【 CASE REPORT 】

Refractory IgG4-related Pleural Disease with Chylothorax: A Case Report and Literature Review

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Abstract:
  We herein report a rare case of a 66-year-old man with refractory chylothorax. Although he had been treated with moderate doses of prednisolone (PSL) on suspicion of pleuritis with Sjögren syndrome, the pleural effusion expanded after the reduction of PSL. Further workup including histopathological examinations of pleura led to the diagnosis of IgG4-RD with bilateral chylothorax without any leakage from the thoracic duct. Combination therapy with high-dose PSL plus rituximab successfully decreased the pleural effusion. This is a very rare case of IgG4-related pleuritis with chylothorax and the first report of its successful treatment with rituximab.

Key words: IgG4-related disease, pleuritis, chylothorax, rituximab

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Introduction

  Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibro-inflammatory disease characterized by serum IgG4 elevation and distinctive histopathological findings, such as lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis (1, 2). Almost all organs in the body, such as the central nervous system (CNS), lacrimal glands, salivary glands, thyroid, lungs, pancreas, biliary duct, liver, gastrointestinal tract, kidneys, prostate, retroperitoneum and lymph nodes, can be affected by IgG4-RD (3).

  While the lungs are involved in 9-18% of IgG4-RD patients (4-7), pleural involvement is observed in only 4% (4, 5). Pleural effusion is uncommon, but previous reports have shown that it is usually exudative (8).

  Chylothorax, which is characterized by milky-appearing pleural fluid with elevated triglyceride levels or the presence of chylomicrons, is caused by the extravasation of chyle into the pleural space due to obstruction or damage of a thoracic duct or its tributaries or transdiaphragmatic flow from the peritoneal cavity (9). The etiologies of chylothorax include several causes, such as trauma (surgical or non-surgical), malignancy, lymphatic disorders, infection, chylous ascites, and other miscellaneous causes (10); however, chylothorax due to IgG4-RD has almost never been reported.

  We experienced a rare case of IgG4-RD with refractory chylothorax that was successfully treated with high-dose prednisolone (PSL) and rituximab (RTX). We report this case with a review of previous case reports of IgG4-related pleuritis.

Case Report

  A 66-year-old Japanese man with a history of pollen allergy and thyroidectomy for Graves-Basedow disease was admitted to another hospital with a 2-month history of leg edema, eyelid edema, and dyspnea on exertion. Computed tomography (CT) demonstrated pleural and pericardial effusions, and a pericardiocentesis revealed the fluid as a non-specific inflammatory effusion with increased numbers of

Table 1. Laboratory Data on 2nd Admission.

Peripheral blood					Pleural effusion		
WBC	8,200 /μL	CRP	0.04 mg/dL		Cell count	810 /μL
Neut	87.7 %	ESR	15 mm/hr		poly	0 /μL
Lymp	8.7 %	Ferritin	85 ng/mL		mono	680 /μL
Mono	3.2 %	IgG	1,500 mg/dL		others	130 /μL
Eosino	0.2 %	IgG4	264 mg/dL		pH	7.5
Baso	0.2 %	IgA	226 mg/dL		specific gravity	1.016
RBC	5.05 ×10⁶/μL	IgM	70 mg/dL		TP	5.7 g/dL
Hb	15.5 g/dL	C3	109 mg/dL		Alb	3.3 g/dL
Plt	288 ×10³/μL	C4	24 mg/dL		Amy	45 U/L
		CH50	59.3 U/mL		Glu	131 mg/dL
		Cryoglobulin	negative		LDH	88 U/L
Biochemistry/Serology					T-cho	84 mg/dL
TP	7.4 g/dL	**Antibody**			TG	300 mg/dL
Alb	4.2 g/dL	ANA	negative		ADA	25.1 U/L
T-Bil	0.5 mg/dL	SS-A	3.3 U/mL		Hyaluronic Acid	6,670 ng/mL
BUN	24.2 mg/dL	SS-B	<1.0 U/mL		CEA	1.8 ng/mL
Cre	1.25 mg/dL	ds-DNA	3.8 U/mL			
UA	9.2 mg/dL	RNP	<2.0 U/mL			
Na	139.5 mEq/L	MPO-ANCA	<1.0 U/mL			
K	3.8 mEq/L	PR3-ANCA	<1.0 U/mL			
Cl	100 mEq/L					
AST	13 U/L	**Tumor marker**				
ALT	10 U/L	sIL-2R	394 U/mL			
LDH	163 U/L	CEA	1.6 ng/mL			
ALP	235 U/L	CYFRA	1.7 ng/mL			
γ-GTP	55 U/L	SCC	0.7 ng/mL			
Amy	62 U/L	proGRP	41.5 ng/mL			
CK	70 U/L					
T-cho	192 mg/dL	**Infection marker**				
HbA1c	7.0 %	procalcitonin	<0.03 ng/mL			
KL-6	193 U/mL	T-SPOT	negative			
BNP	8.0 pg/mL	GPLcore-IgA	negative			
fT3	2.9 ng/dL	CMV-Ag	negative			
fT4	1.7 ng/dL	β-D	<6.0 pg/mL			
TSH	1.67 μIU/mL					

TP: total protein, Alb: albumin, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, UA: uric acid, Amy: amylase, T-cho: total cholesterol, KL-6: Krebs von den Lungen-6, BNP: brain natriuretic peptide, fT3: free triiodothyronine, fT4: free thyroxine, TSH: thyroid-stimulating hormone, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ANA: antinuclear antibody, SS-A: anti-SS-A/Ro antibody, SS-B: anti-SS-B/La antibody, ds-DNA: anti-double-stranded DNA antibody, RNP: anti-RNP antibody, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase3-anti-neutrophil antibody, sIL-2R: soluble interleukin-2 receptor, GPLcore-IgA: glycopeptidolipid core IgA antibody, CMV-Ag: cytomegalovirus antigenemia, β-D: (1-3-)β-D-glucan, ADA: adenosine deaminase

lymphocytes without any infection. Increasing the levothyroxine dose for latent hypothyroidism and initiation of furosemide therapy did not decrease the effusion. He was transferred to our department.

At his first admission to our hospital, whole-body CT demonstrated pericardial effusion, bilateral pleural effusion, and testicular hydrocele. No swelling of the lacrimal or salivary glands nor pancreatic enlargement was observed. The right pleural effusion was exudative with a total cell count of 2,410/mm³ (lymphocytes, 75%) and neither malignant cells nor bacteria. Serum anti-SS-A/Ro antibody was slightly positive (15.4 U/mL; normal range, <10.0 U/mL) on an enzyme-linked immunosorbent assay but negative with the

double immunodiffusion method. Other autoantibodies, including anti-SS-B/La, anti-CCP, anti-dsDNA, anti-RNP, anti-Scl70, and anti-neutrophil cytoplasmic antibodies, were all negative. Sialometry showed a rate of 1.008 mL/minute (within normal range), while salivary gland scintigraphy showed a slightly decreased uptake and secretory function. A lip biopsy demonstrated grade 2 lymphocytic infiltration according to Greenspan's classification (11), with only a few IgG4-positive plasma cells. The Schirmer test and rose bengal dye staining test were positive only in the left eye. Although he did not meet the ACR 2012 classification criteria (12), we suspected Sjögren syndrome with serositis.

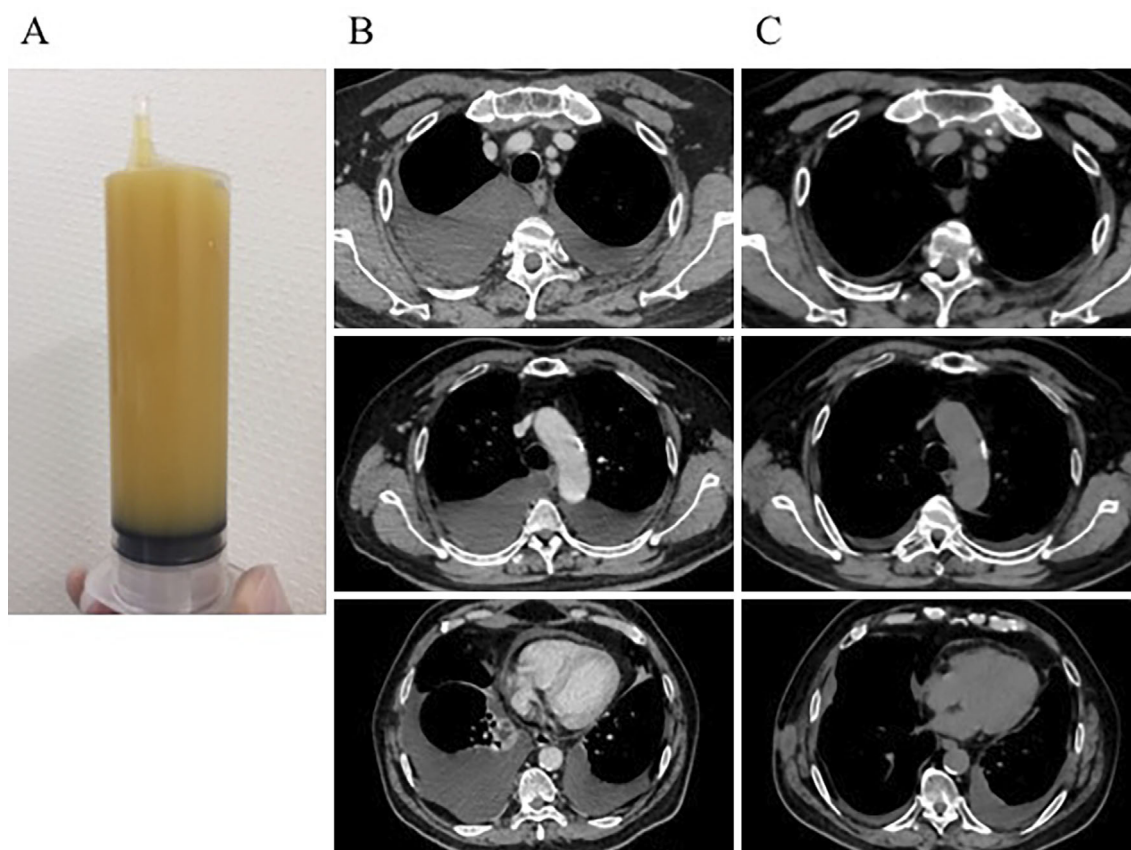PSL 40 mg/day (0.5 mg/kg) was initiated. Both the pleu-

Figure 1. Pleural effusion and CT images before and after treatment. The right pleural effusion appeared as turbid yellow fluid (A). Bilateral pleural effusion and pericardial effusion were seen at the second admission (B). After treatment with a combination of high-dose corticosteroids and rituximab, the pleural and pericardial effusion was significantly decreased (C).

ral and pericardial effusion amount decreased; however, tapering of the PSL led to exacerbation of the pleural effusion.

At his second admission, he presented with swelling of the lacrimal glands. Laboratory data are shown in Table 1. The white blood cell count in the peripheral blood was 8,200/μL (neutrophil 87.7%, lymphocyte 8.7%). Serum IgG and IgG4 levels were 1,500 mg/dL and 264 mg/dL, respectively. Autoantibodies were all negative. Serum levels of C-reactive protein (CRP), soluble interleukin-2 receptor (IL-2 R), free T3, free T4, and thyroid-stimulating hormone (TSH) were also within the normal ranges (0.04 mg/dL, 394 U/mL, 2.9 pg/mL, 1.7 ng/dL and 1.67 μIU/mL, respectively). Chest CT showed marked bilateral pleural effusion with passive atelectasis and slight pericardial effusion (Fig. 1B). Thoracentesis for the right pleural effusion (Table 1) revealed turbid yellow fluid (Fig. 1A) with a total cell count of 810/mm^3 (lymphocytes 84%), total protein 5.7 g/dL, adenosine deaminase (ADA) 25.1 U/L, total cholesterol 84 mg/dL, triglyceride 300 mg/dL, and the presence of chylomicrons, compatible with chylothorax. A cytologic examination was negative for malignancy. General bacterial and mycobacterial cultures of the pleural fluid were negative. He had no history of trauma or thoracic surgery. Lymphangiography did not show any leakage or obstruction of the thoracic duct

(Fig. 2). While thoracoscopy did not reveal any tumor, amyloid deposits, or leakage from the thoracic duct, a thoracoscopic surgical pleural biopsy demonstrated infiltration by lymphocytes and plasma cells with ectopic germinal centers under the pleural mesothelium. Approximately 50% of IgG-positive plasma cells were IgG4-positive (Fig. 3). Storiform fibrosis and obstructive phlebitis were not found in this small specimen.

We performed another lip biopsy, and the specimen showed excessive IgG4-positive plasma cell infiltration [48 cells/high-power field (HPF)] with >50% IgG4/IgG (Fig. 4). According to the diagnostic criteria of IgG4-related respiratory disease (13), the patient met the following: i) pleural involvement with CT, ii) elevated serum IgG4 level, iii) pleural biopsy findings (lymphoplasmacytic infiltration and increased IgG4 positive cells), and iv) IgG4-related sialadenitis confirmed with a lip biopsy. Thus, we diagnosed him with "definite" IgG4-related disease.

Regarding mimickers of IgG4-RD, sarcoidosis was considered unlikely because of the lack of any elevation in the level of angiotensin-converting enzyme (ACE) or hypercalcemia on blood tests and no findings of granulomas in the biopsy specimens. The pleural specimens did not show angiocentricity or granuloma formation, so lymphomatoid granulomatosis was also deemed unlikely in this case. No
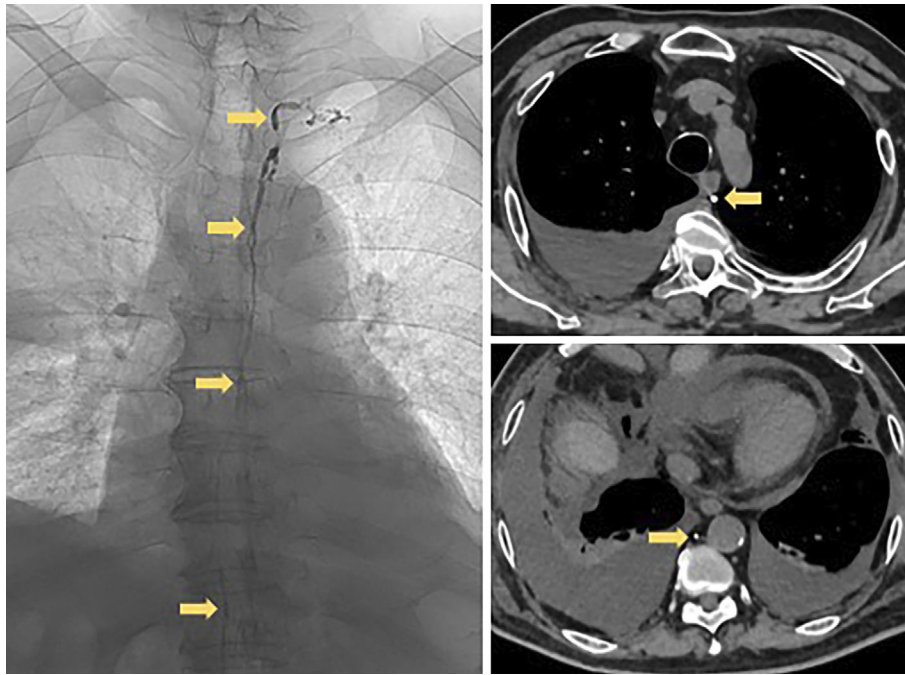
Figure 2.   Lymphangiography images. Lymphangiography showed the intact structure of the thoracic duct (yellow arrows) and revealed no leakage or obstruction of the duct.
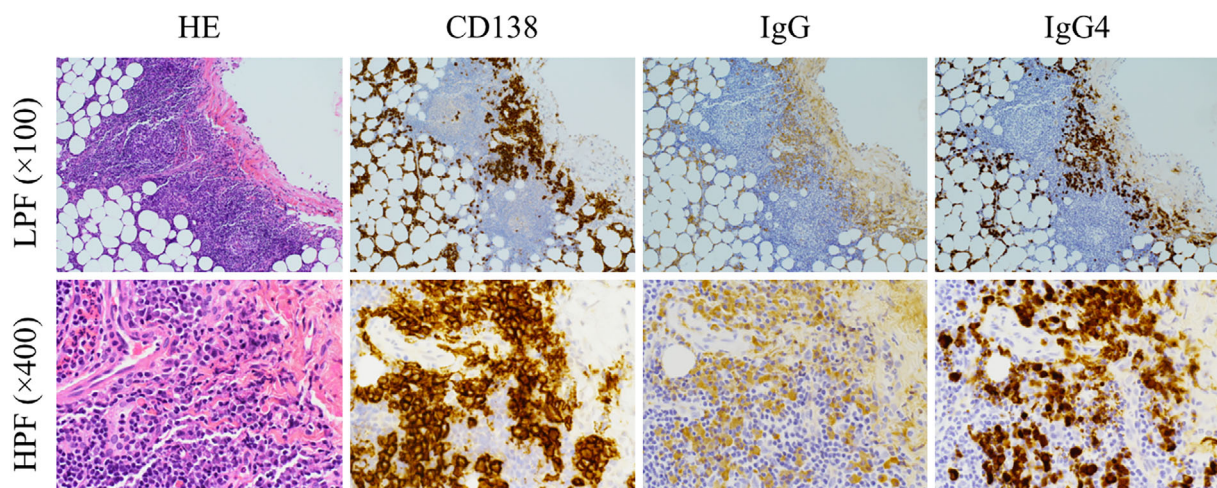

Figure 3.   Histopathological images from the pleural biopsy. A pleural biopsy showed the infiltration of lymphocytes and plasma cells with ectopic germinal centers under the pleural mesothelium, and more than 50% of IgG-positive plasma cells were IgG4-positive. HE: Hematoxylin and Eosin staining, LPF: low-power field, HPF: high-power field

fever or high CRP levels were observed in this patient, which made Multicentric Castleman disease unlikely.

The treatment and clinical course of this patient are shown in Fig. 5. We first performed continuous drainage of the pleural fluid with fasting, intravenous hyperalimentation, and octreotide for two weeks. The octreotide was used in an off-label manner with the patient's consent to reduce lymphatic flow in the thoracic duct (14). The pleural drainage decreased the effusion temporarily, but the production of new fluid did not cease, resulting in the marked loss of serum levels of albumin, IgG, and IgG4. We started high-dose PSL 70 mg (1 mg/kg/day) with RTX (375 mg/m^2, weekly, 4

times). The off-label use of RTX for IgG4-RD was approved by the authorized committee in our hospital [approval number: 2020-012] with informed consent from the patient. The pleural effusion gradually decreased. Later, we switched from PSL to methylprednisolone (mPSL) due to the latter's lower mineralocorticoid activity and better transferability to the lung (15, 16). Six months from induction therapy, the pleural effusion had significantly improved (Fig. 1C).

Discussion

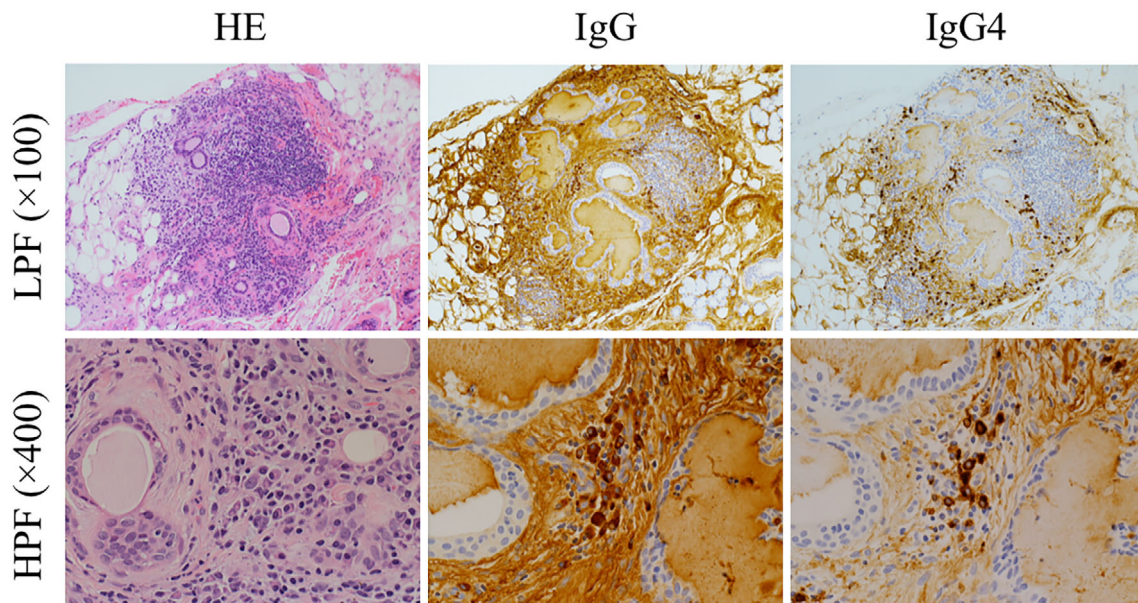The present patient developed refractory chylothorax due

Figure 4. Histopathological images from the lip biopsy. A lip biopsy revealed focal IgG4-positive plasma cell infiltration, with up to 48 cells/HPF and an IgG4/IgG ratio exceeding 50%. HE: Hematoxylin and Eosin staining, LPF: low-power field, HPF: high-power field

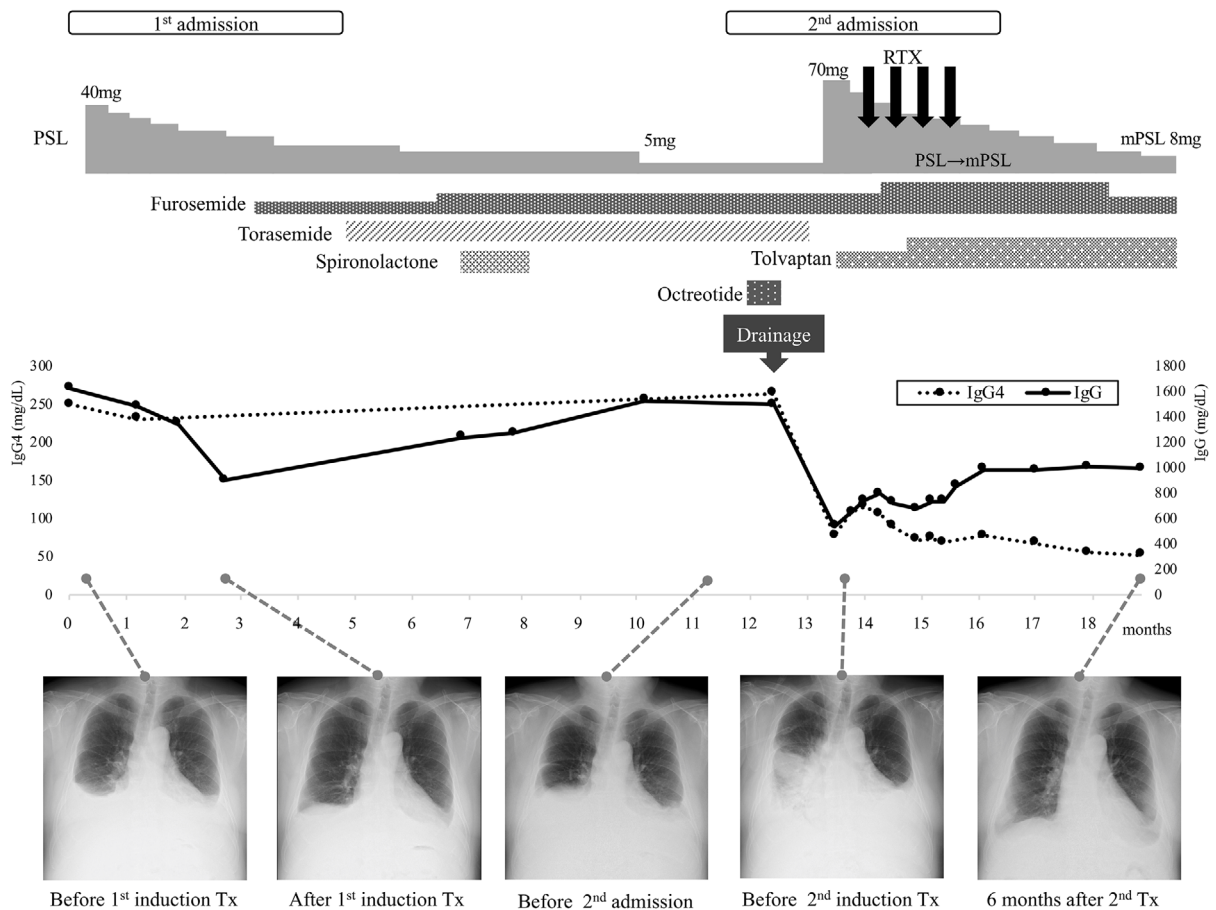**Figure 5.** Summary of clinical course of this patient. The pleuritis showed an insufficient response to the first induction therapy with moderate-dose PSL and diuretics. However, the second induction therapy with high-dose PSL and RTX resulted in the significant improvement of pleuritis and a reduction in the serum IgG4 levels. PSL: prednisolone, mPSL: methylprednisolone, RTX: rituximab, Tx: treatment

Table 2. A Summary of 37 Previous Case Reports with IgG4-RD Related Pleuritis.

Case No.	Reference	Age	Gender	Side	Pleural effusion test						Pleural biopsy		Serum		Associated diseases	Initial PSL dose (/day)	Immuno-suppressant	PSL effect for pleuritis
					(type)	Cell count (/μL)	Lymph (%)	IgG (mg/dL)	IgG4 (mg/dL)	ADA (IU/L)	IgG4-positive plasma cells (/HPF)	IgG4/IgG	IgG (mg/dL)	IgG4 (mg/dL)				
Non-chylothorax cases																		
1	18	74	M	Right	N/D	N/D	N/D	N/D	N/D	N/D	N/D	46	N/D	N/D	none	none	-	Good response
2	19	65	M	Left	Exudative	N/D	lymp 32%, Plasma 32%	3,005	1,510	N/D	N/D	N/D	3,142	1194%	Mikulicz's disease	30 mg	-	Good response
3-7 (5 cases)	20	62 (49-76)	M (all)	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	high in 3/3 cases (100%)	high in 2/4 cases (50%)	3/5 cases	N/D	N/D	N/D
8	21	63	F	Bilateral	bloody	N/D	lymphocyte and plasma cells dominant	N/D	N/D	N/D	N/D	N/D	2,450	420	history of autoimmune pancreatitis	dose unknown	-	Good response
9	22	78	M	Bilateral	Exudative	N/D	mononuclear cell dominant	N/D	590	34.1-46.7	17.6	85.4	1,604	483	-	none	-	Partial response
10	23	85	M	Bilateral (Left dominant)	Exudative	2,600	87%	3,403	2,090	122	N/D	N/D	4,121	2,740	salivary glands, lymph nodes, orbital lesion, bile duct, gastric glands	30 mg	-	Good response
11	24	73	M	Right	Exudative (bloody)	741	69%	3,358	907	59.8	N/D	N/D	4,219	1,500	pericarditis, retroperitoneal fibrosis	30 mg	-	Good response
12	25	68	M	Left	Exudative	4,800	92%	2,809	571	104.4	N/D	N/D	1,471	372	Mikulicz's disease	30 mg	-	Good response
13	26	29	F	Bilateral	Exudative	N/D	93%	N/D	N/D	N/D	>30	92%	N/D	136	pericardium	40 mg	-	Good response
14	26	57	M	Bilateral	N/D	N/D	N/D	N/D	N/D	N/D	N/D	>40%	N/D	970	none	N/D	-	Good response
15	27	69	M	Right	Exudative	N/D	dominant	4,276	N/D	70.6	N/D	50%	3,570	2,380	lymph node	0.5 mg/kg	-	Good response
16	28	71	F	Right	N/D	N/D	N/D	N/D	N/D	N/D	N/D	84%	1,756	684	periaortitis	40 mg	-	Good response
17	29	74	F	Bilateral	Exudative	N/D	N/D	N/D	N/D	normal	91	91%	N/D	740	interstitial pneumonia	25 mg (0.5mg/kg)	-	Good response
18	30	48	M	Bilateral	Exudative	N/D	lymphocyte dominant	N/D	N/D	N/D	N/D	24%	N/D	248	lymph node	0.6 mg/kg	-	Good response
19	31	63	M	Right	Exudative	N/D	N/D	N/D	N/D	N/D	73	>40%	N/D	284	none	40 mg	MTX (for PsA)	Good response
20	32	74	M	Left	Transudative	N/D	N/D	N/D	N/D	N/D	N/D	30%	1,300	217	lymph node, neuromyopathy	40 mg	-	Good response
21	33	68	F	Bilateral	Exudative	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	307	uterine enlargement	0.6 mg/kg	-	Good response
22	34	58	M	Bilateral	N/D	N/D	N/D	N/D	N/D	N/D	52	50%	1,200	141	none	37.5 mg	AZP→MTX	Good response
23	35	32	M	Bilateral	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	550	pericarditis	30 mg	-	Good response
24	36	78	M	Bilateral	N/D	N/D	N/D	N/D	N/D	N/D	100	70%	N/D	760	Sclerosing cholangitis, constrictive pericarditis	N/D	-	Good response
25	37	70	M	Bilateral	N/D	N/D	N/D	N/D	N/D	N/D	none (after treatment)	none (after treatment)	normal	437	pericarditis, Aortitis	high dose mPSL 3days→PSL 1mg/kg	CYC	Good response
26	38	70	M	Right	Exudative	N/D	dominant	N/D	N/D	N/D	N/D	>50%	N/D	224	mediastinitis	0.6 mg/kg	-	Good response
27	38	70	M	Bilateral (Right dominant)	Exudative	5,400	93.80%	4,409	1,070	75.6	>10	>40%	2,518	1,030	none	40 mg	-	Good response
28	39	84	M	Bilateral	N/D	448	Plasma 53%	N/D	N/D	N/D	45	N/D	N/D	306	none	40 mg	-	Good response
29	40	43	F	Right	Exudative	N/D	80-97%	N/D	N/D	4.6-7.0	80	>40%	normal	125	Pericardial effusion, abdominal effusion	30 mg	-	Good response
30	41	55	M	Bilateral	Exudative	1,952	52%	N/D	N/D	N/D	N/D	N/D	3,260	534	pericarditis, lacrimal gland	80 mg	MMF	N/D
31	42	65	M	Bilateral	Exudative	2,700/7,160	90%/97%	N/D	124/125	23.0/20.5	50	40%	1,490	164	none	30 mg	AZP	Partial response
32	43	81	M	Bilateral	Exudative	3,450	69%	N/D	N/D	85.0	>50	<40%	2,807	233	none	30 mg	-	Partial response
33	44	70	F	Bilateral	Exudative	N/D	N/D	3,269	1,280	75.4	N/D	N/D	3,877	>1,500	pericarditis	N/D	N/D	Good response
34	45	72	F	Left	Exudative	5,483	99%	N/D	N/D	80.2	>50	>40%	5,310	>1,500	lymph node	none	-	Good response (naturally dissappered)
35	46	46	M	Bilateral	Exudative	N/D	68%	N/D	256	36.4 (normal)	22	42%	N/D	142	N/D	30 mg	-	Good response
Cylorhorax cases																		
36	47	69	M	Bilateral	Exudative (Chylothorax)	3980/5,870	92%/88.5%	2,690/2,647	571/653	40.8/39.9	N/D	90%	1,539	277	none	30 mg	-	Partial response
37	48	16	M	Bilateral	Exudative (Chylothorax)	N/D	N/D	N/D	N/D	15	62	40% (mediastinal biopsy)	N/D	1,650	none	1 mg/kg	AZP	Poor response (surgical obliteration)
present case	Sakata et al.	66	M	Bilateral	Exudative (Chylothorax)	810	84%	N/D	N/D	25.1	50	50%	1500	264	lacrimal and salivery gland, pericarditis	70mg	RTX	Poor response

M: male, F: female, N/D: not determined, MTX: methotrexate, AZP: azathioprine, CYC: 381 cyclophosphamide, MMF: mycophenolate mofetil, RTX: rituximab

to IgG4-RD diagnosed histopathologically with a pleural specimen. The response to a moderate dose of PSL was poor. High-dose PSL and additional RTX resulted in marked improvement. Chylothorax presenting as IgG4-related pleuritis is quite rare, and to our knowledge, this is the first report of the successful treatment of IgG4-related pleuritis with RTX.

Pleural involvement is reportedly rare; indeed, Fei et al. found that 87 of 248 patients with IgG4-RD in a prospective cohort (35.1%) had intrathoracic involvement (17), although the involvement was mainly in the lungs and lymph nodes, including hilar and mediastinal lymphadenopathy, in 52.9%, solid nodules in the lungs in 25.3%, alveolointerstitial opacities in 20.7%, round ground-glass opacities in 9.2%, and bronchovascular opacities in 20.7%. Pleural nodules and thickening were observed in 16.1%, but pleural effusion was seen in only 4.6%.

We summarized 37 previous case reports with IgG4-RD related pleuritis in Table 2 (18-48). Patients with IgG4-related pleuritis were predominantly men (78%), and the mean age was 63.5±14.7 years old. Bilateral pleural effusion was seen in 21 cases, while 11 cases (right, n=7 cases; left, n=4) had unilateral effusion. In the 24 cases with pleural effusion findings available, 22 showed an exudative pattern, while bloody effusion was seen in 2 cases and transudative effusion in 1 case. Pleural effusion cytometry revealed predominantly lymphocytes among total cases, with a high concentration of IgG4 revealed in 10 cases. Our present findings were consistent with those of previous cases with regard to the age, percentage of men, and rate of bilateral exudative pleural effusion.

Interestingly, in previously reported cases of IgG4-related pleuritis, 10 out of 15 cases showed high levels of ADA in the pleural fluid (>40 U/L), which is usually measured as an auxiliary tool for the diagnosis of tuberculous pleuritis (49). Although careful ruling out of tuberculous pleuritis is necessary using other examinations, such as Ziehl-Neelsen staining (50), elevated ADA levels in pleural fluid may be useful for identifying IgG4-RD pleuritis because such a condition reflects the strong activation of lymphocytes. The levels of ADA in the pleural fluid of the present case were within normal limits.

Only two previous cases of IgG4-related pleuritis presenting as chylothorax have been reported (47, 48). Kato et al. reported a 69-year-old man with IgG4-related pleuritis, demonstrating right-sided chylothorax and left-sided non-chylothorax pleuritis (47). The right-side chylothorax persisted while the left-side pleuritis improved with corticosteroids. Another case, reported by Goag et al., was a young man with bilateral chylothorax (48) unresponsive to high-dose PSL with azathioprine or octreotide and a limited low-fat diet with medium-chain triglyceride supplementation. He ultimately had to undergo exploratory thoracotomy and surgical obliteration. In contrast to most non-chylothorax IgG4-pleuritis patients, who tend to show a good response to treatment, IgG4-related pleuritis with chylothorax is likely to

have a poor response to PSL. The pathogenesis of chylothorax in IgG4-RD is unclear. Lymphangiography in our case did not reveal any leakage from the thoracic duct, suggesting potential micro-damage to the lymphatic channels hampering centripetal lymph propulsion from the periphery of the pleural surface. However, we lacked histological evidence of this, so more cases need to be accumulated to clarify the mechanism involved.

Many kinds of immunosuppressant drugs, such as azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil, have been used to try to treat refractory IgG4-RD, but the optimal drug in combination with PSL is still unclear (51). Reports of the effectiveness of RTX in IgG4-RD have been increasing (51-54). Regarding the mechanisms underlying IgG4-RD, RTX, which depletes peripheral B cells, is a reasonable addition to therapy not only to prevent the repletion of short-lived plasmablasts and plasma cells but also to interfere with the maintenance of CD4^{+} T cell memory (55). Furthermore, a French nationwide study demonstrated the efficacy of RTX for both induction therapy and the maintenance of remission (56). Therefore, we selected RTX in our refractory case, and his pleural effusion gradually disappeared with a steroid-sparing effect. To our knowledge, this is the first case report suggesting the effectiveness of RTX in IgG4-related pleuritis.

In conclusion, we experienced a case of refractory IgG4-related pleuritis with chylothorax that was improved with high-dose PSL and RTX. More cases need to be accumulated in order to clarify the clinical manifestations of IgG4-RD pleuritis and its appropriate treatment.

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

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