or German resulting from these searches, in addition to relevant references cited in these articles, were reviewed. Confirmed diagnosis was performed in accordance with the Japanese Comprehensive Diagnostic Criteria for IgF4-related Disease in 2011.^[11]

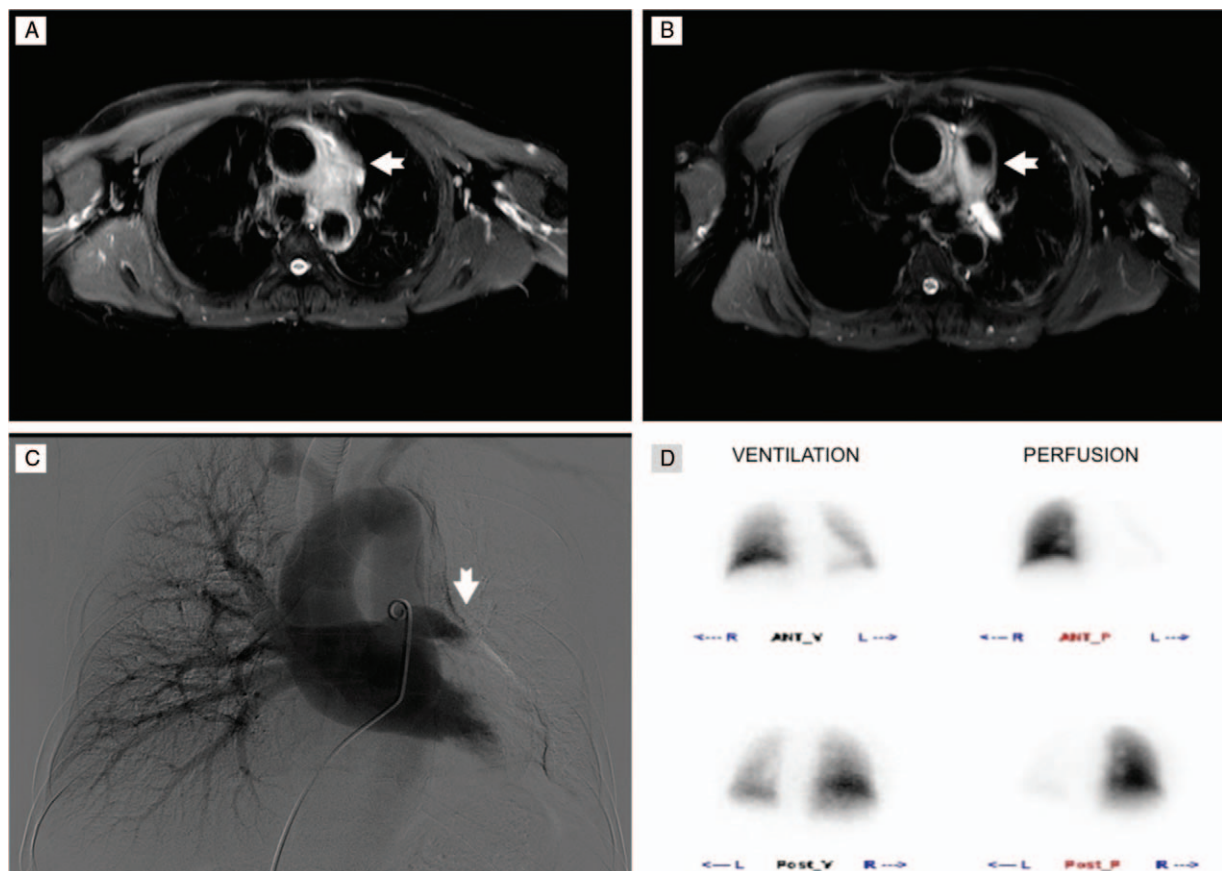


Figure 3. A, B) Chest MRI suspected malignancy in pulmonary artery and periaortic area (arrows). C) Pulmonary angiogram suggested left pulmonary artery obstruction (arrow). D) V/Q scan suggested pulmonary embolism in the left lung and right S5 segment. MRI = magnetic resonance imaging.

3. Results

3.1. Epidemiology

Most IgG4-related disease patients were reported in Japan. The first Japanese nationwide survey conducted in 2009 estimated a total of 8000 IgG4-RD patients in that year.^[12] However, case reports from other countries are now increasing. Racial differences are still unknown at present; the average age of disease onset is in the seventh decade of life, with higher prevalence in men.^[13] Zen reported first IgG4-RD with pulmonary vascular involvement in a cohort analysis in 2010.^[14] First case of IgG4-RD associated with pulmonary hypertension was published in 2014.^[15] In 2015, Yasuhiro K issued IgG4-RD-associated pulmonary hypertension patients with typical obliterative phlebitis in the lung.^[16] Before November 2016, only 15 cases of IgG4-related pulmonary vascular involvement have been reported, and it is suspected that lack of awareness of the disease may be a major reason.

3.2. Clinical manifestations of IgG4-related pulmonary vascular involvement

IgG4-RD is a substantially under-diagnosed disease. The prevalence of various organ involvements also remains unclear.^[3] IgG4-RD's involvement of pulmonary circulation is rare and remains neglected. Literature review revealed 15 cases of IgG4-RD with the pulmonary artery involved, 3 cases with pulmonary arteritis, 2 with pulmonary artery aneurysm, 3 with pulmonary

artery stenosis, 1 with obliterative phlebitis, and 1 with pulmonary embolism and comorbidity of antiphospholipid antibody syndrome (Table 1). In total, 8 patients were associated pulmonary hypertension, 5 of whom were initially diagnosed with idiopathic or hereditary pulmonary hypertension. In these 5 patients, IgG4-RD was suspected to be the result of long-term epoprostenol therapy. While in the other 3 patients, pulmonary hypertension was suspected to be caused by IgG4-related vascular involvement. The latter group was younger in age in comparison with typical IgG4-RD patients. Among all patients, clinical manifestations ranged from asymptomatic to dyspnea or syncope. Except the 3 cases without serum IgG4 data, the average serum IgG4 level of reported patients with pulmonary vascular involvement is 1524.5 ± 1771.8 mg/dL.

4. Discussion

IgG4-RD vascular manifestations have a predilection for adventitia and periaortic/periarterial tissue, with occasional reports in the media or intima regions.^[6–8] By comparison, primary aortic sarcoma affects media or intima, of which intimal types are the most common.^[17] Intimal sarcoma with pulmonary artery involvement mimics pulmonary hypertension, heart failure, or thromboembolic disease, and may also be insidious, presenting as chronic diarrhea in outpatient service.^[18] However, our patient had both intima and periaortic lesions. Although chest MRI and PET/CT suspected malignancy, 2 CT-guided biopsies revealed a benign disease. As the biopsy results suggested

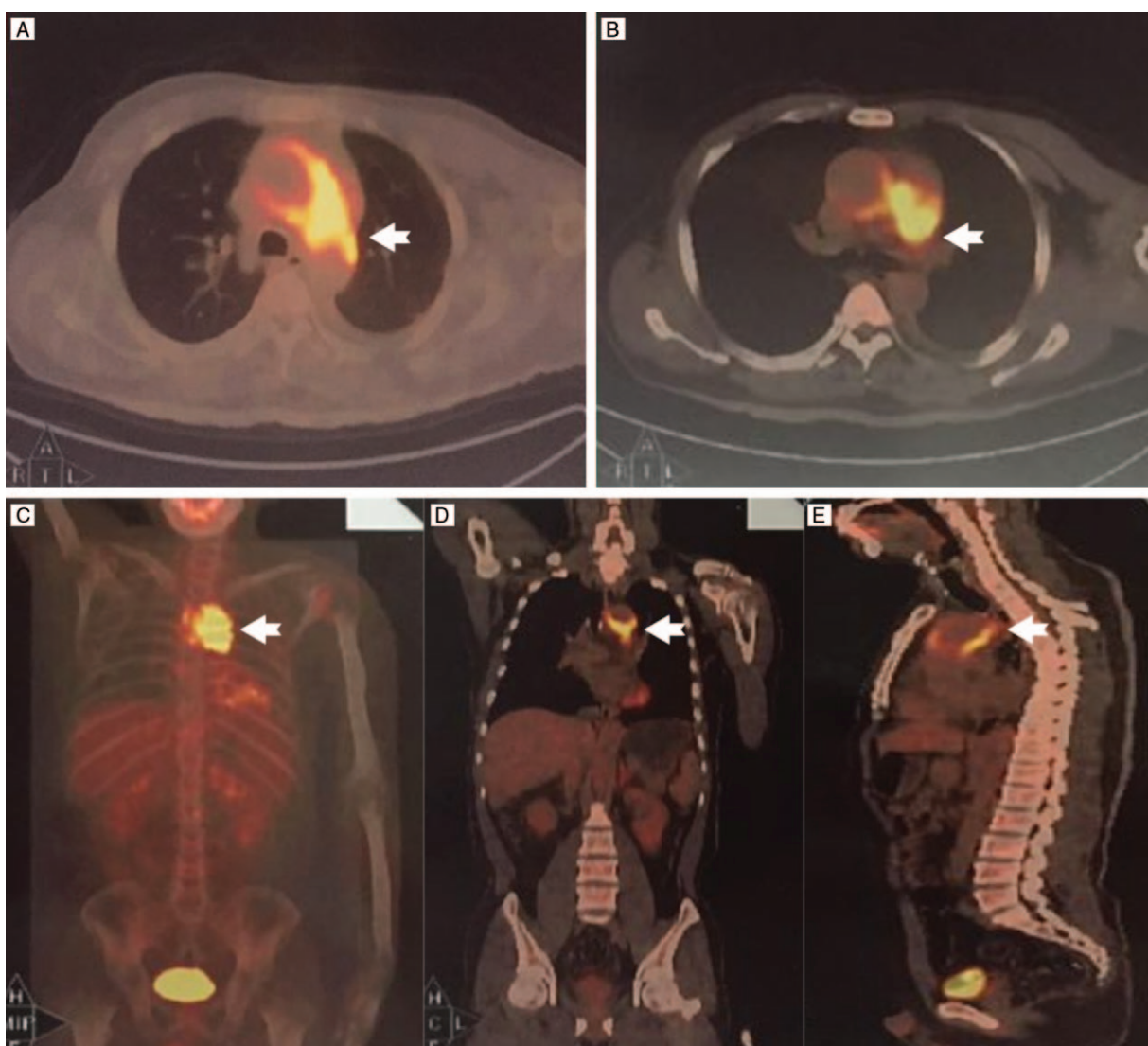


Figure 4. PET/CT suggested FDG-avid lesions in the periaortic areas, extending to the intraluminal pulmonary artery (arrows). PET/CT = positron emission tomography/computed tomography.

“lymphatic tissue” and “fibroadipose with lymphocytic infiltration”, the first suspect was fibrosing mediastinitis with pulmonary embolism, while pulmonary arterial intimal sarcoma was the alternative diagnosis. Fibrosing mediastinitis is a rare disease characterized by fibrous proliferation in the mediastinum and can be idiopathic or secondary to several conditions, such as infections and malignancies.^[19] Clinical symptoms and laboratory findings are of limited help in differential diagnosis, but characteristic presentations and extent of disease upon imaging can afford clues to diagnosis. The pathological morphology and immunostaining are the key to determining the final diagnosis.^[20] Thus, the patient underwent intrathoracic surgical biopsy. The periaortic biopsy revealed focal fibrotic inflammatory changes with high IgG4-positive (IgG4+) plasma cell infiltration, but without evidence of tuberculosis, histoplasmosis, vasculitis, lymphoma, sarcoma, etc. A left lower lobe lesion demonstrated focal necrosis in accordance with pulmonary infarction, suggesting IgG4-RD complicated with pulmonary embolism.

As tissue biopsy is the key for the final diagnosis, definite identification of IgG4-related pulmonary vascular disease always

requires an intrathoracic surgical biopsy, which is a traumatic procedure for suspected patients. CT-guided or EBUS-guided biopsy may be applicable for certain types of patients, but these small specimens may not be diagnostic, and repeated biopsy is necessary because IgG4-RD might have a focal distribution of characteristic lesions. And other diseases, such as lung cancer, could have IgG4+ stromal plasma cell infiltration near the tumor.^[21] IgG4-RD typically affects multiple organs. Organ-specific diagnostic histopathological features and variant cutoff values for IgG4+ plasma cell count can be clarified.^[22] A thorough physical exam with subsequent imaging is needed to find the candidate biopsy site. PET/CT is helpful to define the extent of organ involvement, locate the biopsy site, and monitor disease activity after treatment.^[23] In this review, nearly all 15 cases had more than 1 organ affected, with increased serum IgG4 level. One patient underwent a pulmonary artery biopsy, as the pulmonary artery was the only organ involved. Additionally, the serum IgG4 level is reported to be related to the extent of disease, and increase with respect to the number of affected organs.^[24–27] A previous literature found that the calculated aortic wall area to

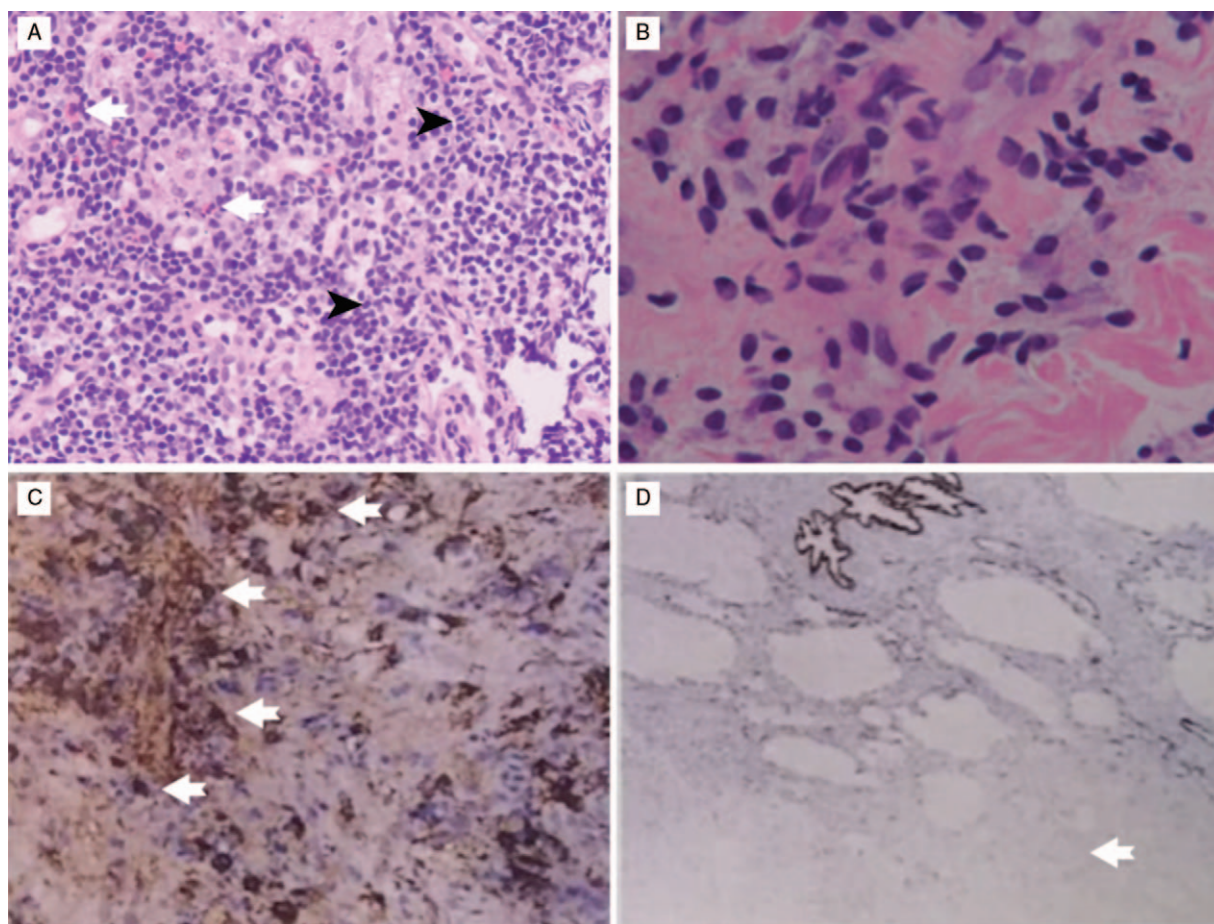


Figure 5. A, B) Biopsy of periaortic area lesion showed storiform fibrosis with diffuse lymphoplasmacytic cells infiltration (black arrows), and occasional eosinophil cells (white arrows). C) Dominant IgG4 immunostaining positive lymphoplasmacytic cells in periaortic area sample (arrows). D) Left lobe lesions consistent with infarction necrosis (arrow).

be significantly associated with serum IgG4 levels.^[28] However, its role in pulmonary vascular involvement is not clear.

The 2015 ESC/ERS guideline for the diagnosis and treatment of pulmonary hypertension has updated the clinical classification.^[29] How IgG4-RD intrathoracic involvement contributes to pulmonary hypertension remains unclear. Yasuhiro et al reported a case with IgG4-related lung obliterative phlebitis, with a hemodynamical change similar to that of pulmonary veno-occlusive disease. Pulmonary veno-occlusive disease is classified as a subgroup of pulmonary arterial hypertension, with the observed post-capillary lesions of septal veins and pre-septal venules consisting of loose, fibrous remodeling of the intima that may completely occlude the lumen. Inconsistent pathological findings with no other organ involvement can be distinguished from IgG4-RD.^[16] Diffuse lung involvement of IgG4-RD has been reported, but pulmonary hypertension related to such impaired lung disorders was underestimated.^[15,30–32] Pulmonary hypertension might also be the result of vascular compression of surrounding tumefied tissue. As with our case, pulmonary hypertension was caused by compression and complicated pulmonary embolism. Interestingly, Kuwana et al reported 5 pulmonary hypertension cases who developed IgG4-RD during long-term epoprostenol therapy. The role of drugs in the development of IgG4-RD needs more studies; since IgG4-RD can result in myocardial infarction and dysfunction, pulmonary vascular obstruction, interstitial lung disease, or fibrosing

mediastinitis. Selected patients should be screened for possible pulmonary hypertension diagnosis, and greater awareness should be placed on evaluating the pulmonary vascular manifestations of IgG4-RD.

4.1. Immunity and inflammation mechanisms of IgG4-RD and pulmonary hypertension

IgG4-RD is a systemic autoimmune disease since it has been first reported in 2001. But its pathogenesis remains largely unknown. High serum levels of IgG4 characterize the disease. But its role in the pathogenesis of the disease is an obvious question. Up to date, whether IgG4 antibody is pathogenic or produced in response to inflammatory stimuli remains unclear.^[4] Generally, a crucial step might be naive T cell activation following antigen presentation by cognate antigen-specific naive or memory B cells, eosinophils or macrophages. Once activated, putative pathogenic T helper and T regulatory cells are thought to produce inflammatory cytokines that include interferon (IFN)- γ , interleukin (IL)-4, IL-10, IL-5, IL-13, and transforming growth factor (TGF)- β . IL-5, IL-13, and TGF- β can lead to the activations of fibroblasts, eosinophils, and macrophages. While IL-4 and IL-10 drive preferential class-switch of antigen-specific B cells to IgG4 and IgE. Thereby it sets up a vicious cycle of mutual activations between B and T lymphocytes.^[33,34]

Pulmonary arterial hypertension is a progressive cardiopulmonary disease with high vessel resistance to blood flow and right

Table 1
Features of IgG4-RD with pulmonary circulation manifestations.

Reference	Age	Sex	Vascular disorder	Biopsy site	Serum IgG4 (g/L)	Pulmonary arterial pressure	Extravascular involvement	Clinical presentation	Comorbidity
John H. Stone ^[6]	52	M	Pulmonary artery + coronary aneurysm abdominal aortitis	Aorta	19.8	NA	Pericardium kidney	Dyspnea palpitations	None
	68	F	Mild pulmonary artery stenosis with PH, abdominal + thoracic aortitis	Subglottis	2.03	44mmHg	ENT lymph nodes	Dyspnea on exertion, carotid bruit	Hypertension
	51	F	Pulmonary + thoracic aortitis	Lymph node	0.6	NA	Retroperitoneum lymph node	Nonvascular symptoms	Hypertension hyperlipidemia smoking antibody syndrome
Kawakami ^[14]	56	M	Distal pulmonary embolism (V/Q scan)	Lymph node	2.96	NA	Lymph node	Occasional dyspnea petechiae	Antiphospholipid antibody syndrome
Zen ^[15]	NA	NA	Distal pulmonary artery stenosis	Lung	NA	NA	NA	NA	NA
Abhishek ^[16]	53	M	Pulmonary + coronary + abdominal aneurysm coronary stenosis	Internal mammary artery pericardium aortic	NA	NA	NA	Chest pain syncope	Chronic renal failure
Dong A ^[17]	60	F	Pulmonary artery bifurcation stenosis	Pulmonary artery	NA	NA	None	Fatigue	NA
Ebe ^[18]	58	F	Pulmonary artery + abdominal + iliac aortitis	Lacrimal gland	7.73	NA	Kidney, infraorbital nerve	NA	Interstitial nephritis
Yasuhiro K ^[19]	45	M	Lung obliterative phlebitis, PH	Lung Lacrimal gland	65.3	42mmHg	Bronchial, Lacrimal gland	Dyspnea	Bronchiolitis
Motoko ^[20]	22	F	Obliterative pulmonary arteritis?, PH	Lung, lip, GI, lymph node	32.3	40mmHg	Lacrimal, Submandibular, parotid gland	Dyspnea	Asthma
Kuwana ^[21]	26	F	PH*	Labial gland	8.24	67mmHg	Lacrimal, salivary gland, pancreas	Dyspnea	Chronic sinusitis
	36	F	PH*	NA	11.9	NA	Lacrimal, salivary gland	NA	Asthma
	54	F	PH*	NA	8.96	NA	Lacrimal, salivary gland	NA	None
	70	F	PH*	NA	22.2	NA	Lacrimal, salivary gland	NA	Chronic sinusitis
	48	F	PH*	NA	0.92	NA	Lacrimal, salivary gland, pancreas	NA	Chronic sinusitis

NA=not applicable, PH* =pulmonary hypertension.

heart failure. Extensive obstruction of small to mid-sized pulmonary arterioles is prevalent. More awareness has been aroused on the frequently reported perivascular inflammation in all types of pulmonary arterial hypertension patients, especially idiopathic and autoimmune disease associated groups. The correlations of the average perivascular inflammation score with vessel wall thickness in pulmonary hypertension support a role for perivascular inflammation in pulmonary vascular remodeling.^[35] Experimental pulmonary hypertension indicated that immunity inflammation that precedes vascular remodeling is a cause of the disease, instead of a consequence.^[36] Varying degrees of perivascular inflammatory infiltrates with T- and B-lymphocytes, macrophages were present in pulmonary hypertension similar with IgG4-RD. Chemokines and cytokines that present in IgG4-RD are also found increased in serum levels of pulmonary arterial hypertension patients, such as IFN- γ , IL-4, IL-10, IL-13. Many clinical and experimental data corroborate the link between IFN exposure and the risk to develop pulmonary arterial hypertension.^[37] IL-4 and IL-13 were found playing roles in pathogenesis of pulmonary hypertension. TGF- β also plays a pathogenetic role in the disease, and TGF- β ligand blockage could improve survival in multiple experimental pulmonary hypertension models.^[38-40] Previous animal and clinical studies indicate that IL-6 is important in pulmonary arterial hypertension. Its role in pathogenesis of pulmonary arterial hypertension is via IL-6/IL-21 axis.^[41] Although high serum IL-6 are common in hyper-IL-6 syndrome, such as rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, mixed connective tissue disease. IgG4-RD could have increased serum IL-6 level, and IL-6 receptor blockade in rheumatoid arthritis patients could selectively reduce IgG4 autoantibody.^[42] Those mutual immuni-

ty and inflammation cytokine/chemokine patterns were published separately. How and to what extent are immunity and inflammation of IgG4-RD related to the pulmonary arterial hypertension need more investigations.

4.2. Histopathology

Characteristic findings of lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis heighten diagnostic specificity, but clinicopathologic correlation is always essential. IgG4-RD pathology consensus statement endorsed 3-tiered diagnostic terminology for the pathological diagnosis, that are:

- (1) histologically highly suggestive,
- (2) histologically probable and
- (3) histologically insufficient evidence.^[22]

In most instances, 2 of the 3 major histological features are required for confident pathological diagnosis. Patients with diagnosis of histologically probable IgG4-RD requires additional evidence, that might be serum IgG4 >135 mg/dL, or other organ involvement demonstrated by radiological or pathological examination. In organ such as lung, storiform fibrosis or obliterative phlebitis may be inconspicuous or absent. A rare case of obliterative phlebitis associated with pulmonary hypertension was published. While obliterative arteritis is often seen in pulmonary manifestations, particularly solid lesions. IgG4 +/IgG+ plasma cell ratio >40% is mandatory for histological diagnosis of IgG4-RD. The cutoff value of IgG4 positive plasma cells/high power field (HPF) for aorta or pulmonary vessel within mediastinum is >50/HPF. But it is different for lung tissues of surgical specimen (>50/HPF) or needle biopsy (>20/HPF).^[22,31]

In all the reported IgG4-RD patients with pulmonary vascular involvement, only 3 patients underwent lung biopsy, 1 patient underwent pulmonary artery biopsy. Although both can cause vessel stenosis or aneurysm, proximal and distal pulmonary vascular involvements are not exactly the same. Stenosis is more common in proximal pulmonary vascular involvement. Because IgG4-RD is a multi-organ involved disease, there are more chances that superficial organs are selected for biopsy. Once IgG4-RD is confirmed and pulmonary vascular involvement, such as stenosis or aneurysm, is consistent with IgG4-RD radiological presentations. It is usually not necessary to confirm the diagnosis with lung biopsy. Good response to steroid therapy adds extra evidence to the diagnosis.

4.3. Laboratory test

As recommended by the Japan guideline on IgG4-RD, elevated serum IgG4 level >135 mg/dL can help to make a diagnosis, if the patient is histopathologically probable.^[11] This cut-off value demonstrated a sensitivity of 97.0% and a specificity of 79.6%.^[43] About 30% to 50% IgG4-RD patients have normal serum IgG4 level.^[44] The average serum IgG4 level of the reported patients with pulmonary vascular involvement is 1524.5 ± 1771.8 mg/dL, that is significantly higher than the diagnostic cut-off value. Direct vascular involvement might be one of the reasons. Elevated serum IgG4 level can also be associated with Castleman's disease, recurrent infections, autoimmune diseases, even carcinomas. Recently, serum plasma-blasts/plasma cells are found to be a potential biomarker independent of serum IgG4 level.^[45] whether it can be adopted to differentiate from those disorders remains unclear. Biomarkers to predict the incidence and prognosis of those IgG4 patients with pulmonary vascular involvement require more research.

4.4. Treatment

According to the International Consensus Guidance Statement on IgG4-RD published in 2015, most patients require treatment with systemic steroids or steroid-sparing agents.^[46] Those with multi-organ disease, significantly elevated serum IgG4 concentrations, involvement of proximal bile ducts or a history of disease relapse will need long-term maintenance therapy. Urgent treatment is recommended when patients represent aortitis, retroperitoneal fibrosis, proximal biliary strictures, tubulointerstitial nephritis, pachymeningitis, pancreatic enlargement, or pericarditis. We believed that some cases of IgG4-RD with pulmonary vascular involvement might deserve urgent treatment, and should also be listed. Some asymptomatic patients, such as those with lymphadenopathy or mild submandibular gland enlargement, may only require a close follow-up. In some highly fibrotic cases, symptoms may reflect fibrotic, "burnt-out" disease as opposed to active IgG4-RD, with less plasma cells infiltration and poor response to pharmacological agents. Surgical debulking or interventional treatment may be alternative treatments. Vascular narrowing cases are rare and have responded well to steroid treatment. It was reported that up to one-third of the patients met the established criteria for pathology of IgG4-RD, who might not require surgery or interventional treatment aside from systemic steroids.^[19,47-49] Prednisone with a dose of 30 to 40 mg/day is a common first-line agent for remission induction in all patients with active, untreated IgG4-RD unless contraindications to such treatment are present. Most experts agree that the initial glucocorticoid dose should be maintained for 2 to 4 weeks.

After that, the dose could taper by 10 mg daily every 2 weeks till to a dose of 20 mg daily. Then a decrease of 5 mg daily every 2 weeks is recommended. The goal of induction therapy at many centers is to discontinue glucocorticoid 3 to 6 months after the start of treatment. Our representative patient demonstrated a good response to steroid treatment, and his pulmonary artery stenosis was normalized. Due to long-term occlusion, his left pulmonary artery remained obstructed. Interestingly, Kuwana et al reported 5 pulmonary hypertensive IgG4-RD patients with epoprostenol therapy who responded poorly to steroid treatment. It was hypothesized that epoprostenol could promote Th2 transition of lymphocytes and boost IgG4-RD disease activity, and more clinical investigation is necessary for validation. Other cases of pulmonary artery stenosis or pulmonary hypertension with lung IgG4-RD displayed good responses to steroid therapy. The role of drugs targeting pulmonary hypertension on patients with poor response to steroid therapy needs more research.

Notably, the duration of IgG4-RD's maintenance therapy on patients with pulmonary vascular involvement is still not clear. PET/CT and serum IgG4 levels may be helpful to follow-up and individualize the duration of treatment. Masako et al have previously reported an IgG4-related bronchial disease with an irreversible obstructive pulmonary function test result, which was successfully reversed while being treated with inhaled corticosteroid.^[50] Similar to inhaled therapy for pulmonary hypertension, whether long-term inhaled corticosteroids for limited IgG4-related pulmonary involvement can replace systemic steroid as maintenance therapy still needs additional observations. In our patient, complicated pulmonary embolism was found on imaging and validated via biopsy; he received 6 months of anticoagulation therapy, according to the recent ACCP anticoagulation guideline in 2016. At present, data on anticoagulation durations for such patients is rare. The IgG4-RD disease activity might affect the therapy duration.

5. Conclusion

IgG4-RD is a recently recognized, immune-mediated chronic fibrotic inflammation that can involve almost all organs, causing organ tumefaction and dysfunction. Its presence in pulmonary circulation is rare and has yet to be investigated. Echocardiogram and contrast-enhanced chest CT are helpful to screen the disease. Here, we present a case with pulmonary artery stenosis, complicated with pulmonary embolism and pulmonary hypertension. literature review included 15 patients with IgG4-RD pulmonary vascular involvement who possessed a range of clinical manifestations, from asymptomatic to dyspnea and even syncope. Eight patients were associated with pulmonary hypertension. Nearly all cases had more than 1 affected organ, and increased serum IgG4 levels. PET/CT is helpful to find affected organs and determine candidate biopsy sites. Characteristic imaging with affected organ biopsies, in addition to increased serum IgG4 levels, are practical for diagnosis. Pharmacological therapy and its recommended duration remain unclear, and the role of surgery or interventional therapy needs more research. Greater awareness is urged to further investigate the pulmonary vascular manifestations of IgG4-RD.

Author contributions

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Resources: Wenjing Ruan, Hangdi Xu.

Supervision: Xiaohong Wu.

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