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Case report

Characteristics of pleural effusion in IgG4-related pleuritis

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ABSTRACT

Here we describe the case of a 78-year-old man with respiratory failure and right pleural effusion. Computed tomography showed right pleural effusion with pleural calcification, tumor-like shadows induced by passive atelectasis, and enlarged mediastinal lymph nodes. Positron emission tomography showed right pleural thickening, rounded atelectasis, and enlarged mediastinal lymph nodes, without fluid accumulation in other organs. The pleural effusion showed lymphocyte-dominated exudates with elevated adenosine deaminase (ADA) levels. Tuberculous pleuritis was suspected, but thoracoscopic pleural biopsy revealed lymphoplasmacytic infiltration and fibrosis, with 10 immunoglobulin G4 (IgG4)-positive plasma cells/high-power field, and IgG4/IgG ratio of 40%. IgG4 concentrations in serum and right pleural effusion were 929 and 1120 mg/dL, respectively. The patient was diagnosed with IgG4-related pleuritis without other systemic manifestations, and reduction in right pleural effusion was confirmed by corticosteroid therapy. IgG4-related disease is typically a systemic disease causing lymphoplasmacytic inflammation in multiple organs. We describe a rare form of IgG4-related pleuritis showing pleural effusion with no other systemic manifestation.

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder characterized by high serum IgG4 levels and IgG4-positive plasma cell proliferation in tissues, with fibrotic, tumorous, and hypertrophic lesions in various organs. Currently, IgG4-RD is shown to affect most organs, including the biliary tree, kidneys, retroperitoneum, prostate, aorta, pericardium, lungs, thyroid, lymph nodes, meninges, and skin. The pleural manifestations of IgG4-RD include pleural mass, pleuritis with fibrosis, and pleural effusion. Several recent studies reported pleural involvement in 28% of patients with IgG4-related lung disease [1,2]. In a cohort of Chinese patients with IgG4-RD, the frequency of thoracic involvement was reported to be 35.1% (87/248), and pleural effusion and thickening were noted in 4.6% and 16.1% of the patients, respectively [3]. Pleural effusions, which are observed in a wide range of diseases, such as congestive cardiac failure and infectious and malignant diseases, are a common presentation of IgG4-RD. Occasionally patients may present with idiopathic exudative effusions even after extensive evaluation, including a thoracoscopic biopsy. Murata et al. reported that 12 of 35 (34%) patients with pleural effusions that were undiagnosed during follow-up (median, 5 years; range, 1–10 years) were found to have marked IgG4-positive plasma cell infiltration in the pleura, which was shown by IgG4 immunostaining, along with elevated IgG4 concentrations in the effusion [4]. These findings may indicate the idiopathic cause of IgG4-RD in some patients. Here we report the case of a patient with IgG4-related pleuritis presenting as exudative pleural effusion. The clinical features of IgG4-related pleuritis are not yet fully understood; therefore, we describe the characteristics of pleural effusion in IgG4-related pleuritis in this case report.

2. Case presentation

A 78-year-old Japanese man was referred from a local hospital with a report of worsening exertional dyspnea caused by right pleural effusion. Dry cough and exertional dyspnea (British Medical Research Council Grade 2) were apparent, with a percutaneous oxygen saturation of 88% in room air. He had no family history of respiratory, pancreatic, collagen, or autoimmune diseases; however, he had a past history of hypertension and stomach cancer, along with a history of smoking and asbestos exposure. Laboratory findings on the first visit were as follows: white blood cell count, 6300 cells/μL (neutrophils, 64.2%; lymphocytes, 21.7%; eosinophils, 4.3%; basophils, 1.0%, and monocytes, 8.8%); hemoglobin, 11.9 g/dL; thrombocytes, 21.7 × 10^4/μL; and C-reactive

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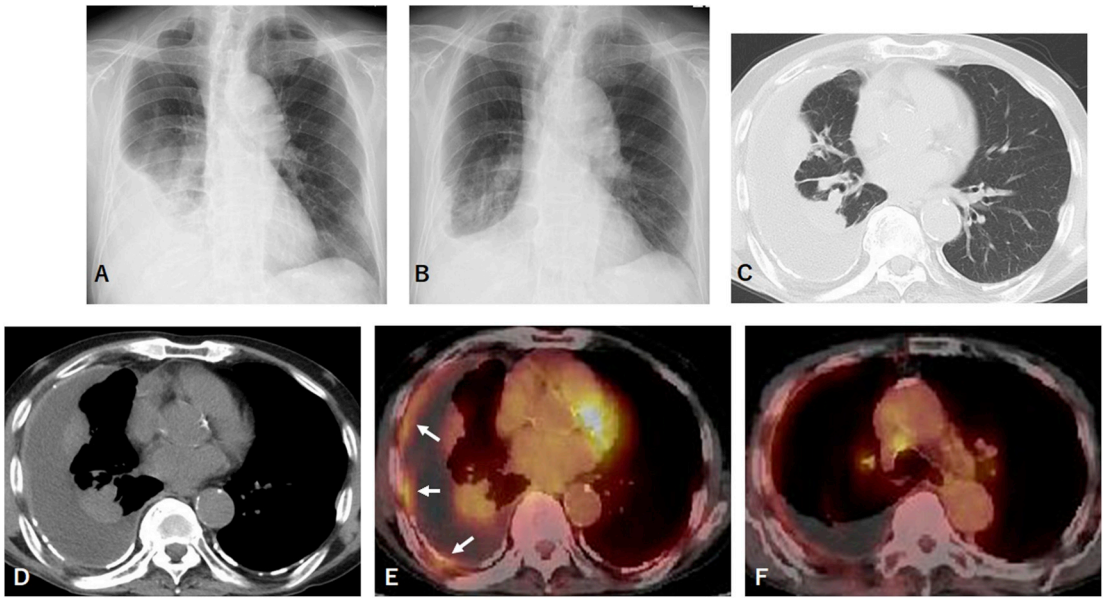

Fig. 1. (A) Chest X-ray showing right pleural effusion at admission. (B) Chest X-ray showing improved right pleural effusion after 4 weeks of steroid treatment. (C, D) CT at admission day showing right pleural effusions with pleural calcification and tumor-like shadows induced by passive atelectasis. (E, F) PET showing fluid accumulation in the right thickened pleura (arrow), rounded atelectasis, and enlarged mediastinal lymph nodes.

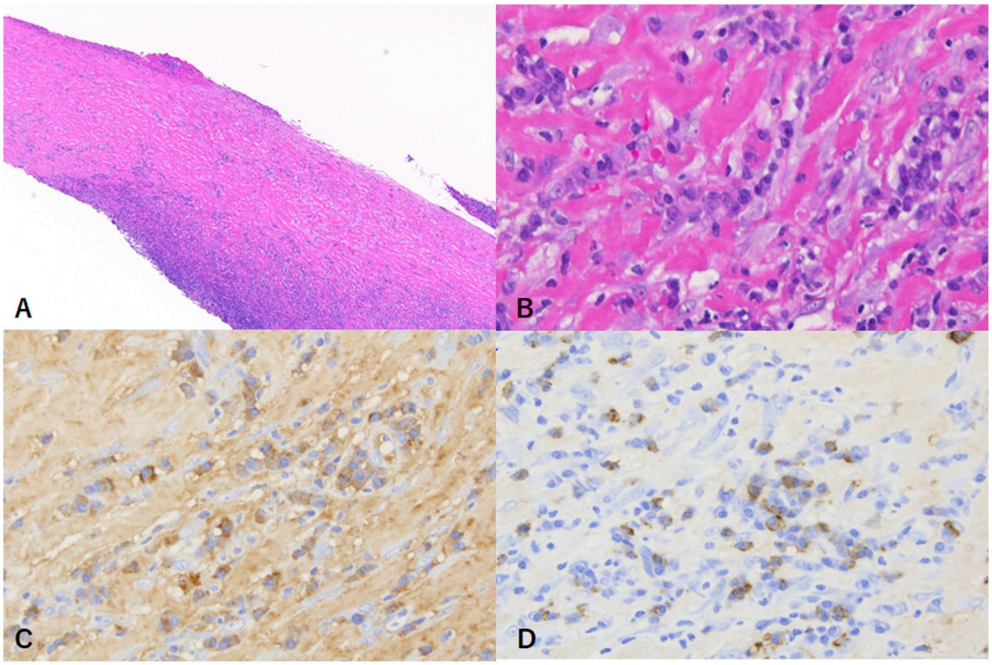

Fig. 2. Histopathologic examination of biopsy specimens from the right pleura showing lymphoplasmacytic infiltration. (A): Hematoxylin–Eosin (H&E) staining, × 40; (B): H&E staining, × 100. Immunohistochemical staining showing IgG4-positive plasma cells: IgG4-positive plasma cells >10/HPF, IgG4/IgG cell ratio of 40%. (C): Immunohistochemical staining for IgG, × 200; (D): Immunohistochemical staining for IgG4, × 200.

protein, 0.28 mg/dL. Serum IgG and IgG4 levels were markedly elevated: 3404 and 929 mg/dL, respectively. Tests to detect autoantibodies for collagen vascular disease (antinuclear antibodies, double-stranded DNA antibodies, anti-CCP antibodies, rheumatoid factor, proteinase 3-antineutrophil cytoplasmic antibody, and myeloperoxidase-antineutrophil cytoplasmic antibody) were negative. Chest X-ray and computed tomography (CT) showed right pleural effusion with pleural calcification, tumor-like shadows induced by passive atelectasis, and mediastinal lymph node swelling (Fig. 1A, C, and D). The right pleural effusion appeared as cloudy yellow fluid with a total cell count of 2300/mm^3 (lymphocytes, 79.2%; neutrophils, 12.9%), total protein concentration of 5.9 g/dL, adenosine deaminase (ADA) level of 71.9 U/L, and IgG4 concentration of 1120 mg/dL. Bacterial cultures and polymerase chain reaction analyses for DNA of *Mycobacterium tuberculosis*, *M. avium*, and *M. intracellulare* were negative. Positron emission tomography (PET) showed fluid accumulation on the right side of the thickened pleura, rounded atelectasis, and enlarged mediastinal lymph nodes, with a maximum standardized uptake value of 5.4 (Fig. 1E and F). No fluid accumulation was found in other organs.

For definitive diagnosis of the unknown pleural effusion, we

Table 1
Reported cases of IgG4-related disease with pleural effusion.

Author	Status		Serum		Pleural effusion				Pathology		
	Age/ sex	side	IgG (mg/ dL)	IgG4 (mg/ dL)	IgG (mg/ dL)	IgG4 (mg/ dL)	ADA (U/L)	Cell counts	Findings	IgG4+/ HPF	IgG4/IgG ratio (%)
Nagayasu et al. [10]	81/M	Bilateral	2807	233	NA	NA	85	lymphocyte-predominant	lymphoplasmacytic infiltration	>50	>40
Yamamoto et al. [11]	78/M	Bilateral	1604	483	2515/ 1491	590/-	34.1/ 46.7	Lymphocyte /neutrophil	lymphoplasmacytic infiltration and fibrosis	17.6	85.4
Tanaka et al. [12]	85/M	Bilateral	4121	2740	3404	2090	122	lymphocyte-predominant	lymphoplasmacytic infiltration (gastric mucosa biopsy)	NA	NA
Suzuki et al. [13]	73/M	Right	4219	1500	3358	907	59.8	lymphocyte-predominant	not performed	NA	NA
Suzuki et al. [13]	68/M	Left	1471	372	2809	571	104.4	lymphocyte-predominant	lymphoplasmacytic infiltration and fibrosis	NA	NA
Hara et al. [14]	69/M	Right	3570	2380	4276	NA	70.6	lymphocyte-predominant	lymphoplasmacytic infiltration and fibrosis	NA	50
Kato et al. [15]	69/M	Bilateral	1539	277	NA	571/ 653	39.9/ 40.8	lymphocyte-predominant	lymphoplasmacytic infiltration and fibrosis	NA	90
Kita et al. [16]	65/M	Bilateral	1490	164	NA	125/ 124	23/ 20.5	lymphocyte-predominant	lymphoplasmacytic infiltration and fibrosis	50	40
Xian et al. [17]	43/F	Right	NA	1250	NA	NA	4.6/ 7.0	lymphocyte-predominant	lymphoplasmacytic infiltration	80	>40
Ikuyama et al. [18]	70/M	Bilateral	2518	1030	4409	2070	75.6	lymphocyte-predominant	lymphoplasmacytic infiltration and fibrosis	>10	>40
Masaki et al. [19]	70/M	Left	1878	352	NA	331	56.7	lymphocyte-predominant	lymphoplasmacytic infiltration and fibrosis	NA	89
Eun et al. [20]	16/M	Bilateral	NA	1650	NA	NA	10.7/ 15.0	NA	lymphoplasmacytic infiltration and fibrosis	62	>40
Present case	78/M	Right	3404	929	3075	1120	71.9	lymphocyte-predominant	lymphoplasmacytic infiltration and fibrosis	10	40

IgG4+/HPF, IgG4-positive plasma cells per high power field; NA, not available.

performed thoracoscopic pleural biopsy, transbronchial lung biopsy, and endobronchial ultrasound-guided transbronchial needle aspiration, referring to the CT and PET findings. As a result, there were no specific findings from the lung and mediastinal lymph node biopsy specimens. However, thoracoscopy revealed right pleural thickening and biopsy specimens retrieved from the right pleura revealed lymphoplasmacytic infiltration associated with fibrosis, with no malignancy or granuloma (Fig. 2A and B). Immunohistochemical staining revealed 10 IgG4-positive plasma cells/high-power field and an IgG4/IgG ratio of 40% (Fig. 2C and D).

The patient met the comprehensive diagnostic criteria for IgG4-RD and was therefore diagnosed with IgG4-related pleuritis with unilateral pleural effusion and no other organ disorder. Treatment with prednisolone 30 mg/day was initiated, and the pleural effusion gradually decreased with the treatment (Fig. 1B). One month after steroid treatment was initiated, his serum IgG4 level decreased to 362 mg/dL. Therefore, prednisolone was gradually tapered to 5 mg/day over a period of 10 weeks. Presently, prednisolone 10 mg/day is being used as a maintenance dose, and his serum IgG4 level is within the normal range.

3. Discussion

The Ministry of Health, Labour and Welfare of Japan proposed the comprehensive diagnostic criteria for IgG4-RD in 2011 as follows: clinical examination showing characteristic diffused/localized swelling or masses in single or multiple organs; hematological examination showing elevated serum IgG4 concentrations (>135 mg/dL); histopathologic examination showing marked lymphocyte and plasmacyte infiltration, fibrosis, and IgG4-positive plasma cell infiltration; and a ratio of IgG4-positive/IgG-positive cells of >40%, with more than 10 IgG4-positive plasma cells/HPF [5]. Additionally, the diagnostic criteria for IgG4-related respiratory disease were also proposed as follows: abnormal shadow on chest CT; serum IgG4 level of >135 mg/dL; histopathologic features fulfilling the comprehensive diagnostic criteria; and presence of extrathoracic lesions [6].

This case report describes the case with IgG4-related pleuritis presenting as pleural effusion and elevated ADA levels. ADA levels in pleural effusion is a frequently used marker for auxiliary diagnosis of tuberculous pleuritis. Although diagnostic performance of ADA depends upon the prevalence of tuberculosis, a previous study reported a sensitivity of 100% and a specificity of 93.9% for tuberculous pleuritis when the cut-off value of ADA was set at 40.3 U/L [7]. We strongly suspected tuberculous pleuritis in our patient due to the predominance of lymphocytes in the pleural effusion and high ADA levels. However, the definitive diagnosis of IgG4-related pleuritis was made by pleural biopsy. IgG4-related pleuritis was difficult to suspect at the first visit because there were no specific clinical laboratory features or imaging findings. Additionally, increased serum IgG4 levels are only typically reported in approximately 30% of patients with IgG4-RD [8,9]. Therefore, we summarized the features of pleural effusion in 13 patients diagnosed with IgG4-related pleuritis in Table 1. To our knowledge, only 12 patients with IgG4-related pleuritis could be identified from the results of pleural effusion analysis in the past reports. According to Table 1, 10/13 patients (77%) had lymphocyte-dominated pleural effusion with high ADA levels and 2/13 patients (15%) had ADA levels of >100 U/L. All 13 patients had serum IgG4 levels of >135 mg/dL, and pleural effusion IgG4 levels were higher than serum IgG4 levels in 5/9 patients (56%). It is still unclear why some patients with IgG4-related pleuritis show elevated ADA levels in pleural effusion. A similar mechanism of ADA-driven cell-mediated immunity in tuberculosis pleuritis may be involved. Considering the characteristics of pleural effusion in IgG4-related pleuritis, patients with exudative pleural effusion containing both lymphocyte-predominant exudates and high ADA levels may need to be evaluated for the possibility of two diagnoses: IgG4-related pleuritis and tuberculosis pleuritis.

4. Conclusions

When we met with patients with exudative pleural effusion containing both lymphocyte predominant exudates and high ADA levels, an

evaluation for the possibility of IgG4 related pleuritis should be considered.

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Ethical approval

Informed consent was obtained from the patient and it is available upon request.

Author contribution

Z.S. designed the case report and drafted the manuscript. M.Y., A.K., K.T., K.K. contributed to review of this manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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