Pulmonary Vascular Involvement of IgG4-Related Disease

Yong Zhou 1,2, Lingyan Shao 1, Kejing Ying 1, Joy Jin 1 and Xiaohong Wu 1,*

1 Department of Respiratory and Critical Care Medicine, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, Zhejiang, China
2 Department of Surgery, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco

Corresponding author: Xiaohong Wu, Associate Professor, Department of Respiratory and Critical Care Medicine, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, Zhejiang, China, Tel: +86-571-86006196; Fax: +86-571-86006191; E-mail: gina68831@163.com

Received date: 06 March, 2017; Accepted date: 20 March, 2017; Published date: 26 March, 2017

Copyright: © 2017 Zhou Y, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Objective: 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.

Methods: We describe a representative IgG4-RD patient with pulmonary artery stenosis and pulmonary embolism, leading to reversible pulmonary hypertension. Literature review was conducted, and references for this review were identified through searches via PubMed, EBSCO, and Web of Science for published articles prior to November 2016.

Results: We analyzed 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.

Conclusion: Clinical manifestations were found to range from asymptomatic to dyspnea or syncope, and nearly all cases had more than one organ affected, with increased serum IgG4 levels. PET/CT aided in identifying affected organs and determining candidate biopsy sites. IgG4-RD pulmonary hypertension can be classified to all five clinical groups. More awareness is urged to evaluate the pulmonary vascular manifestations of this disease.

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, infectious, and inflammatory disorders [2]. The pancreas, sialaden, lacrimal gland, and lymph node are among the most involved organs, and IgG4-RD's clinical presentations in lung have previously 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].

Additionally, 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 result in high mortality and numerous morbidities [6-10]. However, the involvement of pulmonary circulation is rare and has yet to be investigated. Here, we report one case of IgG4-RD with uncommon pulmonary vascular manifestations, and provide a comprehensive review of its clinical features. Furthermore, literature pertaining to IgG4-RD with pulmonary vascular involvement were reviewed.

Representative patient with IgG4-RD pulmonary vascular manifestations

A 54-year-old bank employee presented with shortness of breath on exertion and fatigue for two months. The patient denied cough, chest pain, hemoptysis, and fever, with a chest CT scan suggesting bronchitis, but responded poorly to 10 days of antibiotics and mucolytics, and was subsequently referred to our hospital. His temperature was 36.6, with a pulse at 98 beats per minute, respiratory rate at 20 times per minute, and blood pressure of 142/84 mmHg. The patient 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 soft without tenderness. No palpable hepatosplenomegaly was found, and no edema or varicose veins were present on either leg.

CBC and blood chemistry were within normal ranges except for IgG (45.3 g/L), and CRP was 43.2 mg/L. ABG showed a FiO2 of 33%, PO2 of 127.8 mmHg, PCO2 39.2 mmHg, and P/F of 387; ANA was 1:100 (nucleolus type). Anti-centromere antibody showed as weak positive, while ANCA, antiproteinase antibody, RF, ACE, T-SPOT, and G/GM tests were negative. The patient's pulmonary function test was normal, and an echocardiogram suggested an intraluminal mass in the pulmonary artery, with an EF of 72% and RVSP of 35 mmHg (Figure 1). Emergent CTPA showed a periaortic mass with pulmonary artery stenosis and left branch occlusion. A wedge-shaped lesion was present in the left lower lobe (Figure 2).
Anti-coagulation with low-weight molecular heparin was administered; a second-day scintigraphy suggested pulmonary embolism in the left lung and right S5 segment. A chest MRI suspected malignancy (Figure 3), 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 (Figure 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 tissue, with dominant lymphocyte infiltration; mediastinal fibrosis was suspected.

Stainings for fungus and tuberculosis DNA test were negative, and the patient’s serum IgG4 presented as 6.44 g/L. He underwent angiogram and subsequent thoracoscopy (Figure 3); surgical periaortic specimens confirmed periaortitis associated with IgG4-RD. The left lower lobe pathology showed infarction with necrosis (Figure 5), and systemic methylprednisolone was administered and tapered afterwards according to international IgG4-RD expert consensus. The patient's symptoms then improved, with serum IgG4 levels decreasing back.
within normal range. After one year, CTPA showed normalization of all areas in the pulmonary artery aside from the left pulmonary branch, and an echocardiogram showed RVSP of 26 mmHg.

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

Search strategy and selection criteria

References for this review were identified through searches via PubMed, EBSCO, and Web of Science for published articles prior to November 2016 by use of the terms “Mikulicz’s syndrome”, “Küttner’s tumor”, “Riedel’s thyroiditis”, “Multifocal fibrosclerosis”, “Inflammatory pseudotumor”, “Mediastinal fibrosis”, “Retropertioneal fibrosis”, “Periaortitis and periarteritis”, “Inflammatory aortic aneurysm” or “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].

Epidemiology

Most IgG4-related disease patients were reported in Japan; the first Japanese nationwide survey conducted in 2009 estimated a total of 8,000 IgG4-RD patients in that year [12-14]. 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. Zen reported the first case of IgG4-RD with pulmonary vascular involvement in a cohort analysis in 2010 [15]. Following, the first case of IgG4-RD associated with pulmonary hypertension was published in 2014 [16], and in 2015, Yasuhiro K. noted IgG4-RD associated pulmonary hypertension patients with typical obliterative phlebitis in the lung [17]. Prior to November 2016, only 15 cases of IgG4-related pulmonary vascular involvement were reported, and it is suspected that lack of awareness of the disease may be a major reason.

Clinical manifestations of IgG4-related pulmonary vascular involvement

IgG4-RD is a substantially under-diagnosed disease, and the prevalence of various organ involvement 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 with comorbidity of antiphospholipid antibody syndrome (Table 1). In total, 8 patients presented with 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, IgG4-RD 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.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Vascular Disorder</th>
<th>Biopsy Site</th>
<th>Serum IgG4 (g/L)</th>
<th>Pulmonary Arterial Pressure</th>
<th>Extravascular Involvement</th>
<th>Clinical Presentation</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>F</td>
<td>Mild pulmonary artery stenosis with PH, abdominal + thoracic aortitis</td>
<td>Subglottis</td>
<td>2.03</td>
<td>44mmHg</td>
<td>ENT lymph nodes</td>
<td>Dyspnea on exertion, carotid bruit</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>Pulmonary + thoracic aortitis</td>
<td>Lymph node</td>
<td>0.6</td>
<td>NA</td>
<td>Retroperitoneum lymph node</td>
<td>Nonvascular symptoms</td>
<td>Hypertension, hyperlipidemia, smoking</td>
<td></td>
</tr>
</tbody>
</table>

Citation: Zhou Y, Shao L, Ying K, Jin J, Wu X (2017) Pulmonary Vascular Involvement of IgG4-Related Disease. Angiol 5: 191. doi: 10.4172/2329-9495.1000191
Intimal sarcoma with pulmonary artery involvement mimics [23], and may also be insidious, presenting as chronic diarrhea in patients with lymphoctic infiltration, and inflammatory changes in the mediastinum, and can be idiopathic or secondary to several conditions, including infection and malignancies [25]. Clinical presentations and laboratory findings are of limited help in differential diagnosis, but characteristic presentations and extent of disease upon imaging can afford clues for diagnosis. The pathological morphology and immunostaining are key to determining the final diagnosis [26]; the patient underwent intrathoracic surgical biopsy, with periaortic biopsy revealing focal fibroblast infiltrates 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 final diagnosis [27], definite identification of IgG4-related pulmonary vascular disease always requires an intrathoracic surgical biopsy, which is a traumatogenic procedure for suspected patients. CT-guided or EBUS-guided biopsy may applicable for certain types of patients, but these small specimens may not be diagnostic, and repeated biopsy is necessary, since IgG4-RD can have a focal distribution of characteristic lesions. Other

Table 1: Features of IgG4-RD with Pulmonary Circulation Manifestations.

<table>
<thead>
<tr>
<th>Author</th>
<th>Gender</th>
<th>Age</th>
<th>Localisation</th>
<th>Lesion</th>
<th>Vital Signs</th>
<th>Coexistent Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawakami [14]</td>
<td>M</td>
<td>56</td>
<td>Distal pulmonary arterial stenosis</td>
<td>Lymph node</td>
<td>2.96</td>
<td>NA</td>
</tr>
<tr>
<td>Zen [15]</td>
<td>NA</td>
<td>NA</td>
<td>Distal pulmonary arterial stenosis</td>
<td>Lung</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Abhishek [16]</td>
<td>M</td>
<td>53</td>
<td>Pulmonary + coronary + abdominal + coronary stenosis</td>
<td>Internal mammary artery + pericardium aortic</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dong A [17]</td>
<td>F</td>
<td>60</td>
<td>Pulmonary artery bifurcation stenosis</td>
<td>Pulmonary artery</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Ebe [18]</td>
<td>F</td>
<td>58</td>
<td>Pulmonary artery + abdominal + iliac + aortic stenosis</td>
<td>Lacrimal gland</td>
<td>7.73</td>
<td>Kidney, infraoorbital nerve</td>
</tr>
<tr>
<td>Yasuo K [19]</td>
<td>M</td>
<td>45</td>
<td>Lung obliterator phlebitis, PH</td>
<td>Lung</td>
<td>65.3</td>
<td>42mmHg</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>36</td>
<td>PH</td>
<td>NA</td>
<td>11.9</td>
<td>Lacrimal, salivary gland, pancreas</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>54</td>
<td>PH</td>
<td>NA</td>
<td>8.96</td>
<td>Lacrimal, salivary gland</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>70</td>
<td>PH</td>
<td>NA</td>
<td>22.2</td>
<td>Lacrimal, salivary gland</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>48</td>
<td>PH</td>
<td>NA</td>
<td>0.92</td>
<td>Lacrimal, salivary gland, pancreas</td>
</tr>
</tbody>
</table>

IgG4-RD vascular manifestations have a predilection for adventitia and periarterial/periorterial 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 [22]. Intimal sarcoma with pulmonary artery involvement mimics pulmonary hypertension, heart failure, or thromboembolic disease [23], and may also be insidious, presenting as chronic diarrhea in outpatient service [24]. However, our patient displayed both intima and periaortic lesions. Although chest MRI and PET/CT suspected malignancy, two CT-guided biopsies revealed benign disease, effectively ruling out the former. As the biopsy results suggested “lymphatic tissue” and “fibroadipose with lymphocytic infiltration”, the first suspect was fibrosing mediatinitis with pulmonary embolism, while pulmonary artery intimal sarcoma was the alternative diagnosis. Fibrosing mediatinitis is a rare disease characterized by fibrous proliferation in the mediastinum, and can be idiopathic or secondary to several conditions, including infection and malignancies [25]. Clinical presentations and laboratory findings are of limited help in...
diseases, such as lung cancer, could have IgG4+ stromal plasma cell infiltration [28]. IgG4-RD typically affects multiple organs, with organ-specific diagnostic histopathological features and varying cutoffs for IgG4+ plasma cell count [29]. Thus, 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 [30]. In this review, nearly all 15 cases had more than one organ affected, with increased serum IgG4 levels. 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 increases with respect to the number of affected organs [31-34]. Previous literature found the calculated aortic wall area to be significantly associated with serum IgG4 levels [35], but its role in pulmonary vascular involvement is unclear.

2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension have updated its clinical classification [36], but how IgG4-RD intrathoracic involvement contributes to pulmonary hypertension remains nebulous. Yashuhiro, et al. reported a case of 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 [17]. Diffuse lung involvement of IgG4-RD was previously reported, but pulmonary hypertension related to such impaired lung disorders has been underestimated [16,37-40]. Pulmonary hypertension can also be the result of vascular compression of surrounding tufted tissue; as with our case, pulmonary hypertension was caused by compression and complicated pulmonary embolism. Interestingly, Kuwana, et al. reported five pulmonary hypertension cases who developed IgG4-RD during long-term epoprostenol therapy. Thus, the role of drugs in the development of IgG4-RD needs additional study. Since IgG4-RD can result in myocardial infarction and dysfunction, pulmonary vascular obstruction, interstitial lung disease, or fibrosing mediastinitis, IgG4-RD pulmonary hypertension might be classified to all five clinical groups. 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.

**Immunity and inflammation of IgG4-RD and pulmonary hypertension**

IgG4-RD was labeled a systemic autoimmune disease since it was first reported in 2001. However, its pathogenesis remains largely unknown: high serum levels of IgG4 characterize the disease, but whether IgG4 antibodies are pathogenic or produced in response to inflammatory stimuli remains unclear. Generally, a crucial step might involve 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 including IFN-γ, IL-4, IL-10, IL-13, and TGF-β. IL-5, IL-13, and TGF-β lead to the activation of fibroblasts, eosinophils, and macrophages, while IL-4 and IL-10 drive a preferential class-switch of antigen-specific B-cells to IgG4 and IgE, creating a vicious cycle of mutual activation between B- and T-lymphocytes [41,42].

Pulmonary arterial hypertension is a progressive cardiopulmonary disease with high vessel resistance to blood flow and right heart failure. Extensive obstruction of small to midsized pulmonary arterioles is prevalent. More attention has been focused on the frequently reported perivascular inflammation in all types of pulmonary arterial hypertension patients, especially idiopathic and autoimmune disease associated groups. The correlation of the average perivascular inflammation score with vessel wall thickness in pulmonary hypertension supports a role for perivascular inflammation in pulmonary vascular remodeling [43]. Experimental pulmonary hypertension indicates that immunity inflammation preceding vascular remodeling is a cause of the disease, instead of a consequence [44]. Varying degrees of perivascular inflammatory infiltrates with T- and B-lymphocytes and macrophages were present in pulmonary hypertension, similar to IgG4-RD. Chemokines and cytokines present in IgG4-RD, such as IFN-γ, IL-4, IL-10, and IL-13, were also found to be increased in serum levels of pulmonary arterial hypertension patients. Many clinical and experimental data corroborate the link between interferon exposure and the risk of developing pulmonary arterial hypertension [45]; IL-4 and IL-13 were found to play a role in pathogenesis of pulmonary hypertension, while IL-10 was reported to be protective [46-48]. TGF-β also plays a pathogenetic role in the disease, and TGF-β ligand blockade could improve survival in multiple experimental pulmonary hypertension models [49-51]. Previous animal and clinical studies indicate that IL-6 is important in pulmonary arterial hypertension, and its role in pathogenesis of pulmonary arterial hypertension is via the IL-6/IL-21 axis [52]. Although high serum IL-6 is common in hyper-IL-6 syndromes, including rheumatoid arthritis, Sjogren’s syndrome, systemic lupus erythematosus, and mixed connective tissue disease, IgG4-RD could also have increased serum IL-6 levels. An IL-6 receptor blockade in rheumatoid arthritis patients could thus selectively reduce IgG4 autoantibody presence [53]. However, these mutual immunity and inflammation cytokine/chemokine patterns were published separately; how and to what extent they are related to pulmonary arterial hypertension needs further investigation.

**Histopathology**

Characteristic findings of lymphoplasmacytic infiltrate, storiform fibrosis, and obliterator phlebitis heighten diagnostic specificity, but clinicopathologic correlation is always essential. The IgG4-RD pathology consensus statement endorsed 3-tiered diagnostic terminology for pathological diagnosis as [1] histologically highly suggestive, [2] histologically probable, and [3] histologically insufficient evidence. In most instances, two of the three major pathological features is required for confident pathological diagnosis. Patients with diagnoses of histologically probable IgG4-RD require additional evidence, such as serum IgG > 135 mg/dl, or other organ involvement demonstrated by radiological or pathological examination. In organs such as lung, storiform fibrosis or obliterator phlebitis may be inconspicuous or absent. In the past, a rare case of obliterator phlebitis associated with pulmonary hypertension was also published, and obliterator arteries is often seen in pulmonary manifestations, particularly solid lesions. IgG4+/IgG ratio of >40% is mandatory for histological diagnosis of IgG4-RD, and cutoff values of IgG4+ plasma cells/HPF for aorta or pulmonary vessel within mediastinum is >50/HPF. This value is different for lung tissues of surgical specimen (>50/HPF) or needle biopsy (>20/HPF) [29,38]. In all reported IgG4 patients with pulmonary vascular involvement, only three underwent lung biopsy, and one underwent pulmonary artery
biopsy. Proximal and distal pulmonary vascular involvements are not exactly the same, although both can induce vessel stenosis or aneurysm; stenosis is more common in proximal pulmonary circulation involvement. Because IgG4-RD is a multi-organ involved disease, there is a greater probability 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 unnecessary to confirm the diagnosis with a lung biopsy. Positive response to steroid therapy adds extra evidence to the diagnosis.

**Laboratory Test**

Elevated serum IgG4 levels >135 mg/dl can aid in making a diagnosis if the patient is histopathologically probable. This cut-off value demonstrated a sensitivity of 97.0% and a specificity of 79.6% [54], and about 30%-50% IgG4-RD patients have normal serum IgG4 levels [55]. Elevated serum IgG4 levels can also be associated with Castleman's disease, recurrent infections, autoimmune diseases, and carcinoma. Serum plasmablasts/plasma cells have also been found to be potential biomarkers independent of serum IgG4 levels [32,56]. Many IgG4-RD patients with vascular involvement have been reported, but biomarkers predicting the incidence and prognosis of such patients require additional study, especially for patients with pulmonary vascular involvement.

**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 [57]. 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 present aortitis, retroperitoneal carcinoma. Serum plasmablasts/plasma cells have also been found to be potential biomarkers independent of serum IgG4 levels [32,56]. Many IgG4-RD patients with vascular involvement have been reported, but biomarkers predicting the incidence and prognosis of such patients require additional study, especially for patients with pulmonary vascular involvement.

**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 by pulmonary embolism and pulmonary hypertension. IgG4-RD pulmonary hypertension may be classified to all five clinical groups; 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. Nearly all cases had more than one affected organ, with increased serum IgG4 levels. PET/CT is helpful to identify affected organs and determine candidate biopsy sites, and characteristic imaging with other affected superficial organ biopsies, in addition to increased serum IgG4 levels, are practical for diagnosis. However, 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.

**Acknowledgements**

This work was supported by Department of Education of Zhejiang Province [Grant numbers Y201226271] and Health and Family Planning Commission of Zhejiang Province [Grant numbers 2016150952].
References


51. Elevated levels of plasma transforming growth factor-ß1 in idiopathic and heritable pulmonary arterial hypertension., (2016).


