Etiology of IgG4-Related Pulmonary Hypertension

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Dear Editor,

IgG4-related disease (IgG4-RD) affects every single organ of the body [1–6], but little is known about pulmonary hypertension associated with IgG4-RD. Appropriate treatment is generally crucial for the prevention of irreversible organ damage in IgG4-RD [7–10], but especially with pulmonary hypertension because it is frequently serious and fatal.

We conducted a literature review of IgG4-related pulmonary hypertension and identified a total of 7 patients [1, 11–15], who satisfied the IgG4-RD comprehensive diagnostic criteria [16] (Fig. 1a). Their age ranged from 22 to 69 years. Four were male and 3 were female. All patients presented with dyspnea. Pulmonary hypertension was assessed by right heart catheterization in 5 patients and by echocardiography in 2 patients (Fig. 1a). Remarkably, those cases could be classified into two types based on imaging possibly related to causal etiology: (i) “IgG4-related fibrosing mediastinitis type” or (ii) “IgG4-related lung disease type” as shown in Figure 1a.

IgG4-related fibrosing mediastinitis lesion was determined by tumefactive mediastinal lesions in the images. All 5 patients with IgG4-related fibrosing mediastinitis showed no evidence of IgG4-related lung disease lesions (Fig. 1a). On the other hand, the 2 patients with IgG4-related lung dis-

ease did not show any evidence of IgG4-related mediastinitis lesions as well as pulmonary large-vessel compression in the images (Fig. 1a). This suggests that there are 2 different etiologies of IgG4-related pulmonary hypertension (Fig. 1b). In the IgG4-related fibrosing mediastinitis type, the proximal medium-to-large-sized pulmonary artery was mechanically compressed from the outside by tumefactive mass lesions within the mediastinal space. In the IgG4-related lung disease type, the intense lymphoplasmacytic infiltration secondary to obliterative phlebitis or obliterative arteritis in the lungs occupied distal pulmonary microvessels as a causal etiology of pulmonary hypertension [1].

While IgG4-related fibrosing mediastinitis has recently been proposed as a possible etiology of idiopathic fibrosing mediastinitis [5], fibrosing mediastinitis itself is classically known as a cause of pulmonary hypertension by compressing the medium-to-large-sized proximal pulmonary artery [17]. IgG4-related fibrosing mediastinitis shows elevated levels of serum C-reactive protein without multi-organ involvement [4], in line with the cases with pulmonary hypertension of “IgG4-related fibrosing mediastinitis type” (Fig. 1a). On the other hand, IgG4-related lung disease causes obliterative vasculitis of microvessels, which

can lead to pulmonary hypertension. A study examined the tissue sections from patients with IgG4-related lung disease and revealed the frequent presence of obliterative vasculitis lesions in the lungs [18].

IgG4-related lung disease frequently presents with multiple organ involvements and normal serum C-reactive protein, which is consistent with the IgG4-related lung disease type in our present study (Fig. 1a). Moreover, we need to note that there is the possibility of another etiology of pulmonary hypertension which has yet to be reported; pulmonary vasculitis due to IgG4-RD. Pulmonary vasculitis has been reported to cause pulmonary hypertension in other vasculitic diseases [19, 20], and IgG4-RD causes systemic vasculitis [6]. The reason for no previous reports with this etiology might be the difficulty in obtaining specimens of pulmonary vessels for histopathological confirmation.

Glucocorticoid treatment is usually effective for patients with IgG4-RD [2]. Importantly, all 7 patients with IgG4-related pulmonary hypertension responded well to immunosuppressive treatments including glucocorticoid without pulmonary vasodilators such as prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors (Fig. 1a). Therefore, we need to be attentive to clinical

Authors	Age, years	Sex	Symptoms	Mean pulmonary artery pressure, mm Hg	Image findings	Other organ involvements	Serum IgG4, mg/dL	Serum C-reactive protein, mg/dL	Treatments	Outcome	Type of causal etiology of pulmonary hypertension
Fukihara et al.	45	Male	Dyspnoea	42	Diffuse bilateral centrilobular nodules and prominent peripheral pulmonary vascular markings in lungs	Dacryoadenitis, sinusitis, lymphadenopathy	1,500	Normal	Prednisolone and cyclosporine	Improved	IgG4-related lung disease (biopsy-proven)
Ishida et al.	22	Female	Dyspnoea	40	Consolidation, solid nodules and irregular thickening of broncho-vascular bundles and interlobular septa in lungs	Dacryoadenitis, sialadenitis, lymphadenopathy, gastrointestinal tract	3,230	Normal	Prednisolone	Improved	IgG4-related lung disease
Tan et al.	60	Female	Dyspnoea	Not applicable (estimated pulmonary systolic pressure; 103 mm Hg)	Tumefactive mediastinal lesions at the pulmonary artery trunk	None	158	Elevated	Prednisolone and surgery	Improved	IgG4-related fibrosing mediastinitis (biopsy-proven)
Deng et al.	47	Male	Dyspnoea	48	Tumefactive mediastinal lesions at the pulmonary artery trunk	None	221.4	Not applicable	Prednisolone and rituximab	Improved	IgG4-related fibrosing mediastinitis (biopsy-proven)
Deng et al.	32	Male	Dyspnoea	59	Tumefactive mediastinal lesions at the pulmonary artery trunk	None	Elevated	Not applicable	Prednisolone and cyclophosphamide	Improved	IgG4-related fibrosing mediastinitis (biopsy-proven)
Zhou et al.	54	Male	Dyspnoea	30	Tumefactive mediastinal lesions at the left pulmonary artery trunk	Periaortitis	644	Elevated	Prednisolone	Improved	IgG4-related fibrosing mediastinitis (biopsy-proven)
Perugino et al.	69	Female	Dyspnoea	Not applicable (estimated pulmonary systolic pressure; 44 mm Hg)	Tumefactive mediastinal lesions at the left pulmonary artery trunk	Periaortitis and laryngeal mass	471	Elevated	Rituximab	Improved	IgG4-related fibrosing mediastinitis

a

b

Fig. 1. a. Summary of the reported cases of IgG4-related pulmonary hypertension. **b.** Model for the two possible etiologies of IgG4-related pulmonary hypertension.

manifestations of IgG4-related pulmonary hypertension to avoid a delay in diagnosis and immunosuppressive treatment initiation for this serious but treatable organ involvement. Echocardiography, right heart catheterization, and biopsy should be con-

sidered in cases of unexplained dyspnea complicated with IgG4-related mediastinitis or lung disease.

IgG4-RD frequently relapses during glucocorticoid tapering [21], and long-term outcome remains unclear particularly

in IgG4-related pulmonary hypertension. Further accumulations of cases and longitudinal studies are needed for a better understanding of the disease and for establishing treatment strategies for patients with IgG4-related pulmonary hypertension.

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