

[CASE REPORT]

Pulmonary Alveolar Proteinosis with Ulcerative Colitis

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Abstract:

A 65-year-old Japanese man was referred to our hospital for the further assessment of cough and dyspnea. He had a history of ulcerative colitis for which he was receiving treatment. Chest computed tomography showed a crazy-paving pattern. His bronchoalveolar lavage fluid had a milky appearance, and a transbronchial lung biopsy specimen revealed acellular periodic acid-Schiff stain-positive bodies. The serum anti-granulocyte macrophage-colony stimulating factor (GM-CSF) antibody titer was elevated. The diagnosis was autoimmune pulmonary alveolar proteinosis (PAP). There are few reports of autoimmune PAP in patients with ulcerative colitis. Some reports suggest that PAP and inflammatory bowel disease might have a common pathogenesis involving the anti-GM-CSF antibody.

Key words: anti-GM-CSF antibody, Crohn's disease, inflammatory bowel disease

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare lung disease caused by the accumulation of surfactant components in the alveoli and terminal airways. There are three main types of PAP: hereditary, secondary, and autoimmune, all of which are caused by insufficient surfactant clearance by alveolar macrophages. Autoimmune PAP, which accounts for 90% of cases of PAP, is caused by immunoglobulin G autoantibodies that block the effect of granulocyte macrophage-colony stimulating factor (GM-CSF), a crucial step in the maturation of macrophages, leading to the accumulation of surfactant proteins and cellular debris in the alveolar space and disruption of gas exchange (1-3). It has been reported that 35-70% of patients with autoimmune PAP have comorbidities (2, 4).

Inflammatory bowel disease (IBD) is a term that describes a miscellany of inflammatory diseases of the gastrointestinal tract, with the two most common entities being Crohn's disease (CD) and ulcerative colitis (UC) (5). Up to 50% of pa-

tients with IBD experience at least 1 extra-intestinal manifestation, which may include the lung (6).

We herein report a patient with UC who developed autoimmune PAP.

Case Report

A 65-year-old Japanese man was referred to our hospital for the further assessment of cough and dyspnea. He had been diagnosed with UC 20 years earlier, for which he had been receiving symptomatic treatment with salazosulfapyridine. A colonoscopy performed one year before the diagnosis of PAP revealed scarring throughout the colon and longitudinal ulceration affecting the transverse and descending colon in particular. His stools were loose, and testing for fecal occult blood was negative. At that time, he was assessed as having mild total colitis. He had also been diagnosed with prostate cancer four years earlier that was treated with flutamide, and there had been no metastasis. He had quit smoking at 28 years of age and had no history of dust exposure.

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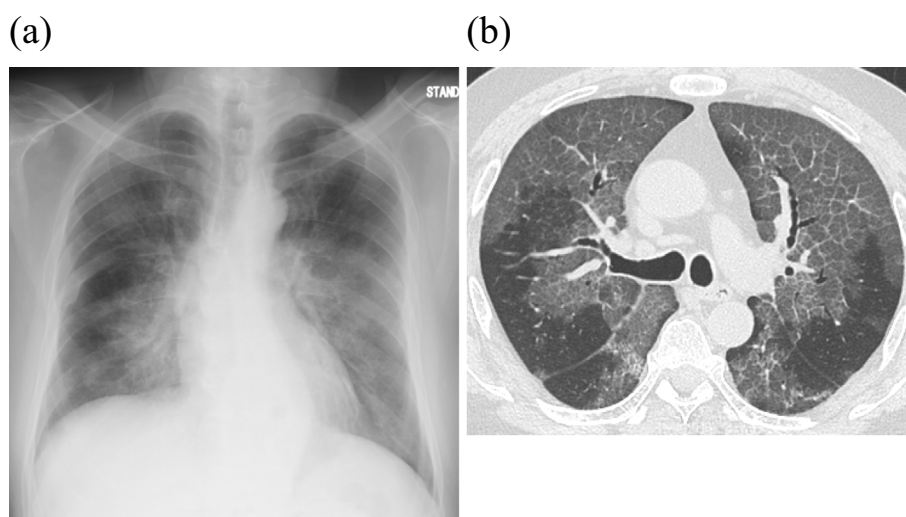


Figure. Radiological findings on admission. (a) A chest radiograph showing ground glass shadows in the lower lung field bilaterally. (b) A chest computed tomographic image showing diffuse ground glass attenuation accompanied by thickened interlobular septa with a crazy-paving appearance.

A physical examination on admission revealed a temperature of 36.4°C, blood pressure of 141/98 mmHg, and a regular pulse of 98 beats/min. Lung auscultation revealed normal vesicular sounds in both lungs. Laboratory findings included the following: white blood cells, 5,900/ μ L; hemoglobin, 14.9 g/dL; lactate dehydrogenase, 405 IU/L; Krebs von den Lungen-6 level, 2,154 U/mL; and prostate-specific antigen, 0.042 ng/mL. Arterial blood gases while breathing room air in the supine position revealed a partial pressure of oxygen of 64.8 Torr. Sputum microbiology revealed normal flora. Pulmonary function tests showed a percent vital capacity of 114.7%, a forced expiratory volume in one second/forced vital capacity of 89.4%, and a diffusing capacity of the lungs for carbon monoxide of 48.5%. A chest radiograph showed bilateral ground glass attenuation, predominantly in the lower fields (Figure a). Chest computed tomography also showed diffuse ground glass attenuation, which was accompanied by thickened interlobular septa with a crazy-paving appearance (Figure b). The bronchoalveolar lavage fluid had a milky appearance, and a transbronchial lung biopsy specimen contained acellular periodic acid-Schiff stain-positive bodies. The serum anti-GM-CSF antibody titer was elevated at 62.8 μ g/mL. The diagnosis was autoimmune PAP. The patient underwent segmental bronchoalveolar lavage but developed subarachnoid hemorrhage at the time of the second lavage. Whole-lung lavage was performed after surgery for the subarachnoid hemorrhage. Thereafter, there was marked improvement in his symptoms, exercise desaturation levels, and findings on chest radiography.

Discussion

The present patient had a pre-existing diagnosis of UC and developed autoimmune PAP that improved after whole-lung lavage. A small proportion of patients with autoim-

mune PAP have other inflammatory diseases, including UC (2). Previous studies have reported UC as a comorbidity in 4.2% (1/24), 3.1% (2/64), and 0.5% (1/212) of patients with autoimmune PAP (2, 4, 7).

IBD is known to have extra-intestinal manifestations, including in the lungs (8). The pulmonary complications of IBD include inflammation of the small and large airways, pulmonary parenchymal disease, serositis, and pulmonary embolism (9). However, we could not find any reports of PAP as a pulmonary manifestation of IBD.

GM-CSF is a cytokine that promotes the survival and activation of mature myeloid cells and therefore contributes to the maintenance of innate immune homeostasis (10). Previous studies have suggested that GM-CSF also has proinflammatory activity and plays a critical role in the development of autoimmune and inflammatory diseases (11, 12). Major sources of GM-CSF include activated T-cells and B-cells, monocytes/macrophages, endothelial cells, and fibroblasts; other sources include epithelial cells and Paneth cells (13). Higher levels of GM-CSF secretion have been detected in mucosal lesions in patients with CD and those with UC than in controls with normal mucosa (14), suggesting that GM-CSF in the intestinal mucosa reflects the host response to external stimuli (e.g., microbial infection) and has a role in inflammatory and autoimmune reactions (15). GM-CSF knockout mice are reportedly more susceptible to dextran sulfate sodium-induced colitis than wild type mice (16), and clinical trials of GM-CSF in patients with CD have demonstrated a reduction in disease activity (17, 18). Therefore, there are lines of evidence indicating that GM-CSF has an important role in the intestinal mucosa in terms of repair of injury and the immune and inflammatory responses (15).

Anti-GM-CSF antibodies are known to be elevated in serum and in the bronchoalveolar lavage fluid of patients with autoimmune PAP, playing a crucial role in the pathogenesis

of the disease, but the reasons why these antibodies are produced are unclear (1, 2). Anti-GM-CSF antibodies were found to be produced in the lamina propria by mononuclear cells isolated from ileal resection specimens and to be elevated in the serum and associated with disease activity, prediction of relapse, and a higher likelihood of needing IBD-related surgery, especially in patients with CD (19-23). Anti-GM-CSF antibodies are present at low levels in healthy individuals and have been suggested to play a regulatory role in the healthy state (24), but the mechanism by which these antibodies are produced and their role in IBD are unclear. Compared with CD, relatively limited data have been reported on anti-GM-CSF antibodies in patients with UC. Although the anti-GM-CSF antibody levels in patients with CD are reported to be elevated compared with those in patients with UC (21, 25), serum anti-GM-CSF antibody levels have been found to be significantly higher in patients with active UC than in those with inactive UC (25). Further research is needed to identify the reason for the difference in the anti-GM-CSF antibody levels between CD and UC and the association between GM-CSF and UC.

The patient described here also had prostate cancer. Three publications on comorbid malignancy in patients with autoimmune PAP have reported rates of 4.2% (1/24), 0% (0/64), and 1.9% (4/212) (2, 4, 7). We could not find any reports on PAP complicated by prostate cancer in the literature.

We considered the possibility that long-term production of anti-GM-CSF antibodies as a result of UC might have triggered the development of autoimmune PAP in our patient. However, the diagnosis of UC preceded that of PAP by 20 years, the UC was not active at the time of the diagnosis of PAP, and the time course of the serum anti-GM-CSF antibody titer was not known in this case. Therefore, speculation regarding a link between elevated anti-GM-CSF antibody levels and autoimmune PAP might be premature. Further studies are needed to clarify this association and the role of the anti-GM-CSF antibody in such diseases.

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

References

- Ben-Dov I, Segel MJ. Autoimmune pulmonary alveolar proteinosis: clinical course and diagnostic criteria. *Autoimmun Rev* **13**: 513-517, 2014.
- Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am J Respir Crit Care Med* **177**: 752-762, 2008.
- Uchida K, Nakata K, Trapnell BC, et al. High-affinity autoantibodies specifically eliminate granulocyte-macrophage colony-stimulating factor activity in the lungs of patients with idiopathic pulmonary alveolar proteinosis. *Blood* **103**: 1089-1098, 2004.
- Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. *Respir Med* **105**: 1908-1916, 2011.
- Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. *Lancet* **369**: 1627-1640, 2007.
- Harbord M, Annesse V, Vavricka SR, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. *J Crohns Colitis* **10**: 239-254, 2016.
- Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK. Pulmonary alveolar proteinosis: clinical features and outcomes. *Chest* **114**: 1357-1362, 1998.
- Majewski S, Piotrowski W. Pulmonary manifestations of inflammatory bowel disease. *Arch Med Sci* **11**: 1179-1188, 2015.
- Mahadeva R, Walsh G, Flower CD, Shneerson JM. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. *Eur Respir J* **15**: 41-48, 2000.
- Hamilton JA, Achuthan A. Colony stimulating factors and myeloid cell biology in health and disease. *Trends Immunol* **34**: 81-89, 2013.
- El-Behi M, Ciric B, Dai H, et al. The encephalitogenicity of T(H) 17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. *Nat Immunol* **12**: 568-575, 2011.
- Codarri L, Gyulveszi G, Tosevski V, et al. ROR γ t drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. *Nat Immunol* **12**: 560-567, 2011.
- Shiomi A, Usui T. Pivotal roles of GM-CSF in autoimmunity and inflammation. *Mediators Inflamm* **2015**: 568543, 2015.
- Noguchi M, Hiwatashi N, Liu ZX, Toyota T. Increased secretion of granulocyte-macrophage colony-stimulating factor in mucosal lesions of inflammatory bowel disease. *Digestion* **63**(Suppl 1): 32-36, 2001.
- Egea L, Hirata Y, Kagnoff MF. GM-CSF: a role in immune and inflammatory reactions in the intestine. *Expert Rev Gastroenterol Hepatol* **4**: 723-731, 2010.
- Xu Y, Hunt NH, Bao S. The role of granulocyte macrophage-colony-stimulating factor in acute intestinal inflammation. *Cell Res* **18**: 1220-1229, 2008.
- Valentine JF, Fedorak RN, Feagan B, et al. Steroid-sparing properties of sargramostim in patients with corticosteroid-dependent Crohn's disease: a randomised, double-blind, placebo-controlled, phase 2 study. *Gut* **58**: 1354-1362, 2009.
- Korzenik JR, Dieckgraefe BK, Valentine JF, Hausman DF, Gilbert MJ; Sargramostim in Crohn's Disease Study G. Sargramostim for active Crohn's disease. *N Engl J Med* **352**: 2193-2201, 2005.
- Jurickova I, Collins MH, Chalk C, et al. Paediatric Crohn disease patients with stricturing behaviour exhibit ileal granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibody production and reduced neutrophil bacterial killing and GM-CSF bioactivity. *Clin Exp Immunol* **172**: 455-465, 2013.
- Dykes DM, Towbin AJ, Bonkowski E, et al. Increased prevalence of luminal narrowing and stricturing identified by enterography in pediatric Crohn's disease patients with elevated granulocyte-macrophage colony stimulating factor autoantibodies. *Inflamm Bowel Dis* **19**: 2146-2154, 2013.
- Gathungu G, Kim MO, Ferguson JP, et al. Granulocyte-macrophage colony-stimulating factor autoantibodies: a marker of aggressive Crohn's disease. *Inflamm Bowel Dis* **19**: 1671-1680, 2013.
- Han X, Uchida K, Jurickova I, et al. Granulocyte-macrophage colony-stimulating factor autoantibodies in murine ileitis and progressive ileal Crohn's disease. *Gastroenterology* **136**: 1261-1271, e1-e3, 2009.
- Nylund CM, D'Mello S, Kim MO, et al. Granulocyte macrophage-colony-stimulating factor autoantibodies and increased intestinal permeability in Crohn disease. *J Pediatr Gastroenterol Nutr* **52**: 542-548, 2011.
- Uchida K, Nakata K, Suzuki T, et al. Granulocyte/macrophage-colony-stimulating factor autoantibodies and myeloid cell immune functions in healthy subjects. *Blood* **113**: 2547-2556, 2009.
- Dabritz J, Bonkowski E, Chalk C, et al. Granulocyte macrophage colony-stimulating factor auto-antibodies and disease relapse in in-

inflammatory bowel disease. *Am J Gastroenterol* **108**: 1901-1910, 2013.

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