[CASE REPORT]

Autoimmune Pulmonary Alveolar Proteinosis Complicated with Sarcoidosis: the Clinical Course and Serum Levels of Anti-granulocyte-macrophage colony-stimulating Factor Autoantibody

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Abstract:

Autoimmune pulmonary alveolar proteinosis (APAP) is caused by macrophage dysfunction due to anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody. We experienced 2 cases of APAP complicated with sarcoidosis in a 42-year-old woman and a 51-year-old man (age at the sarcoidosis diagnosis). APAP preceded sarcoidosis in the woman, and both diseases were diagnosed simultaneously in the man. Sarcoidosis lesions were observed in the lung, skin, and eyes, and the pathological findings of APAP were not marked at the diagnosis of sarcoidosis in either case. Low-grade positive serum anti-GM-CSF autoantibody was suspected to be correlated with the occurrence of sarcoidosis and resolution of APAP.

Key words: autoimmune pulmonary alveolar proteinosis, sarcoidosis, anti-granulocyte-macrophage colony-stimulating factor autoantibody

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Introduction

Pulmonary alveolar proteinosis (PAP) is characterized by phospholipid and surfactant protein (SP) accumulation in the alveolar spaces (1-4). Autoimmune pulmonary alveolar proteinosis (APAP) is caused by macrophage dysfunction due to anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody (2-5). APAP is known to trigger complications in various diseases, including collagen vascular and interstitial lung diseases (3). APAP complicated with sarcoidosis was previously reported (6); however, we believe that the pathophysiological link between the two diseases

was not clarified sufficiently.

We experienced two such cases and examined the relationship between the serum anti-GM-CSF autoantibody levels and the clinical course.

Case Reports

Subjects

Out of 102 APAP cases diagnosed in the National Hospital Organization (NHO) Kinki-Chuo Chest Medical Center between 2002 and 2017, 2 were complicated with sarcoidosis. We obtained informed consent to conduct anti-GM-CSF

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Figure 1. Radiological findings of Case 1. High-resolution computed tomography (HRCT) findings are shown. Ground glass opacity (GGO) with a “crazy-paving” pattern was noted on HRCT at the time of the APAP diagnosis at 30 years of age. (B) After granulocyte-macrophage colony-stimulating factor inhalation therapy, the GGO had decreased by 35 years of age. (C) GGO had decreased, but reticular opacity persisted at 39 years of age. (D) At 41 years of age, reticulonodular opacities scattered mainly in the lower lung field and air trapping suggesting bronchiolar lesions were noted. Hilar and mediastinal lymphadenopathy was also found at 41 years of age (E).

autoantibody measurements. The institutional review board of the Kinki-Chuo Chest Medical Center approved this retrospective study (Approved Number 674).

The diagnosis of APAP

PAP was diagnosed by bronchoalveolar lavage (BAL) and/or histological findings from a transbronchial lung biopsy (TBLB) or surgical lung biopsy (SLB) (3, 4). APAP was defined as anti-GM-CSF autoantibody-positive PAP (3, 4).

Anti-GM-CSF autoantibody measurement

We measured the anti-GM-CSF autoantibody by an enzyme-linked immunosorbent assay (ELISA), as previously reported, using a cut-off of 0.5 µg/mL (3).

The diagnosis of sarcoidosis

Sarcoidosis was diagnosed based on the 2006 Diagnostic Criteria and Guidelines for Sarcoidosis published by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (JSSOG) (7, 8). In both cases, lung disease was pathologically diagnosed with a BAL/TBLB or SLB. The disease spread outside the lung, and non-necrotizing epithelioid granulomas were histologically observed in both cases.

Case 1: The diagnosis of APAP preceded that of sarcoidosis

A 29-year-old non-smoking woman consulted our hospital because of bilateral pulmonary infiltrative shadows. High-resolution computed tomography (HRCT) revealed a “crazy-paving” pattern, suggesting PAP (Fig. 1A). BAL fluid (BALF) was milky, and a cell analysis revealed macrophages at 72.0%, lymphocytes at 27.6%, and neutrophils at 0.4%. TBLB specimens showed periodic acid-Schiff (PAS)-positive proteinaceous material in the alveolar spaces (Fig. 2C). The serum anti-GM-CSF autoantibody level was 102 µg/mL, and the serum Krebs von den Lungen-6 (KL-6), surfactant protein (SP)-D, SP-A, carcinoembryonic antigen (CEA), and cytokeratin fragment 21-1 (CYFRA) levels were elevated (Table 1). She was diagnosed with APAP and treated with GM-CSF inhalation for 6 months at 30 years old. Following treatment, her ground glass opacity (GGO) decreased, and her disease condition was stable for nine years (Fig. 1A-C). The serum anti-GM-CSF autoantibody levels decreased along with a decrease in the serum KL-6 and SP-D levels.

At 40 years of age, the patient’s shortness of breath deteriorated from modified medical research council score

Figure 2. Pathological findings of Case 1. (A, B) Transbronchial lung biopsy (TBLB) specimens revealed well-formed non-necrotizing epithelioid cell granulomas, consistent with sarcoidosis. (C) TBLB specimens showed periodic acid-Schiff positive fine granular proteinaceous material in the alveolar spaces, which was surfactant protein-A positive by immunohistochemistry. (D) A histological examination of the skin lesions observed on the back and upper and lower extremities also revealed non-necrotizing epithelioid granulomas in the dermis.

Table 1. Laboratory Findings of Case 1 (Onset of APAP Preceding Sarcoidosis).

Parameters	At APAP diagnosis	At sarcoidosis diagnosis
KL-6, U/mL	2,070	2,318
SP-D, ng/mL	205	604
SP-A, ng/mL	158	158
CEA, ng/mL	6.6	2.1
CYFRA, ng/mL	7.7	3.2
Anti-GM-CSF autoantibody, µg/mL	102	3.53
Soluble IL-2R, µg/mL	359	1,600
ACE, IU/L	14.2	43.2
Lysozyme, µg/mL	NA	19.3
BAL		
Milky appearance	Yes	No
TCC, ×10 ⁵ /mL	1.43	1.99
Cell fraction, %		
Macrophages	72.0	53.5
Lymphocytes	27.6	35.9
Neutrophils	0.4	8.8
Eosinophils	0.0	1.4
CD4/CD8	NA	8.6

APAP: autoimmune pulmonary alveolar proteinosis, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein-D, SP-A: surfactant protein-A, CEA: carcinoembryonic antigen, CYFRA: cytokeratin fragment 19, GM-CSF: granulocyte-macrophage-colony-stimulating factor, IL-2R: interleukin-2 receptor, ACE: angiotensin-converting enzyme, BAL: bronchoalveolar lavage, TCC: total cell count, NA: not available

(mMRC) grade 0 to grade 1. The serum KL-6 and SP-D levels increased, and her forced vital capacity (FVC) decreased despite reduced serum anti-GM-CSF autoantibody levels. The patient showed hilar and mediastinal lymphadenopathy (Fig. 1E), and reticulonodular opacities were scattered predominantly in the lower lung fields (Fig. 1D). A high-intensity signal for mediastinal and hilar lymphadenopathy with a maximal standardized uptake value (SUV_{max}) of 3.5 was shown by ¹⁸F-fluorodeoxyglucose positron emission tomography. Angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R) levels increased to 43.2 IU/L and 1,600 U/mL, respectively (Table 1). The BALF was not milky, and a cell analysis of BAL showed elevated lymphocytes (35.9%) with an increased CD4/CD8 ratio (8.6) (Table 1). TBLB and skin biopsy specimens (Fig. 2A, B, D) also revealed well-formed non-necrotizing epithelioid granulomas consistent with sarcoidosis. Infectious organisms were not detected in the BALF or histological specimens. She complained of misty vision, and an ophthalmologic inspection revealed active uveitis. She was diagnosed with sarcoidosis based on these clinical findings. The serum markers (ACE, sIL-2R, lysozyme, KL-6, SP-D) decreased and respiratory dysfunction improved after prednisolone administration (30 mg daily).

Case 2: Simultaneous APAP and sarcoidosis diagnoses

A 51-year-old former-smoking man (19 pack-years) con-

Figure 3. Radiological findings of Case 2. High-resolution computed tomography (HRCT) findings are shown. HRCT revealed diffuse ground glass opacity (GGO) with reticular opacity, showing a mosaic pattern (A, B). Hilar and mediastinal lymphadenopathy was also noted (C).

Table 2. Laboratory Findings of Case 2 (simultaneous APAP and Sarcoidosis).

Parameters	At APAP and sarcoidosis diagnoses	At start of PSL treatment
KL-6, U/mL	22,148	23,148
SP-D, ng/mL	1,181	1,044
SP-A, ng/mL	97.0	97.2
CEA, ng/mL	8.5	9.3
CYFRA, ng/mL	10.7	17.8
Anti-GM-CSF autoantibody, µg/mL	18.5	6.2
Soluble IL-2R, µg/mL	954	1,210
ACE, IU/L	35.5	33.0
Lysozyme, µg/mL	14.5	17.5
BAL		
Milky appearance	No	No
TCC, $\times 10^5$ /mL	8.40	8.03
Cell fraction, %		
Macrophages	9.8	20.1
Lymphocytes	85.9	73.1
Neutrophils	0.3	1.2
Eosinophils	2.4	5.6
CD4/CD8	6.38	6.7

APAP: autoimmune pulmonary alveolar proteinosis, PSL: prednisolone, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein-D, SP-A: surfactant protein-A, CEA: carcinoembryonic antigen, CYFRA: cytokeratin fragment 19, GM-CSF: granulocyte-macrophage-colony-stimulating factor, IL-2R: interleukin-2 receptor, ACE: angiotensin-converting enzyme, NA: not available, BAL: bronchoalveolar lavage, TCC: total cell count

sulted our hospital with shortness of breath and a dry cough. He had been suffering from a dry cough for about two years. HRCT revealed GGO and reticular opacity (Fig. 3A, B), and hilar and mediastinal lymphadenopathy was observed (Fig. 3C). Serum KL-6, SP-D, SP-A, CEA,

and CYFRA levels were elevated (Table 2). Interstitial pneumonia was suspected, and he underwent an SLB. Cellular interstitial pneumonia with various-sized epithelioid cell granulomas involving the peribronchiolar and alveolar walls were observed in the SLB specimens, suggesting sarcoidosis

Figure 4. Pathological findings of Case 2. We obtained lung specimens by video-assisted thoracoscopic surgery. (A, B) Well-formed, non-necrotizing epithelioid granulomas were detected in these specimens. We also observed the accumulation of (C) periodic acid-Schiff and (D) surfactant protein A positive fine granular proteinaceous material in the alveolar spaces.

or hypersensitivity pneumonia (HP) (Fig. 4A, B). Fine granular proteinaceous material (Fig. 4C, D) suggesting PAP was also noted in the alveolar spaces. The anti-GM-CSF autoantibody test was positive, with a value of 18.5 $\mu\text{g/mL}$ (Table 2); however, sarcoidosis was predominant. HP was rejected because his lung disease did not improve spontaneously after being admitted to our hospital and anti-bird and anti-*Trichosporon asahii* antibodies, the most common etiologies of HP in Japan, were negative. In addition, his elbows and knees showed erupted skin, which revealed well-formed non-necrotizing epithelioid granuloma on a biopsy, findings that were compatible with sarcoidosis. He suffered from a visual field defect, and an ophthalmologic inspection revealed uveitis. Infectious organisms were not detected in the BALF or histological specimens. Given these laboratory findings, we diagnosed the patient with APAP complicated with sarcoidosis.

Six months after diagnosis of the two diseases, his FVC decreased while his KL-6, SP-D, and sIL-2R increased, corresponding to a decrease in serum anti-GM-CSF autoantibody levels. The patient complained of shortness of breath and needed oxygen inhalation. His serum markers (ACE, sIL-2R, lysozyme, KL-6, and SP-D) decreased, and his respiratory dysfunction improved following prednisolone administration (30 mg daily).

Discussion

We presented two cases of APAP complicated with sarcoidosis. In one case, sarcoidosis occurred after the remission of APAP, while in the other case, sarcoidosis was the predominant disease, and APAP was diagnosed simultaneously. Of note, the serum anti-GM-CSF autoantibody results were positive in both cases, but the levels were low at the time of the diagnosis of sarcoidosis. We therefore suspect a pathophysiological link between APAP and sarcoidosis.

Sarcoidosis is a systemic granulomatous disease with an unknown etiology that is histologically characterized by well-formed non-necrotizing epithelioid granuloma (9, 10). It commonly affects young and middle-aged adults and shows bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and cutaneous lesions. Previous investigators have suggested environmental exposure of microbial agents, including mycobacterium and *Propionibacterium acnes*, as possible causative factors (10). The infiltration of macrophages and T-lymphocytes, as well as various cytokines, including tumor necrosis factor- α and GM-CSF, contributes to granuloma formation (10). Increased GM-CSF messenger ribonucleic acid (mRNA) in the BAL is correlated with the clinical activity of sarcoidosis and lymphocytes in the BAL, while serum ACE levels can be significantly elevated in cases of sarcoidosis with an increased ex-

Table 3. Reported Cases of APAP Complicated with Sarcoidosis and Our Cases.

	Case A ^[6]	Case B ^[23]	Case C ^[24]	Case 1 ^{**}	Case 2 ^{**}
Gender	Female	Female	Female	Female	Male
Age at APAP diagnosis, years	57	65-66	58	29	51
Age at sarcoidosis diagnosis, years	58-59	64	51	40	51
Other conditions	No	Scleroderma	No	ANA (Nucleolar)	Anti-MAC Ab(+)
Preceding disease	APAP	Sarcoidosis	Sarcoidosis	APAP [*]	Simultaneous
Trigger of APAP	No	Steroid	No	No	No
Trigger of sarcoidosis	WLL	No	No	No	No
Serum levels of anti-GM-CSF Ab at sarcoidosis diagnosis, µg/mL	NE	35.1	NE	3.53	18.5 (6.2*)
Serum levels of anti-GM-CSF Ab at APAP Diagnosis, µg/mL	NE	10.8	4.8	102	18.5
Steroid use at onset of APAP	No	Yes	No	No	No
Steroid for respiratory failure due to sarcoidosis	(-)	(+)	(-)	(+)	(+)
Organs of sarcoidosis	Lung, hilar LN	Lung, hilar LN, eye, liver, muscle	Lung, hilar LN	Lung, hilar LN, eye, skin	Lung, hilar LN, eye, skin

APAP: autoimmune pulmonary alveolar proteinosis, ANA: anti-nuclear antibody, MAC: mycobacterium avium complex, WLL: whole lung lavage, GM-CSF: granulocyte-macrophage-colony-stimulating factor, LN: lymph nodes

*: Anti-GM-CSF antibody decreased at the start of corticosteroid when disease activity of sarcoidosis of Case 2 was worsened.

**: Case 1 and Case 2 were reported in this manuscript.

pression of GM-CSF mRNA (11).

The pathophysiologic role of GM-CSF differs between APAP and sarcoidosis. APAP cases are generally immunocompromised owing to dysfunctional macrophages and neutrophils due to the presence of anti-GM-CSF autoantibodies (12, 13). Previous reports have therefore described cases of chronic infection of mycobacterium, fungus, and nocardia (14, 15). Bacteria can grow subclinically in APAP patients before apparent infectious foci occur in the body with clinical symptoms. For example, *Mycobacterium avium* (MAC) was detected in fluids recovered from the lung washed by whole-lung lavage (16), despite no apparent radiological findings indicative of MAC infection being detected on HRCT films of APAP. Therefore, the causative microbial agents of sarcoidosis may accumulate in the lungs of APAP patients before the clinical presentation.

In Case 1, sarcoidosis occurred following remission of APAP. In Case 2, disease conditions associated with sarcoidosis worsened after the simultaneous diagnosis of sarcoidosis and APAP. In both cases, the serum anti-GM-CSF autoantibody levels continuously decreased, and functionally normalized macrophages may have responded to the increased causative microbial agents and either induced or aggravated sarcoidosis. Trapnell et al. suggested the critical threshold of serum anti-GM-CSF autoantibody level for determining a normal macrophage function to be around 10 µg/mL (17, 18). In both of our cases, prednisolone treatment was needed to control sarcoidosis when the anti-GM-CSF autoantibody levels dropped below 10 µg/mL. Boerner et al. also reported an APAP case complicated with sarcoidosis (Table 3, Case A), in which sarcoidosis occurred after the remission of APAP treated with whole-lung lavage (6). It is possible that the normalized macrophage function induced

sarcoidosis in the patient (Case A). Hoffman et al. reported that the alveolar macrophage function of PAP cases improved after the whole-lung lavage (19); however, serial levels of serum anti-GM-CSF autoantibody were not measured in this study.

There are a few reports supporting our hypothesis that some infection-related diseases, including sarcoidosis, occur following APAP remission. Our institution reported a case of tuberculous lymphadenitis that occurred after remission of APAP treated with GM-CSF inhalation therapy (20). The serum anti-GM-CSF autoantibody levels of that case at the time of the tuberculous lymphadenitis diagnosis were also about 10 µg/mL (unpublished data). Possible causative pathogens of sarcoidosis, including mycobacterium and *P. acnes*, were not detected by culture in the biopsy specimens of the two cases presented in our manuscript. However, immune-staining using PAB antibody (21) might be able to detect *P. acnes* in biopsy specimens, although we did not perform that kind of investigation for our two cases.

Granulomas are generally formed to confine pathogens, restrict inflammation, and protect surrounding tissues (10). In APAP cases, the pathogen can easily enter the lymphatic system without being contained in a granuloma at the initial infected site, as the granuloma may not be sufficiently formed. Therefore, a causative pathogen contracted via the airway can easily spread to systemic organs through the bloodstream. The presence of cutaneous and ocular lesions associated with sarcoidosis in both of our cases was consistent with the hypothesis that macrophage dysfunction observed in two previous APAP cases caused the systemic spread of microbes that were potentially causative for sarcoidosis.

Cutaneous and pulmonary diseases improved in both

cases following treatment with corticosteroids. Akasaka et al. reported that corticosteroid administration induced aggravation of APAP activity because corticosteroids suppressed the function of alveolar macrophages in addition to anti-GM-CSF autoantibodies in the blood (22). Indeed, Yamasue et al. reported a preceding case of sarcoidosis in which PAP occurred after introducing steroid therapy (Table 3, Case B) (23). Anti-GM-CSF autoantibodies were retrospectively detected in preserved serum material collected before steroid therapy (23). We have reduced the corticosteroid dose as much as possible for our two cases and are cautiously observing the disease activity of sarcoidosis in order to prevent APAP recurrence.

Three previously reported cases (6, 23, 24) and our two present cases of APAP complicated with sarcoidosis were reviewed in Table 3. Sarcoidosis preceded APAP in two cases (Case A, Case 1), APAP preceded sarcoidosis in two cases (Case B, C), and both diseases were simultaneously diagnosed in one case (Case 2). The pathophysiology of sarcoidosis preceding APAP (Case B, C) might differ from that of APAP preceding sarcoidosis. In Case B and C, chronic inflammation of sarcoidosis may have been associated with the induction or upregulation of anti-GM-CSF antibody levels, leading to APAP. Immunosuppressive therapy for sarcoidosis might also have affected the occurrence of APAP in Case B. Regarding Case B, anti-GM-CSF antibody was positive at the sarcoidosis diagnosis, so APAP might have occurred insidiously before the sarcoidosis diagnosis and then reoccurred after the immunosuppressive therapy (25). From the standpoint of this hypothesis, the multiorgan involvement of sarcoidosis observed in Case B is thus considered to be consistent with our cases.

In conclusion, we experienced two cases of APAP complicated with sarcoidosis. Low-grade positive serum anti-GM-CSF autoantibody was suspected to be correlated with the occurrence of sarcoidosis and resolution of APAP. Further studies are needed to draw definite conclusions concerning the pathophysiologic link between APAP and sarcoidosis.

Author's disclosure of potential Conflicts of Interest (COI).

Yoshikazu Inoue: Advisory role, Boehringer Ingelheim.

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