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## Case report

## A case of immunoglobulin G4-Related disease with pleural effusion, requiring exclusion of tuberculous pleurisy

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## ABSTRACT

Immunoglobulin G4 (IgG4)-related pleurisy is a rare type of IgG4-related disease. We present the case of a 69-year-old woman with left pleural effusion and elevated adenosine deaminase levels. Initially, tuberculous pleuritis was suspected; however, the bacterial cultures and polymerase chain reaction test results for tuberculosis were negative. Thoracoscopic pleural biopsy revealed dense lymphocytic infiltrates with large numbers of IgG4-positive plasma cells. The ratio of IgG4-positive to IgG-positive plasma cells exceeded 40%. The patient was diagnosed with IgG4-related disease.

## 1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is characterized by high serum immunoglobulin G4 (IgG4) levels and concentrated infiltration of IgG4-positive plasma cells into the tissues of multiple organ. Cases of IgG4-related inflammatory pseudotumors and interstitial pneumonia have been reported previously. However, few cases of IgG4-RD with pleural effusion have been reported [1].

IgG4-related pleural effusion is a rare phenotype of IgG4-RD [2]. It is commonly characterized by high levels of lymphocytes and adenosine deaminase (ADA) [3]. However, pleural effusion and elevated ADA levels are also suggestive of tuberculous pleurisy. Thus, distinguishing between IgG4-related pleural effusion and tuberculous pleurisy based on only pleural effusion findings is challenging. Moreover, a case of IgG4-RD complicated by tuberculous pleurisy has also been reported [4]. Thus, tuberculous pleurisy should be excluded before initiating corticosteroid therapy for IgG4-RD. We present a rare case of IgG4-RD, accompanied by pleural effusion and elevated ADA levels, requiring surgical biopsy of the pleura to exclude tuberculous pleurisy.

## 2. Case presentation

A 69-year-old Japanese woman was referred from a local hospital for left pleural effusion noted on a chest radiograph during a routine hospital visit. The patient had mild dyspnea and normal oxygenation without any other symptoms. She had smoked 10 cigarettes per day for 29 years but denied any occupational exposure to dust. She reported no history of allergy, tuberculous infection, or pancreatic or autoimmune disease.

On physical examination, she exhibited normal vital signs and peripheral oxygen saturation at room air. However, the left lung had

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**Table 1**  
Laboratory findings of the patient.

<CBC>		<Biochemistry>	
White blood cells	3800/ $\mu$ L	Total protein	8.9 g/dL
Neutrophil	65.6%	Albumin	4.0 g/dL
Eosinophil	5.0%	Total bilirubin	0.56 g/dL
Monocyte	6.6%	Aspartate aminotransferase	26 U/L
Lymphocyte	22.8%	Alanine aminotransferase	12 U/L
Red blood cells	$447 \times 10^4$ / $\mu$ L	Alkaline phosphatase	449 U/L
Hemoglobin	13.6 g/dL	Lactate dehydrogenase	194 U/L
Platelet	$20.9 \times 10^4$ / $\mu$ L	Blood urea nitrogen	10.9 mg/dL
		Creatinine	0.63 mg/dL
<Serology>		<Tumor marker>	
C-reactive protein	0.44 mg/dL	CEA	2.8 ng/mL
Mycobacterium avium complex	negative	CA19-9	6.9 U/mL
Rheumatoid factor (qualitative test)	negative	SCC	1.2 ng/mL
Anti-citrullinated protein antibody	0.6 U/mL	CYFRA21-1	3.6 ng/mL
IgG	3065 mg/dL	ProGRP	33 pg/mL
IgG4	724 mg/dL	NSE	10.65 ng/mL
IgA	290 mg/dL		
IgM	60 mg/dL		
IgE	5309 IU/mL		
C3	102 mg/dL		
C4	17 mg/dL		
CH50	48 U/mL		
Antinuclear antibody	$\times 40$		
Interferon-gamma release test	negative		

Abbreviations: Ig, immunoglobulin; CH50, hemolytic complement 50; C4, complement component 4; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; SCC, squamous cell carcinoma antigen; CYFRA21-1, cytokeratin fraction 21-1; ProGRP, progastrin-releasing peptide; NSE, neuron-specific enolase; CBC, complete blood count.

**Fig. 1.** A chest radiograph revealing left pleural effusion.**Table 2**  
Thoracentesis findings of the patient.

<Cell count>		<Biochemistry>	
White blood cells	9500/ $\mu$ L	Total protein	6.1 g/dL
Neutrophil	1.30%	Glucose	114 mg/dL
Lymphocyte	76.70%	Lactate dehydrogenase	138 U/L
Eosinophil	1.30%	Adenosine deaminase	69.7 U/L
Macrophages	20.70%	CEA	2.4 ng/mL
		CYFRA21-1	12.6 ng/mL
<Microbiological test>		Hyaluronate	20,100 ng/mL
Smear	negative	Rheumatoid factor	1 U/L
Culture	negative	ADA	69.7 U/L

Abbreviations: CEA, carcinoembryonic antigen; CYFRA21-1, Cytokeratin fraction 21-1; ADA, adenosine deaminase.

decreased lung sounds on auscultation. Laboratory testing (Table 1) revealed a white blood cell count of 3800/ $\mu$ L with 65.5% polymorphonuclear leukocytes and 5.0% eosinophils. Chest radiography revealed moderate left pleural effusion (Fig. 1). The pleural fluid was drained via thoracentesis. It exhibited findings consistent with lymphocyte-dominant exudative pleural effusion, and the ADA level was elevated to 69.7 U/L (Table 2). Tuberculous pleurisy was suspected; however, the pleural fluid bacterial cultures and polymerase chain reaction (PCR) tests for tuberculosis and nontuberculous mycobacteria, and the interferon-gamma release test yielded

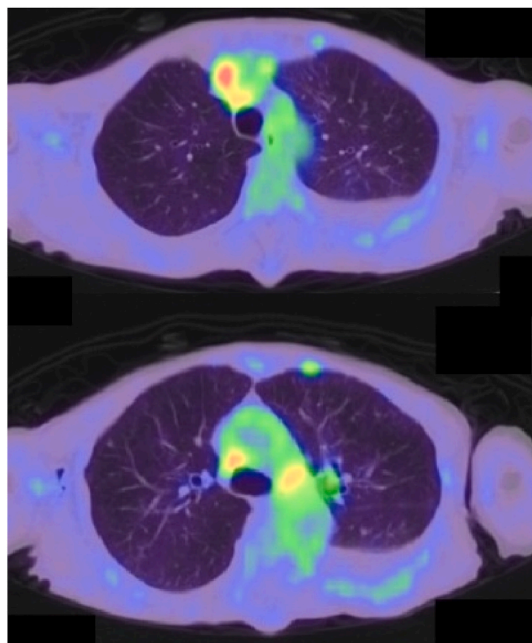


Fig. 2.  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography and computed tomography showing accumulation of FDG in the mediastinum.

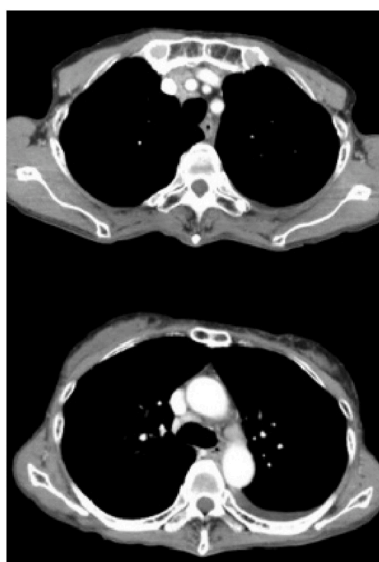
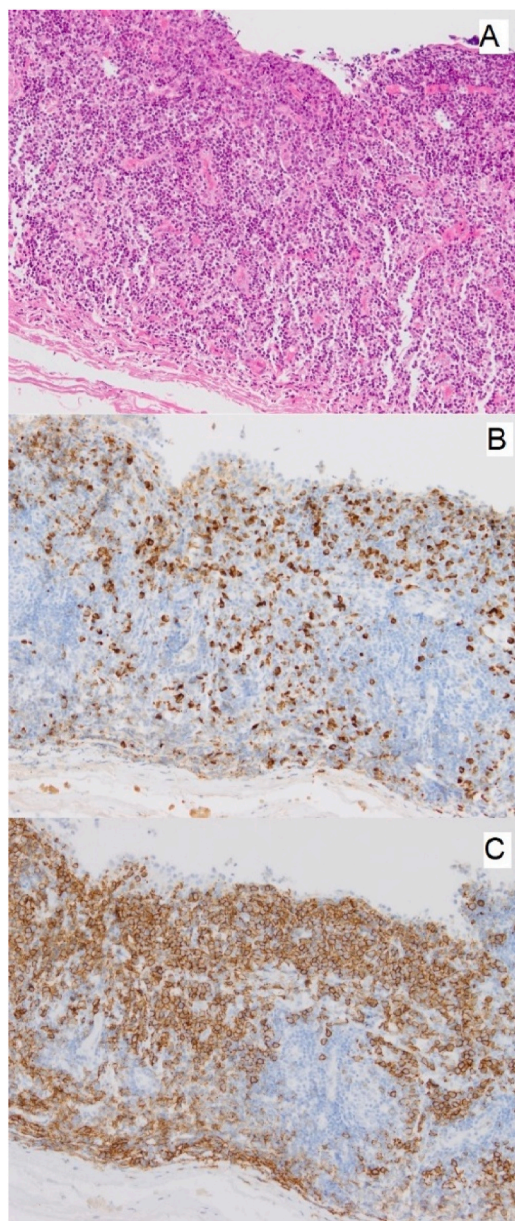


Fig. 3. Contrast-enhanced computed tomography showing the absence of lymphadenopathy or pleural thickening in the mediastinum.

negative findings. In addition, the rheumatoid factor, anti-cyclic citrullinated peptide antibodies, antinuclear antibody, and the analysis for tumor markers were negative. We excluded rheumatoid pleuritis, systemic lupus erythematosus, and carcinomatous pleurisy based on the clinical findings. Fluorodeoxyglucose (FDG) positron emission tomography imaging revealed FDG accumulation in the mediastinal and cervical lymph nodes (Fig. 2). Neither lymphadenopathy nor pleural thickening was detected on contrast-enhanced computed tomography of the neck to the pelvis (Fig. 3).

The culture positivity rate of the pleural fluid in tuberculous pleurisy is low. Based on the clinical findings, IgG4-RD and tuberculous pleurisy were suspected. However, distinguishing between IgG4-RD and tuberculous pleurisy is challenging since both the diseases are characterized by pleural effusion and high ADA levels. We ascertained that tissue diagnosis for definitive diagnosis was warranted for both tuberculous pleurisy and IgG4-related pleurisy; thus, thoracoscopy was conducted. The histological analysis revealed dense lymphocytic infiltrates and mild eosinophilic infiltrates with no malignancy or granuloma (Fig. 4A). Additional blood tests revealed a serum immunoglobulin G (IgG) level of 3065 mg/dL, IgG4 of 724 mg/dL, and serum immunoglobulin E level of 5309



**Fig. 4.** Histological examination of biopsy specimens from the left pleura showing lymphoplasmacytic infiltration (A): Hematoxylin-eosin (H&E) staining,  $\times 40$ ; (B): Immunohistochemical staining for immunoglobulin (Ig)G4,  $\times 40$ ; (C): immunohistochemical staining for IgG,  $\times 40$ .

mg/dL. Immunohistochemical staining revealed 286 IgG4-positive plasma cells/high-power field in the pleural membranes (Fig. 4B); the ratio of IgG4 to IgG-positive plasma cells (IgG4/IgG) was 46% (Fig. 4B and C), which met the diagnostic criteria for IgG4-RD [5]. Hence, the patient was diagnosed with IgG4-related pleural effusion [5].

She was treated with prednisolone (PSL) at 40 mg/day (0.6 mg/kg/day), which achieved complete resolution of the pleural effusion. The responsiveness to PSL further supported the diagnosis of pleurisy secondary to IgG4-RD.

### 3. Discussion

This report described a case of IgG4-related pleural effusion with elevated ADA levels. When the concentration of ADA in lymphocyte-predominant pleural effusion is high, IgG4-associated pleurisy should be suspected as well as tuberculous pleurisy. This case posed a diagnostic challenge because tuberculous pleurisy needed to be excluded. Many cases of pleural effusion due to IgG4-RD with high levels of ADA have been reported [3]. However, ADA has been commonly used as a marker for tuberculous pleural effusion [6–8]. Moreover, it was difficult to distinguish between IgG4-related pleural effusion and tuberculous pleurisy. Distinguishing between the two diseases is critical since they are managed differently. The first-line treatment for IgG4-RD is glucocorticoid therapy [9], which

exacerbates tuberculosis [10]. Thus, tuberculosis should be excluded before initiating glucocorticoid therapy for IgG4-RD.

Our patient presented with lymphocyte-dominant exudative pleural effusion and a high ADA level. Rheumatoid arthritis (RA) and tuberculous pleurisy were initially suspected. However, there were no clinical symptoms of RA, and the serological marker of RA was negative. Therefore, RA was excluded.

The exclusion of tuberculous pleuritis can be challenging. The definitive diagnosis of tuberculous pleurisy requires the detection of tuberculous bacilli in the sputum, pleural fluid, or pleural biopsy [11]. In approximately 65% of the cases, the diagnosis is confirmed via bacterial cultures and PCR tests [12,13]. However, cultures can take up to 33 days to test positive [14]. Since these tests are inconvenient, ADA has been used as a marker for tuberculous pleural effusion. In this case, the relevant tests were negative, and there was no history of exposure. Therefore, the patient was not diagnosed with tuberculous pleurisy.

The mechanism behind the association between IgG4-RD and high ADA levels is unknown. According to previous reports, high ADA levels were attributed to lymphocyte activation owing to IgG4-RD [1,4,15,16]. Another case report suggested an association between IgG4-RD and tuberculous disease [17]. The interpretation of the ADA levels in evaluating lymphocytic pleural effusion is complex. In previous studies, setting the cut-off value of ADA at 40.3 U/L yielded a sensitivity of 100% and a specificity of 93.9% for tuberculous pleuritis [18]. In a large prospective study of 410 patients, only seven patients (1.7%) had elevated ADA levels despite having lymphocytic pleural fluid [19]. Thus, elevated lymphocyte and ADA levels in the pleural fluid warrant further evaluation, including a pleural biopsy. The 2020 revised comprehensive diagnostic criteria for IgG4-RD included the pathological diagnosis for certain organs [5]. In this case, thoracoscopic pleural biopsy aided in confirming the diagnosis and excluding tuberculous pleurisy.

#### 4. Conclusion

We presented the case of a patient with IgG4-related pleural effusion and high ADA levels. Before the initiation of glucocorticoid therapy, tuberculous pleurisy should be ruled out. Thoracoscopic biopsy and tuberculous acid culture helped confirm the diagnosis.

When the concentration of ADA in lymphocyte-predominant pleural effusion is high, IgG4-associated pleurisy as well as tuberculous pleurisy should be suspected.

No other organ lesions may be present in some cases of IgG4-associated pleurisy.

#### Declaration of competing interest

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

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