

[CASE REPORT]

Immunoglobulin G4-related Pleuritis Complicated with Minimal Change Disease

Yoshiko Mizushina^{1,2}, Jun Shiihara¹, Motoko Nomura¹, Hiromitsu Ohta¹,
Fumiyoshi Ohyanagi¹, Yoshiyuki Morishita³, Hiroyoshi Tsubochi^{4,5},
Akira Tanaka⁶ and Yasuhiro Yamaguchi¹

Abstract:

A 70-year-old woman with bilateral pleural effusion and respiratory failure was admitted to our hospital. Nephrotic syndrome due to minimal change disease had been diagnosed four months before admission. Because blood tests and a pleural fluid analysis did not reveal the etiology of her condition, we performed a video-assisted thoracoscopic pleural biopsy. No specific thoracoscopic findings were noted. The pathological findings revealed an increase in immunoglobulin G4 (IgG4)-positive cells; IgG4-related pleuritis was diagnosed. Her pleuritis improved with oral corticosteroid therapy. A further investigation was performed on previous kidney samples; however, the etiology of the nephrotic syndrome was not IgG4-related disease but minimal change disease.

Key words: IgG4-related disease, pleuritis, minimal change disease, video-assisted surgical pleural biopsy

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Introduction

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is characterized by the infiltration of IgG4-positive plasma cells in tissues and the elevation of the IgG4 serum level. IgG4-positive cell infiltration occurs in various organs, including the pancreas, lungs, salivary glands, and kidneys (1).

The incidence of intrathoracic lesions has been reported to be 17.6-23.4% among patients with IgG4-RD (1-3). IgG4-related pleuritis, an IgG4-related respiratory disease, is characterized by uni- or bilateral pleural effusion containing lymphocytes and IgG4-positive plasma cells (1, 4). However, our understanding of IgG4-related-pleuritis is limited; in addition, there is little awareness that IgG4-related pleuritis is a cause of pleural effusion.

We herein report a case of IgG4-related pleuritis that was diagnosed by a video-assisted thoracoscopic (VATS) right

pleural biopsy four months after the diagnosis of minimal change disease.

Case Report

A 70-year-old woman presented with a persistent cough from September 2018. The cough improved with medication prescribed by her family doctor; further details were unknown. In March 2019, she was admitted to the Department of Nephrology in our hospital for the investigation of the etiology of proteinuria. She had hand edema, general fatigue, and appetite loss, which had appeared two weeks before the admission. The patient's total urinary protein level was 5,012 mg/day; in addition, she showed hypoproteinemia and hypoalbuminemia (serum total protein level 5.9 g/dL and serum albumin level 1.2 g/dL).

A renal biopsy was performed to investigate the pathology of her kidney disease. A light microscopic analysis

¹Division of Pulmonary Medicine, Saitama Medical Center, Jichi Medical University, Japan, ²Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, Japan, ³Division of Nephrology, Saitama Medical Center, Jichi Medical University, Japan, ⁴Division of Thoracic Surgery, Saitama Medical Center, Jichi Medical University, Japan, ⁵Department of Thoracic Surgery, Jichi Medical University, Japan and ⁶Department of Pathology, Saitama Medical Center, Jichi Medical University, Japan

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Correspondence to Dr. Yoshiko Mizushina, mizushina@jichi.ac.jp



Figure 1. Chest X-ray findings on admission. Chest X-ray revealed substantial bilateral pleural effusion.

showed no abnormality in the glomerulus, with mild infiltration of leukocytes in the tubulointerstitial space and moderate intimal thickening of the small artery. An immunofluorescence analysis revealed no deposition of immunoglobulins (i.e. IgA, IgG, and IgM), complements (i.e. C3c, C1q, and C4), and fibrinogens in the glomerulus. An electron microscopic analysis showed global foot process effacement of podocytes, with no significant abnormality of the glomerular basement membrane or electron dense-deposits. In addition, her selectivity index was high at 0.14. Based on her clinical history and the abovementioned findings, we diagnosed her with minimal change nephrotic syndrome.

Her urinary protein level decreased (total urinary protein level 100 mg/day) without medication, and she was discharged. She underwent periodic examinations, and the severity of her proteinuria fluctuated from mild to moderate (urinary protein/creatinine ratio: 0.15-1.09 g/gCr). Leg edema was not observed.

In July 2019, she had dyspnea and was diagnosed with bilateral pleural effusion at another hospital. She was admitted to that hospital and underwent bilateral thoracic drainage. Blood and the pleural effusion examinations did not reveal the etiology; her bilateral chest drains were thus removed, and she was discharged. As the etiology of her condition was still unknown, she visited our department first in August 2019, one week after the chest drain removal. Although further examinations were scheduled, she developed dyspnea and leg edema three days after her initial visit. She was admitted on an emergency basis four days later - a week after her first visit - because of substantial bilateral pleural effusion, dyspnea exacerbation, and respiratory failure.

She never smoked but drank occasionally. Her occupational history was as a primary school teacher. She had undergone surgery for a pancreatic cyst at 40 years old, but no other anamnesis was reported. There was no particular family history, including cancer, tuberculosis, or collagen disease.

Her vital signs were as follows: body temperature, 36.2°C; pulse rate, 93 bpm; respiratory rate, 20/min; and oxygen saturation 90% under inhalation of 6 L/min mask oxygen. Coarse crackles and wheezes were auscultated in the bilateral lung fields. There was pitting edema in both legs.

Chest X-ray showed extensive bilateral pleural effusion (Fig. 1). Chest computed tomography (CT) showed bronchial wall and interlobular septum thickening with bilateral pleural effusion (Fig. 2). No other findings were noted, including lymph nodes or intra-abdominal organs. The bilateral kidneys were also normal in size (right kidney: 10.9 cm; left kidney: 10.2 cm).

Blood test results showed hypoproteinemia, hypoalbuminemia, and an elevated C-reactive protein level. The IgE serum level was elevated, whereas the total IgG serum level was within normal limits (Table 1). Urinary test results showed mild proteinuria, although it did not meet the criteria for nephrotic syndrome (total urinary protein level 125 mg/day), and the urinary protein/creatinine ratio was 0.31 g/gCr (Table 1). The pleural effusion was exudative and had an increased cell component, predominantly lymphocytes, although no significant findings were noted in cultures or cytology (Table 2).

Bilateral thoracic drainage was performed, but the respiratory failure and wheezes did not improve. Further investigation was needed; therefore, we performed a VATS right pleural biopsy. No particular abnormalities were observed by thoracoscopy. Pathological findings showed moderate small lymphocytic infiltration in the pleura. There were lymphoid follicles. Some plasma cells were observed without storiform fibrosis or obliterative phlebitis. There were no findings suggesting cancer or malignant lymphoma. A large amount of CD138-positive plasma cells was observed, and the IgG4+/IgG+ ratio was >50%. The number of IgG4-positive cells/high-power field (hpf) was 50-60. No evidence of *Mycobacterium tuberculosis* infection, such as caseating granuloma, was present (Fig. 3).

Because the pathological findings suggested IgG4-RD, we examined the IgG4 levels in the serum and pleural effusion and found them to be elevated in both [serum IgG4 level 270 mg/dL; pleural effusion IgG4 level 169 mg/dL (right) and 164 mg/dL (left)].

IgG4-related pleuritis was diagnosed, and oral corticosteroid treatment (30 mg per day of prednisolone) was started, after which the pleural effusion discharge from the thoracic drains gradually decreased until the bilateral drains were removed a week after starting the corticosteroid treatment. The clinical findings of leg edema, wheeze, and respiratory failure as well as the radiological findings improved (Fig. 4). She also had a severe cough before corticosteroid administration. Although oral corticosteroids improved the cough as well, night-time cough persisted. An inhaled corticosteroid with a long-acting β agonist was added, and subsequently, the cough improved. The patient was discharged 18 days after starting the corticosteroid treatment.

Although additional pathological examinations were per-

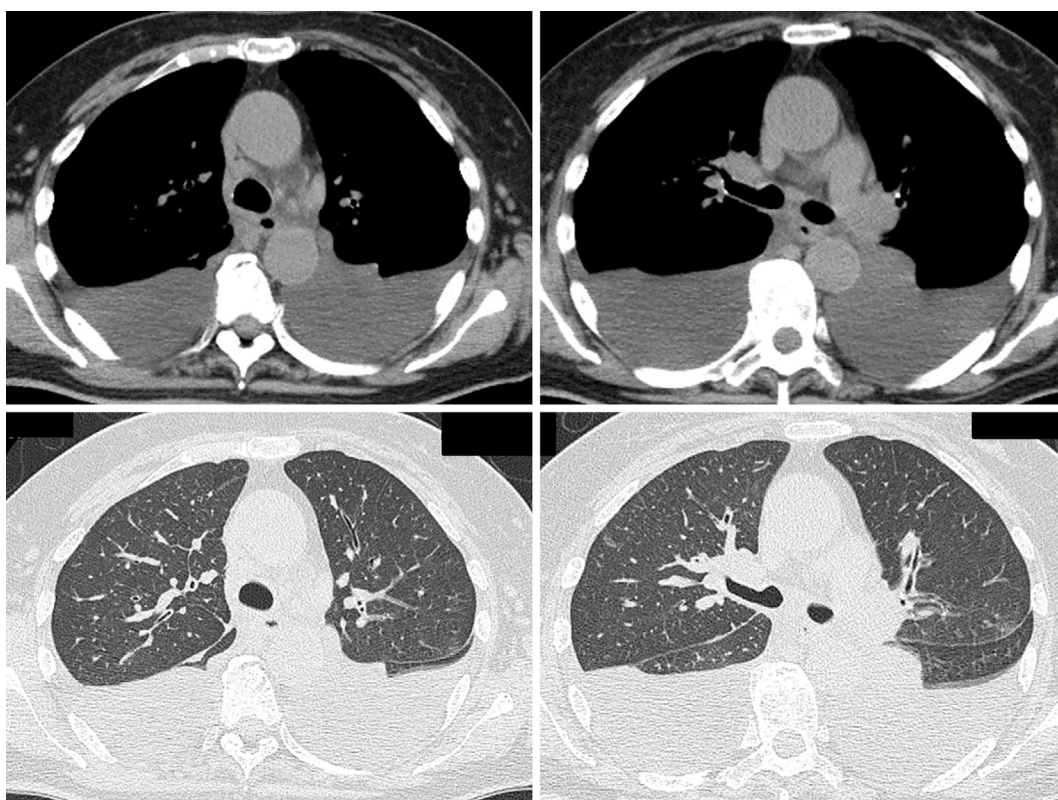


Figure 2. Chest computed tomography (CT) findings on admission. Chest CT revealed bronchial wall and interlobular septum thickening with bilateral pleural effusion. No other findings were identified, including in the lymph nodes or intra-abdominal organs.

Table 1.

Blood test				Urinary test			
WBC	7,940 $10^3/\mu\text{L}$	CRP	6.51 mg/dL	CEA	1.7 ng/mL	Qualitative analysis	
Neutrophil	64 %	LDH	167 U/L	CYFRA	1.6 ng/mL	Gravity	1.025
Lymphocyte	24 %	TP	5.9 g/dL	ProGRP	51.8 pg/mL	pH	5.5
Eosinophil	1 %	Albumin	2.2 g/dL	sIL2 receptor	839 U/mL	Protein	(1+)
Monocyte	7 %	BUN	22 mg/dL	Rheumatoid factor	≤ 10 IU/mL	Glucose	(-)
Basophil	1 %	Creatinine	0.52 mg/dL	ANA	Negative	Urobilinogen	(+/-)
RBC	503 $10^4/\mu\text{L}$	AST	14 U/L	Anti-dsDNA Ab	<10 U/mL	Bilirubin	(-)
Hb	14.6 g/dL	ALT	6 U/L	Anti-RNP Ab	Negative	Acetate	(1+)
Plt	51.1 $10^4/\mu\text{L}$	CPK	35 U/L	Anti-Sm Ab	Negative	RBC	(-)
		γ GTP	12 U/L	PR3-ANCA	<1.0 IU/mL	Nitrite	(-)
		Na	141 mEq/L	MPO-ANCA	<1.0 IU/mL	Urinary protein/creatinine ratio	0.31 g/gCreatinine
		K	3.9 mEq/L	CCP-Ab	<0.6 U/mL	Total urine protein	125 mg/day
		Cl	100 mEq/L	IgG	1,390 mg/dL	NAG	15.3 IU/L
		Calcium* 10.9 mg/dL		IgA	501 mg/dL	$\beta 2$ -microglobulin	3,041 $\mu\text{g/L}$
		(*corrected by Alb)		IgM	41 mg/dL		
				IgE	8,600 IU/mL		
				Procalcitonin	0.04 ng/mL		

RBC: red blood cell, Plt: platelet, CRP: C-reactive protein, LDH: lactate dehydrogenase, TP: total protein, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CPK: creatine phosphokinase, γ GTP: γ -glutamyltranspeptidase, Na: sodium, K: potassium, Cl: chloride, CEA: carcinoembryonic antigen, CYFRA: cytokeratin 19 fragment, ProGRP: pro-gastrin releasing peptide, sIL2 receptor: soluble interleukin 2 receptor, ANA: anti-nuclear antibody, anti-dsDNA Ab: anti-double strand DNA antibody, anti-RNP Ab: anti-U1 ribonucleoprotein antibody, anti-Sm Ab: anti-Smith antibody, PR3-ANCA: proteinase-3-anti-neutrophil cytoplasmic antibodies, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibodies, NAG: N-acetyl- β -D-glucosaminidase

Table 2.

Pleural effusion		lt.	
rt.(post-operation)			
Albumin	1.3 g/dL	Albumin	2.1 g/dL
LDH	244 U/L	LDH	143 U/L
Adenosine deaminase	17.9 IU/L	Adenosine deaminase	25.4 IU/L
Hyaluronic acid	18,500 ng/mL	Hyaluronic acid	8,630 ng/mL
TP	3.2 g/dL	TP	4.1 g/dL
Glucose	167 mg/dL	Glucose	131 mg/dL
Total cell counts	3,060 / μ L	Total cell counts	3,830 / μ L
Neutrophils	23.2 %	Neutrophils	1.0 %
Lymphocytes	46.4 %	Lymphocytes	90.6 %
Eosinophils	14.4 %	Eosinophils	2.2 %
Basophils	1.6 %	Basophils	0.2 %
Plasma cells	1.0 %	Plasma cells	3.6 %
Mesothelial cells	1.0 %	Mesothelial cells	1.0 %
Atypical lymphocytes	0.4 %	Atypical lymphocytes	1.4 %
RBC	1,420 / μ L	RBC	1,160 / μ L
Gravity	1.024	Gravity	1.029
Culture	Negative	Culture	Negative
Tbc-PCR	Negative	Tbc-PCR	Negative
MAC-PCR	Negative	MAC-PCR	Negative
Cytology	Negative	Cytology	Negative

Tbc: mycobacterium tuberculosis, MAC: mycobacterium avium complex, PCR: polymerase chain reaction

formed on the previously collected renal biopsy specimens, infiltration of very few inflammatory and only a small number of IgG4-positive cells was observed in the kidney. Therefore, the diagnosis of minimal change disease was maintained, as there were no findings suggesting IgG4-RD, such as tubulointerstitial nephritis or membranous nephropathy.

Following discharge, the corticosteroid treatment was tapered to 5 mg for 6 months, and no recurrence was observed.

Discussion

We reported a patient who developed dyspnea because of increasing bilateral pleural effusion with asthmatic symptoms in whom IgG4-related pleuritis was diagnosed by a VATS right pleural biopsy during clinical follow-up for minimal change disease. The patient's condition was diagnosed as IgG4-RD according to the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD (pleural biopsy specimen showed dense lymphocytic infiltration; IgG4+/IgG+ ratio 41-70%, IgG4-positive cells/hpf \geq 10, IgG4 serum level 2-5-times the upper limit of normal, and chest CT showing peribronchovascular and septal thickening) (5). Because her clinical signs were only bilateral pleural effusion and wheezing in addition to a normal IgG serum level, we had not placed IgG4-RD high in the list of differential diagnoses until the pathological findings of the VATS biopsy suggested

IgG4-related pleuritis. Furthermore, no significant thoracoscopic findings were noted. Therefore, a pleural biopsy should be performed even if the thoracoscopic findings are normal. A VATS biopsy is also useful for clarifying the etiology of pleural effusion and distinguishing it from tuberculous pleurisy, as previous reports have described cases of IgG4-related pleuritis in which the pleural fluid adenosine deaminase (ADA) levels were elevated, although the pleural fluid ADA was not elevated in the present case (6-8).

The present patient had developed nephrotic syndrome from minimal change disease before IgG4-RD was diagnosed. Her kidney size was normal, and proteinuria showed improvement compared with the first admission. A small amount of urinary protein had been detected persistently but had not increased since the first admission. Upon her emergency admission, we performed a detailed examination and concluded that the minimal change disease had not been exacerbated, and her leg edema was caused by systemic inflammation. Although the disease progression of minimal change disease and IgG4-related pleuritis was not parallel, she developed IgG4-related pleuritis just four months after minimal change disease was diagnosed. Therefore, we additionally examined the possibility of IgG4-RD in the renal biopsy specimens obtained when the minimal change disease was diagnosed, but the IgG4-positive cells were not increased in the kidney. However, a previous study reported a case of minimal change disease complicated with IgG4-RD (9). Although the details of the clinical condition of minimal change disease remained unclear, several T cell

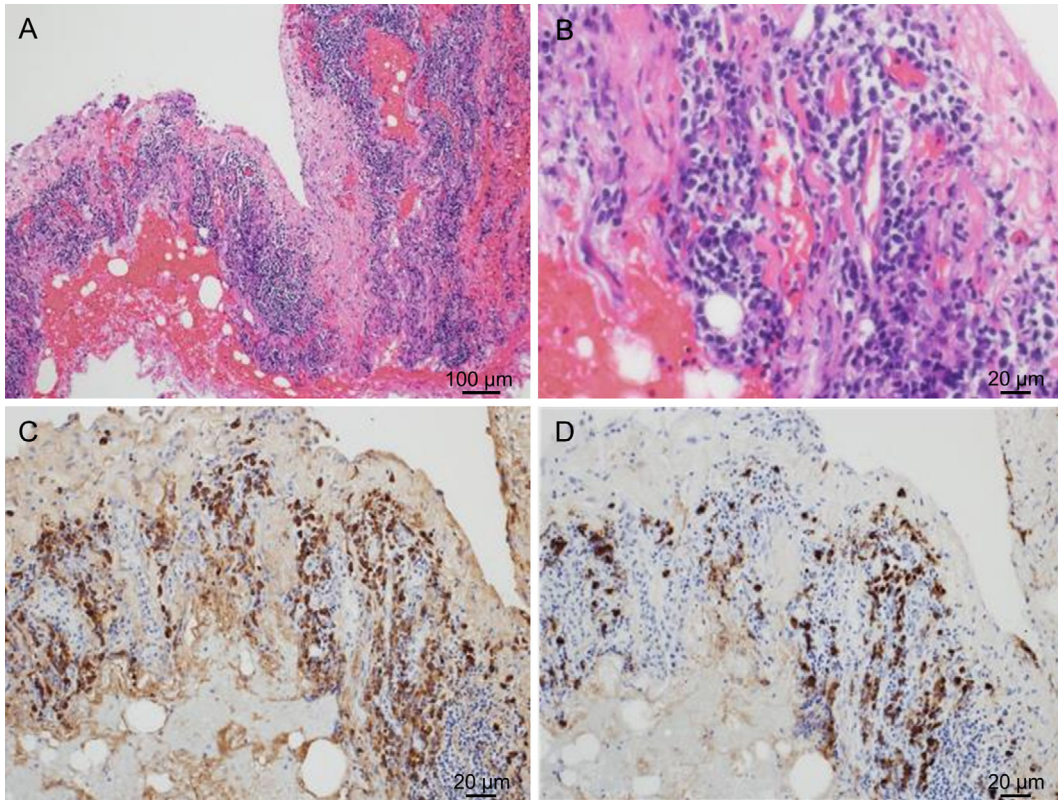


Figure 3. Pathological findings of the pleura collected by video-assisted thoracoscopic biopsy. (A, B) Pleural specimens were stained with Hematoxylin and Eosin staining; (A) low-power field and (B) high-power field. Moderate small lymphocytic infiltration was observed in the pleura. Lymphoid follicles were noted. Some plasma cells were observed without storiform fibrosis or obliterative phlebitis. There were no findings suggesting cancer or malignant lymphoma. (C, D) Pleural specimens were immunohistochemically stained with (C) anti-IgG or (D) anti-IgG4 antibody. Increased IgG4-positive cells were observed in the pleura. The IgG4+/IgG+ratio was >50%, and the number of IgG4-positive cells/high-power field was 50-60.

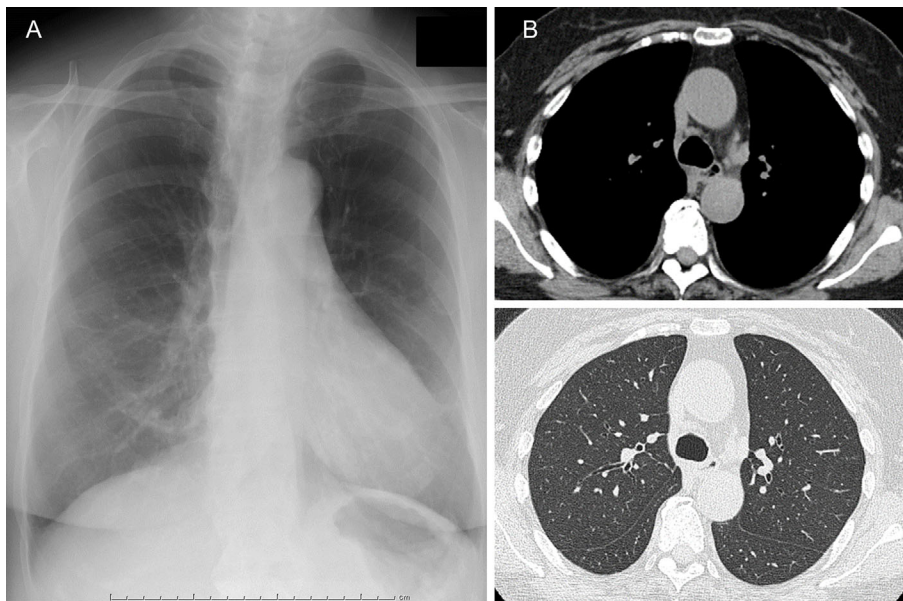


Figure 4. Chest X-ray and computed tomography (CT) following the initiation of oral corticosteroid therapy. (A) Chest X-ray. Bilateral pleural effusion disappeared. (B) Chest CT. No pleural effusion. The bronchial wall and interlobular septum thickening were improved compared with the findings on admission.

subsets are reportedly involved in minimal change disease, and B cells are related to the disease relapse in addition to T cells (10). In the pathogenesis of IgG4-RD, increasing CD4-positive cytotoxic T cells, T follicular helper cells, and B cells play critical roles (11). These reports suggest that minimal change disease did not occur incidentally with IgG4-RD, but rather both diseases developed in parallel with similar immunological backgrounds.

This patient had a persistent cough almost a year before IgG4-RD was diagnosed. In addition, at the time of admission, wheezes were auscultated in the bilateral lung fields, and bronchial wall thickening was observed on chest CT. Airway diseases are also observed in IgG4-RD as IgG4-positive plasma cells infiltrate the bronchial mucosa (1, 12, 13). Ito et al. reported three cases of bronchial asthma preceding the onset of IgG4-related pancreatitis (13). Our patient also showed preceding asthmatic symptoms, which were ameliorated by oral and inhaled corticosteroids along with a long-acting β agonist. Although bronchial asthma may have been incidentally complicated by IgG4-RD, her asthmatic symptoms may have also been associated with IgG4-RD.

The present patient had a history of a pancreatic cyst that had been resected at 40 years old. IgG4-related autoimmune pancreatitis has been reported to be occasionally complicated with a pancreatic cyst at the body and tail of the pancreas (14-16). Although we were unable to ascertain the details of the etiology of the pancreatic cyst because it was over 30 years ago, the pancreatic cyst might have developed as part of IgG4-RD.

We encountered a case of IgG4-related pleuritis with asthmatic symptoms that was diagnosed by a VATS pleural biopsy and complicated with minimal change disease. It is important to consider IgG4-RD in the differential diagnosis of pleuritis of uncertain origin. Furthermore, a VATS pleural biopsy is useful for exploring the etiology of pleuritis; a biopsy should be performed even if there are no specific thoracoscopic findings. Our case is a rare case of IgG4-RD complicated with minimal change disease; further studies involving more patients are warranted to identify the underlying mechanism.

The authors state that they have no Conflict of Interest (COI).

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