IgG4-related disease in asbestos-related pleural disease

Yasutaka Onishi, Yasuharu Nakahara, Katsuya Hirano, Shin Sasaki, Tetsuji Kawamura & Yoshiro Mochiduki

Department of Respiratory Medicine, National Hospital Organization Himeji Medical Center, Himeji City, Japan.

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Correspondence
Yasutaka Onishi, Department of Respiratory Medicine, National Hospital Organization Himeji Medical Center, Honnmachi 68, Himeji City 670-8520, Hyogo, Japan. E-mail: yonishi@hmj-net.hosp.go.jp

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Abstract
A 67-year-old man with a history of asbestos exposure and rounded atelectasis complained of cough and swelling in the left submandibular region. Computed tomography showed an increase in size of the right lower lung lobe lesion, which was recognized as the pre-existing rounded atelectasis, as well as swelling of the pancreas and submandibular glands. Biopsy from a submandibular gland and the pulmonary lesion led to a diagnosis of immunoglobulin G4-related disease (IgG4-RD). IgG4-RD is a recently recognized disease that was first reported as an autoimmune disease; however, some reports have indicated another pathogenesis of an allergic nature that is characterized by type 2 helper T cell (Th2) inflammation. Additionally, it is recognized that long-term exposure to asbestos can cause immune dysregulation. Here we present a case of IgG4-RD associated with asbestos-related pleural disease. Asbestos-induced immune dysregulation may be one etiology of IgG4-RD.

Introduction
Since the first report on immunoglobulin G4-related disease (IgG4-RD) in 2001, many reports have demonstrated that excessive Th2-dominant inflammation triggers the development of IgG4-RD through the recruitment of regulatory T cells (Tregs), class switching to IgG4, and enhanced TGF-β production resulting in systemic fibrotic changes. Meanwhile, factors that promote and sustain excessive Th2 immune reaction have been little investigated [1].

Recent studies have shown that asbestos exposure can induce development of immunological disorders because of the immunotoxicological effects on Tregs. In addition, nanoparticles of asbestos act as Th2 adjuvants and induce Th2 immune responses such as activation of mast cells and promotion of IgE [2].

We present here a case of IgG4-RD who had been exposed to asbestos and discuss the relationship between IgG4-RD and asbestos.

Case Report
Our patient is a 67-year-old man who worked in interior finishing work and had used asbestos from 20 to 62 years of age, and smoked one pack of tobacco per day for 20 years. He had regular medical checkups because of pleural thickening and subpleural consolidation in the right lower lobe, which had been diagnosed as asbestos-related rounded atelectasis, and that had been stable for 8 years. He consulted our hospital because of a cough and swelling of his left submandibular region. The physical examination revealed bilateral swelling of the submandibular glands. Chest X-ray and computed tomography (CT) revealed increased size of the right lower lobe consolidation (Fig. 1A, B). Swelling of the pancreas, submandibular glands, and mediastinal lymph nodes were also observed (Fig. 1C). Positron emission tomography/CT showed increased uptake of 18-fluorodeoxyglucose in the consolidation in the right lower lobe (SUVmax = 4.9), pancreas (SUVmax = 5.0), left submandibular gland (SUVmax = 10.2), and mediastinal lymph nodes (SUVmax = 5.6) (Fig. 1D). A magnetic resonance cholangiopancreatography revealed irregular narrowing of the main pancreatic duct. His serum IgG (3159 mg/dL; normal range, 870–1700 mg/dL), IgG4 (1430 mg/dL; normal <105 mg/dL), and IgE (407 IU/mL; normal <232 IU/mL) values were elevated. His total protein, albumin, amylase, renal function, and liver function were normal. He was negative for a variety of
autoimmune antibodies, including anti-nuclear and anti-neutrophil cytoplasmic antibodies.

This characteristic distribution of affected organs and high serum IgG4 suggested the development of IgG4-RD. A biopsy specimen from the left submandibular gland revealed dense lymphoplasmacytic infiltration in the acinar tissue, interstitial fibrosis, and atrophy of the acinus (Fig. 2A). Immunostaining showed remarkable infiltration of IgG4-positive plasma cells (IgG4-positive/IgG-positive plasma cell ratio was more than 50%) (Fig. 2B). Histological findings obtained by transbronchial biopsy of the right lower lobe consolidation showed significant infiltration of lymphocytes and plasma cells, and fibrosis in the alveolar interstitium (Fig. 2C). Similarly, immunostaining revealed infiltration of IgG4-positive plasma cells (IgG4-positive/IgG-positive plasma cell ratio was more than 50%) (Fig. 2D).

These clinical features and histopathological findings confirmed a diagnosis of IgG4-RD. Swelling of the pancreas with narrowing of the main pancreatic duct was considered to be autoimmune pancreatitis. Administration of prednisolone (PSL) at a dose of 40 mg/day (0.6 mg/kg/day) reduced his serum IgG and IgG4 values, and improved the swelling of the submandibular glands, pancreas, and the consolidation in the right lower lobe, although the rounded atelectasis persisted (Fig. 1E). His clinical course has been uneventful during the tapering course of PSL.

Discussion

IgG4-RD is a disease with an unknown cause that impairs multiple organs. In our case, asbestos exposure seemed to have been related to the onset of IgG4-RD because a pulmonary lesion emerged around the rounded atelectasis that was considered to be a consistent manifestation of ARPD. Hitherto, two cases of IgG4-RD with a history of asbestos exposure were reported; however, the direct relationship between the two was not discussed [3, 4].

Asbestos is defined as the fibrous form of mineral silicates containing silica, iron, and magnesium, and because of its remarkable stability, the immune system cannot get rid of this toxic material. It is well known that asbestos exposure can cause pernicious diseases such as malignant mesothelioma, while recent studies revealed that asbestos may induce development of immunological disorders. Otsuki et al. reported that long-term asbestos exposure caused the dysfunction of Tregs, which usually regulate immune reactions [2]. On the other hand, Zen et al.
reported that Tregs were increased in the affected organs in a case of IgG4-RD to suppress excessive Th2 reaction, although the Tregs may have been functionally abnormal [5]. Thus, dysfunction of Tregs caused by asbestos exposure may be related to the development of IgG4-RD.

IgG4-RD, which was first reported as an autoimmune disease, is now gradually being considered to be potentially allergic in nature. The predominant Th2 and regulatory cytokines and elevated serum IgE, which are often found in allergic disorders such as bronchial asthma, are also seen in IgG4-RD. Further, Takeuchi et al. reported that mast cells, which are thought to have interdependent roles with IgE in chronic inflammation and tissue remodeling, showed strong positivity for IgE in IgG4-RD [1]. In addition, most particulate adjuvants like silica or asbestos are considered to stimulate Th2-mediated humoral immune responses and promote IgE production. Taking these findings into account, asbestos exposure could trigger IgG4-RD through induction of persistent Th2 responses and mast cells activated by sustained IgE production.

In summary, this case reports a potential relationship between asbestos exposure and the pathogenesis of IgG4-RD.

Disclosure Statements
No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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