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Elevated Pleural Adenosine Deaminase Levels in IgG4-related Disease With Pleural Effusion: A Case Series

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Dear Editor,

Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory disorder affecting various organs [1]. Elevated serum IgG4 levels are highly suggestive but not definitive of IgG4-RD, and the diagnosis is based on histopathologic findings [2]. IgG4-RD involving the pleura is an uncommon presentation of the disorder found in 1.6% of IgG4-RD patients [3]. Sporadic cases of IgG4-RD with pleural effusion have been associated with elevated pleural fluid adenosine deaminase (ADA)-a biomarker of tuberculous pleurisy [4, 5]. Awareness of the laboratory characteristics of IgG4-RD involving pleura would facilitate the proper diagnosis of IgG4-RD. We retrospectively analyzed the characteristics of pleural fluid samples from patients with IgG4-RD involving the pleura admitted to Seoul St. Mary's Hospital, Seoul, Korea, between November 2019 and November 2021. The Institutional Review Board of Seoul St. Mary's Hospital (KC21RISI1001) approved the study and waived the need for informed consent.

Four patients with IgG4-RD involving the pleura were identified; their demographic data, clinical characteristics, and laboratory findings were collected (Table 1). The diagnosis of IgG4-RD was based on the 2011 Comprehensive Diagnostic Criteria for IgG4-RD [6]. All patients were elderly men; respiratory symptoms were present at initial presentation. Two patients had a history of tuberculosis, whereas two had no history of respiratory diseases. Two patients had non-pleural lesions (of the peritoneum or pericardium). Serum IgG4 levels were elevated (>1.35 g/L) in three patients at presentation; one had an elevated pleural fluid IgG4 level (3.00 g/L), despite a serum IgG4 level of 1.10 g/L. Serum protein electrophoresis revealed polyclonal gammopathy in three patients.

Pleural fluid analysis results were consistent with exudates according to Light's criteria [7]. White blood cell (WBC) counts were highly variable but revealed lymphocyte predominance in all cases. Pleural fluid ADA levels were elevated (>40 IU/L) in all patients. In one patient, pleural fluid ADA isoenzymes were assessed using erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride, an ADA_1-specific inhibitor, using an established method [8]. The results revealed an ADA_1-to-total pleural ADA (ADA_p) ratio of 0.54. A pleural fluid ADA_1/ADA_p ratio of <0.42 shows superior diagnostic performance to elevated pleural fluid ADA for tuberculous pleurisy [9].

Given the elevated pleural fluid ADA level, we evaluated *Mycobacterium tuberculosis* infection in all patients using acid-fast stain, mycobacterial culture, and PCR, with negative results. Ultimately, the diagnosis of IgG4-RD was based on histopathological assessments of pleural (N=2), pericardial (N=1), and bone marrow (N=1) biopsies. Histopathological findings included tissue infiltration by lymphoplasmacytic cells, with immunohistochemical evidence of IgG4+ plasma cells as a IgG4/IgG ratio

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Table 1. Characteristics of four male patients with IgG4-related pleural effusion

Variable	Case number			
	1	2	3	4
Age (yr)	74	86	65	59
Serum				
Protein (g/L)	76	87	69	79
Albumin (g/L)	32	22	38	45
Glucose (mmol/L)	8.72	5.22	8.17	9.17
LDH (U/L)	313	162	316	208
IgG (g/L)	29.19	48.55	33.84	NA
IgG4 (g/L)	2.42	8.17	14.76	1.10
Pleural fluid				
pH	7.6	8.2	7.2	7.0
Protein (g/L)	65	43	40	44
Albumin (g/L)	24	14	20	28
Glucose (mmol/L)	7.89	3.94	5.94	5.17
LDH (U/L)	271	588	187	492
Rheumatoid factor (IU/L)	<2,000	<2,000	<2,000	NA
IgG4 (g/L)	NA	NA	NA	3.00
ADA (IU/L)	155.0	94.7	80.0	63.4
ADA_1/ADA_p	NA	NA	NA	0.54
WBC count ($\times 10^9$ cells/L)	4.36	0.02	3.62	4.00
Neutrophils (%)	1	6	3	5
Lymphocytes (%)	78	82	71	68
Eosinophils (%)	7			8
Basophils (%)	3			1
Macrophage (%)	8	12	24	18
Mesothelial cells (%)	3		2	

Abbreviations: LDH, lactate dehydrogenase; ADA, adenosine deaminase; WBC, white blood cell; NA, not available.

>40% and/or >10 IgG4+ plasma cells/high-powered field. According to the Comprehensive Diagnostic Criteria for IgG4-RD [6], three cases fulfilled the criteria of definite IgG4-RD and one case of probable IgG4-RD because of a normal serum IgG4 level. Glucocorticoid therapy was started after the diagnosis of IgG4-RD was established; the patients showed therapeutic responses during follow-ups.

Elevated pleural fluid ADA levels are associated with high sensitivity and specificity (92% and 90%, respectively) for distinguishing tuberculous from nontuberculous effusion and are frequently used in the auxiliary diagnosis of tuberculous pleurisy [10]. Lymphocytic exudates not due to tuberculosis generally have ADA levels <40 IU/L. However, this study showed that an elevated pleural fluid ADA level in lymphocytic exudates is a consistent finding in IgG4-RD with pleural effusion; hence, it is important to consider the possibility of IgG4-RD in patients with lymphocytic pleural exudates with elevated ADA levels. Our study, for the first time, suggests that the ADA_1/ADA_p ratio can differentiate between IgG4-RD with pleural effusion and tuberculous pleurisy. In IgG4-RD, the increase in pleural ADA is due to a greater increase in ADA_1 than in ADA_2. The increase in the ADA_1/ADA_p ratio is plausible considering the lymphocytic nature of the pleural fluid and that ADA_1 is abundant in lymphocytes and monocytes. In tuberculosis pleurisy, high ADA activity is mainly due to the presence of ADA_2, which is found in monocytes/macrophages stimulated by phagocytosed microorganisms. Although this finding needs to be confirmed, an increased ADA_1/ADA_p ratio is an additional finding suggestive of IgG4-RD rather than tuberculous pleurisy.

This study is the first to describe multiple Korean patients with IgG4-RD involving the pleura and emphasizes that the laboratory community should be aware that elevated ADA in lymphocytic pleural exudates is a consistent feature of IgG4-RD involving the pleura. This is noteworthy as an unopposed association of elevated pleural ADA and tuberculous pleural effusion may lead to unnecessary investigations and anti-tuberculous therapy, while delaying the diagnosis of IgG4-RD, especially in countries where tuberculosis is prevalent.

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AUTHOR CONTRIBUTIONS

Chae S drafted the manuscript. Lee JJ was involved in the retrospective analysis. Cho H and Chae H designed the study. Chae H and Oh EJ supervised the study. All authors have read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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