Abstract
Paragonimiasis is a parasitic pleuropulmonary infection caused by eating raw crustaceans and wild boar meat and this infection is endemic in Asia. We herein report two cases of pulmonary *Paragonimus westermani* infection associated with elevated levels of serum immunoglobulin (Ig) G4 and dense infiltration of IgG4-positive plasma cells in the lung lesions. Treatment with praziquantel resolved the pulmonary lesions and decreased the serum levels of IgG4. IgG4-related disease is a systemic disease occasionally involving the lungs and leads to increased serum levels of IgG4. Our findings suggest that *P. westermani* infection requires a differential diagnosis from IgG4-related diseases and the serum IgG4 level may be a potentially useful marker of *P. westermani* infection.

Introduction
Paragonimiasis is an endemic foodborne trematode infection by *Paragonimus westermani* in Asia, including Japan, which results from the consumption of raw crustaceans and wild boar meat [1]. As the number of immigrants and travelers from endemic areas increase worldwide, more cases of *P. westermani* in non-endemic areas have also been reported. We herein report two cases of paragonimiasis with elevated serum immunoglobulin (Ig) G4 levels and the infiltration of IgG4-positive plasma cells in the pulmonary lesions. These findings suggest that paragonimiasis should therefore be included in the differential diagnosis of IgG4-related diseases.

Case Report

**Case 1**
A 49-year-old man without any complaints demonstrated consolidation in the right upper lobe on a chest X-ray and computed tomography (CT) imaging (Fig. 1A) and the consolidation was spontaneously resolved. Two years later, he developed hemoptysis and the chest CT imaging showed a new solitary pulmonary nodule in the right middle lobe (Fig. 1B). We then performed a transbronchial biopsy of the lesion. The pathology of the lesion showed *Paragonimus ova* (Fig. 1D) infiltrated by IgG4-positive plasma cells (Fig. 1E and F). The tissue eosinophils were not prominent. The serum level of IgG4 was elevated (201 mg/dL; normal range: 4.8–105 mg/dL), but those of IgE was not elevated (206 U/I). The patient’s history included previous consumption of raw wild boar meat and a high titer of serum IgG for *P. westermani* was detected by an enzyme-linked immunosorbent assay (ELISA). According to these results, the patient was diagnosed with paragonimiasis. Praziquantel treatment improved his symptoms and the pulmonary shadow resolved (Fig. 1C); 4 months after the treatment, the serum level of IgG4 decreased to within the normal range (75.6 mg/dL) (Table 1).

**Case 2**
A 56-year-old woman developed hemoptysis. A cavitary lesion in the left upper lobe was found by chest CT imaging. Bronchoscopy did not indicate any diagnostic findings and the shadow spontaneously shrunk after 3 months. Ten months later, the CT imaging revealed a new
cavitary lesion in the left lower lobe. The pathology of a transbronchial biopsy specimen from the lesion showed inflammation with an increased number of plasma cells. The tissue eosinophils were not prominent. Although *Paragonimus* ova were not detected in the tissue, a high titer of serum IgG for *P. westermani* was detected via ELISA. According to these findings and her repeated history of cooking raw boar meat, the patient was diagnosed with paragonimiasis. Elevated serum levels of IgG4 and IgE were detected (374 mg/dL and 2895 U/I) and the majority of plasma cells infiltrating the lesion were IgG4-positive. Praziquantel treatment improved the pulmonary shadow and decreased the serum level of IgG4 to 114 mg/dL 11 months after the treatment (Table 1).

**Discussion**

We herein describe two cases of pulmonary paragonimiasis with increased serum levels of IgG4 and infiltration of IgG4-positive plasma cells in the lesions. These cases indicated that making a differential diagnosis of pulmonary paragonimiasis and IgG4-related disease is difficult in patients with pulmonary nodules or infiltration and increased serum levels of IgG4. To the best of our
knowledge, this is the first report to suggest the usefulness of serum IgG4 levels as a diagnostic and treatment marker of *P. westermani* infections.

*Paragonimiasis* is caused by eating raw or undercooked crustaceans (as a second intermediate host) or wild boar meat (as a paratenic host) [1]. The metacercariae of *P. westermani* penetrates the duodenum and reaches the pleural spaces and lungs via the diaphragm. As a result, various symptoms and radiological findings occur, such as abdominal pain, fever, hemosputum, pleural effusion, pulmonary nodules, and infiltrations.

IgG4-related disease is a recently recognized, novel fibroinflammatory disease which affects various organs, such as the pancreas, periorbital tissues, salivary glands, kidneys, and lungs. This disease is characterized by elevated serum IgG4 levels and tumefactive lesions with dense IgG4-positive plasma cells infiltrations [2, 3]. Because the pleuropulmonary lesions in IgG4-related disease are associated with a variety of radiologic abnormalities [4], *P. westermani* infections and IgG4-related disease are occasionally indistinguishable by the radiological findings alone. Without carefully noting the patients’ previous histories, including eating habits, the present cases may have been diagnosed as an IgG4-related disease.

It is well known that helminth infections promote Th2 immune responses which in turn elevate both the IgE and IgG4 levels including paragonimiasis [5]. In the other helminth infections, schistosomiasis and filariasis, elevated serum IgG4 levels have also been reported. IgG4 has been considered to be a blocking antibody due to its ability to compete with IgE antibodies. The balance of immune responses in helminth parasite infections could be changed by pathophysiological conditions. For example, in silent or chronic helminth infections, predominant Th2 immune response was reported. In the present cases, the lack of eosinophilia and elevated IgG4 levels probably represent predominant Th2 immune response and chronic infectious conditions.

However, the roles of IgG4 in *P. westermani* infection have not yet been fully elucidated and the serum levels of IgG4 after treatment have not yet been examined. The present cases demonstrated that treatment with praziquantel improved the pulmonary lesion infiltrated with IgG4-positive plasma cells and decreased the serum levels of IgG4, thus suggesting serum IgG4 to be a potentially useful marker of *P. westermani* infection. However, further investigation into the precise roles of IgG4 in *P. westermani* infection is necessary.

**Disclosure Statements**

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

**References**

1. Mukae H, Taniguchi H, Matsumoto N, et al. 2001. Clinicoradiologic features of pleuropulmonary *Paragonimus westermani* on Kyusyu island, Japan. Chest 120:514–520.
2. Stone JH, Zen Y, and Deshpande V. 2012. IgG4-related disease. N. Engl. J. Med. 366:539–551.
3. Umehara H, Okazaki K, Masaki Y, et al. 2012. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod. Rheumatol. 22:1–14.
4. Matsui S, Hebisawa A, Sakai F, et al. 2013. Immunoglobulin G4-related lung disease: clinicoradiological and pathological features. Respirology 18:480–487.
5. Garraud O, Perraut R, Riveau G, et al. 2003. Class and subclass selection in parasite-specific antibody responses. Trends Parasitol. 19:300–304.