INTERNAL MEDICINE

□ CASE REPORT □

IgG4-related Lung Disease in a Worker Occupationally Exposed to Asbestos

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Abstract

A case of IgG4-related lung disease in a worker who had been exposed to asbestos is described. The patient had nocturnal cough and wheeze that responded to inhaled corticosteroid, and the radioallergosorbent test was positive against common allergens, suggesting an association with atopic asthma. IgE elevation is reported in asbestos-exposed workers, and asbestos exposure may cause atopic conditions. Predominance of Th2 cytokines and up-regulation of regulatory T lymphocytes have been reported in IgG4-related disease. IgG4-related disease may occur from hypersensitivity of the regulatory immune system to atopic conditions. Asbestos exposure may be a causal factor of IgG4-related disease.

Key words: IgG4-related systemic sclerosing disease, asbestos, bronchial asthma

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Introduction

IgG4-positive plasma cell infiltration can occur in almost all major organs, including the lungs. Some of these IgG4-related diseases include autoimmune pancreatitis, sclerosing sialadenitis, and sclerosing cholangitis. These conditions share clinical and pathological characteristics, such as high serum IgG4 concentrations, sclerosing inflammation with many IgG4-positive plasma cells, and effectiveness of corticosteroid therapy, and this is recognized as IgG4-related systemic sclerosing disease (1, 2). However, the pathogenesis of IgG4-related systemic sclerosing disease has not been fully clarified. A case of IgG4-related lung disease in a worker who was occupationally exposed to asbestos is described, and a possible relationship between IgG4-related systemic sclerosing disease and asbestos exposure is discussed.

Case Report

A 57-year-old man complaining of nocturnal cough, wheeze, and exertional dyspnea of 2 years' duration was referred to our hospital. He had a history of smoking (30 cigarettes per day for 30 years), and he had been occupationally exposed to asbestos released during building demolition for 10 years. Physical examination revealed swelling of bilateral cervical and submandibular lymph nodes, as well as the right subauricular lymph nodes. Chest auscultation revealed bilateral fine crackles in both lungs.

A chest radiograph showed bilateral reticular shadows and emphysema (Fig. 1a). HRCT imaging of the lung revealed multiple consolidations (Fig. 1b), nodules, and a subpleural curvilinear shadow (Fig. 1c), as well as ground-glass opacities and emphysema. A pleural plaque and hilar and mediastinal lymphadenopathy were also observed (Fig. 1d). Gallium-67 scintigraphy imaging showed uptake in bilateral cervical, submandibular, and hilar lymph nodes, in the right subauricular lymph nodes, and in bilateral lower lung fields. Pancreatic uptake was not observed, and swelling of the pancreas was not seen on abdominal CT scan.

Laboratory results included: C-reactive protein, 5.9 mg/dL; erythrocyte sedimentation rate, 119 mm/hr; total protein, 12.4 g/dL; albumin, 1.4 g/dL; γ-globulin, 69.1%; IgG, 8,396

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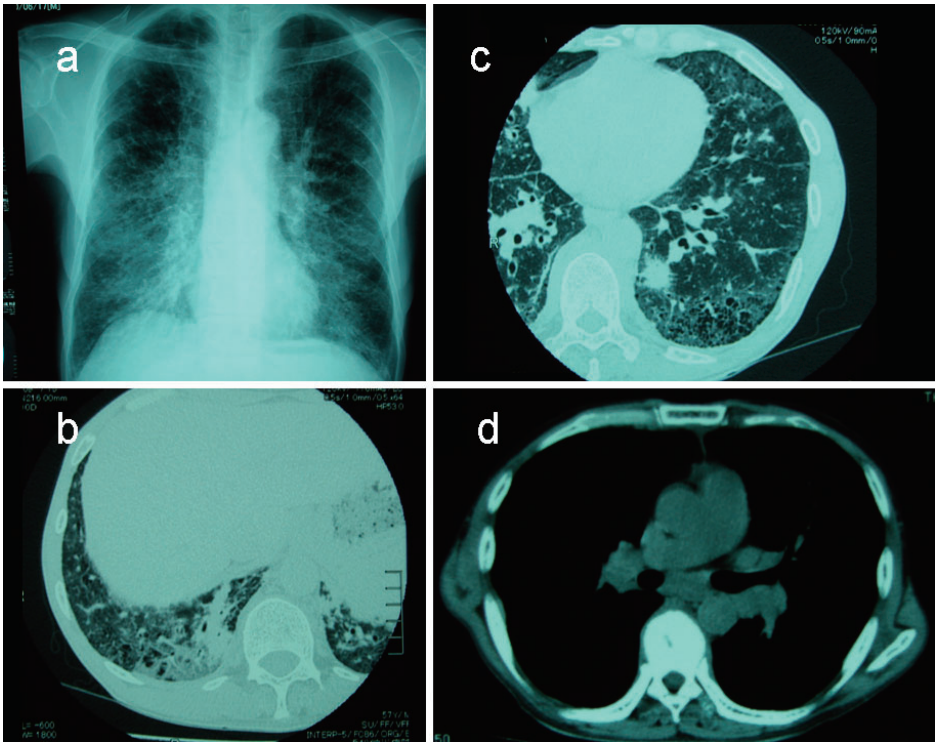

Figure 1. **A chest radiograph shows hyperinflation and reticular and linear shadows in bilateral lung fields (a). High-resolution computed tomography of the chest demonstrates multiple consolidations (b), nodules (c), and a subpleural curvilinear shadow (c), in addition to ground-glass opacities and emphysema. A pleural plaque and swelling of hilar and mediastinal lymph nodes are also observed (d).**

mg/dL; IgG4, 3,520 mg/dL; IgE, 4,940 IU/ml; and KL-6, 711 U/mL. Serum electrolytes, amylase, renal function, and liver function were normal. M-protein was not detected. Radioallergosorbent testing (RAST) for common allergens revealed: dermatophagoides, score 4; moth, score 4; cockroach, score 3; dog scurf, score 2. Respiratory function testing showed a vital capacity of 3.94 L (113.5% predicted) and a forced expiratory volume in one second of 2.44 L (89.4% predicted). Bronchial reversibility after inhalation of procaterol hydrochloride with ultrasonic nebulizer was 1.6%. Arterial blood gas analysis results on room air were: pH, 7.442; PaO_2, 65.4 mmHg; $PaCO_2$, 36.4 mmHg. On the sputum smear, numerous eosinophils were observed.

Transbronchial lung biopsy yielded no significant findings. Video-assisted thoracoscopy was performed, and a nodule at left S^{10} was resected. The surgical specimen showed interstitial and perivascular hyaline sclerosing-type fibrosis associated with lymphoplasmacytic infiltration (Fig. 2a). Immunostaining for IgG and IgG4 was performed using mouse monoclonal antibodies against human IgG (Dako Cytomation, Glostrup, Denmark) and human IgG4 (ZYMED Laboratory, San Francisco, CA, USA). Immunostaining revealed infiltration of numerous IgG4-positive plasma cells in the interstitium (Fig. 2b). IgG4-positive plasma cells accounted for 55.7% of the IgG-positive plasma cells. Thus, the patient was diagnosed as having IgG4-related lung disease and pulmonary emphysema.

Exertional dyspnea improved with tiotropium bromide hydrate, but nocturnal cough and wheeze continued. However, the nocturnal cough and wheeze disappeared after fluticasone propionate (500 μg) and salmeterol xinafoate (50 μg) twice daily were started. Systemic corticosteroid therapy was not given because his respiratory symptoms improved, and no involvement of other organs was observed. His IgG 4-related lung disease and lymphadenopathy have remained stable for more than 2 years after his initial presentation.

Discussion

This report describes a case of IgG4-related lung disease in a worker exposed occupationally to asbestos. The history of asbestos exposure is circumstantial because quantification of asbestos in lung tissue was not performed in this case. However, this patient appears to have certainly been exposed to asbestos because the chest CT scan revealed a pleural plaque, which is only observed in asbestos-exposed individuals in Japan (3). The pathogenesis of IgG4-related systemic sclerosing disease is unclear. However, Zen et al proposed a possible relationship between IgG4-related lung disease and atopic conditions. They reported a predominance of Th2 cytokines and up-regulation of regulatory T lymphocytes in IgG4-related sclerosing pancreatitis and cholangitis, and they proposed that the up-regulated functions of regulatory T lymphocytes in atopic conditions might play a role in this disorder (4). Miura et al also speculated that asbestos

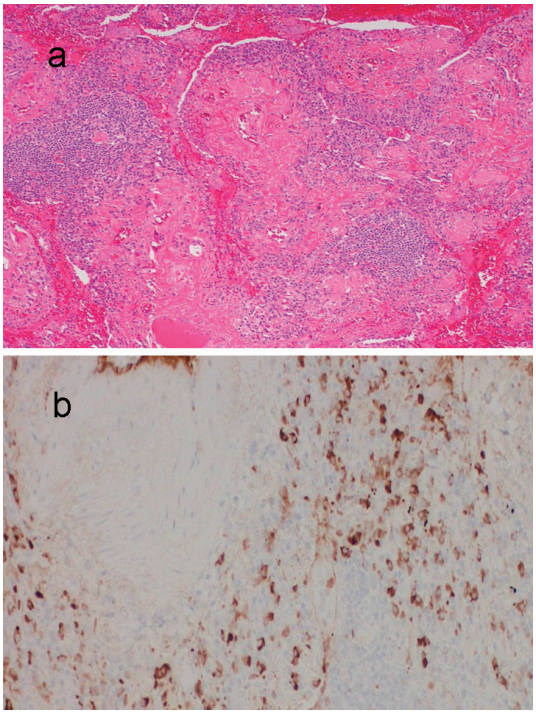

Figure 2. Surgical lung biopsies show interstitial and perivascular hyaline sclerosing-type fibrosis with associated lymphoplasmacytic infiltration (a). Immunostaining of the lung biopsy specimen shows infiltration of numerous IgG4-positive plasma cells in the interstitium (b).

might up-regulate functions of regulatory T lymphocytes in a human T-cell leukemia virus type-1-immortalized human polyclonal T cell line (5).

In the present case, RAST was positive to some common allergens, and numerous eosinophils were observed in the sputum smear. The nocturnal cough and wheeze disappeared with inhaled corticosteroid therapy, suggesting the presence of bronchial asthma, even though bronchial reversibility was not detected. Although the possibility that he had an atopic condition before asbestos exposure cannot be completely excluded, his atopy appears to have developed after asbestos exposure, because he did not have childhood asthma, and his asthmatic symptoms appeared after asbestos exposure. Elevated IgE levels have been reported in asbestos-exposed workers, and asbestos-exposed subjects may develop an atopic environment and, therefore, become more sensitive to allergic stimuli than nonexposed people (6, 7). However, we could not find any studies indicating a relationship between asbestos exposure and bronchial asthma. IgG4 is known to be a blocking antibody to IgE (8). In addition, asbestos exposure has been proposed as a causal factor for both pleural and retroperitoneal fibrosis (9-11), which is known to also be an IgG4-related condition (12). An association between lymphoplasmacytic pancreatitis and bronchial asthma has also been reported (13). Practically, it is thought that IgG4-related systemic sclerosing disease often accompanies atopic diseases such as bronchial asthma (14).

Based on these previous reports, the present patient's exposure to asbestos may have resulted in bronchial asthma, and up-regulated functions of regulatory T lymphocytes to atopic conditions may have induced infiltration of IgG4-positive plasma cells into the lungs, though the mechanisms of the development of atopic conditions in asbestos-exposed subjects remain unknown. However, our hypothesis is only speculative, with no supporting evidence.

In the present case, systemic corticosteroid therapy was not given because the respiratory symptoms disappeared with inhaled corticosteroid and bronchodilator therapy, and no involvement of other organs was observed. Zen et al reported that patients without respiratory symptoms were not treated with systemic corticosteroid in their cases of IgG4-related lung disease (15). There is no consensus report regarding the treatment of IgG4-related lung disease. To establish a treatment guideline for IgG4-related lung disease, further studies involving a large number of patients will be needed.

In conclusion, IgG4-related sclerosing disease may occur as a result of up-regulated functions of regulatory T lymphocytes to atopic conditions. To clarify this point, further investigations on allergic and environmental conditions of IgG 4-related sclerosing disease will be needed.

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