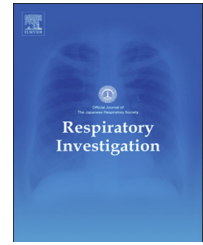




ELSEVIER

Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Case report

Development of pulmonary alveolar proteinosis following exposure to dust after the Great East Japan Earthquake



Shu Hisata^{a,*}, Hiroshi Moriyama^b, Ryushi Tazawa^c, Shinya Ohkouchi^a, Masakazu Ichinose^a, Masahito Ebina^a

^aDepartment of Respiratory Medicine, Tohoku University Graduate, School of Medicine, 1-1 Seiryō-machi, Aoba-ku, Sendai 980-8574, Japan

^bDivision of Respiratory Medicine, Graduate School of Medical and Dental Sciences, Niigata University, 1-757, Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan

^cBioscience Medical Research Center, Niigata University Medical and Dental Hospital, 1-754 Asahimachi-dori, Chuo-ku, Niigata 951-8520, Japan

ARTICLE INFO

Article history:

Received 13 March 2013

Received in revised form

20 April 2013

Accepted 23 April 2013

Available online 4 June 2013

Keywords:

Pulmonary alveolar proteinosis

Earthquake

GM-CSF autoantibody

Whole lung lavage

ABSTRACT

We report a unique case of pulmonary alveolar proteinosis that developed 3 weeks after the Great East Japan Earthquake and the subsequent tsunami. The patient had inhaled dust repeatedly while visiting her devastated neighborhood without wearing a protective mask. Five weeks after the earthquake, lung samples taken from the patient showed foreign particle deposition; however, her serum was negative for GM-CSF autoantibody. The patient's clinical symptoms resolved following whole lung lavage. We conclude that inhalation of fine dust particles after natural disasters may cause the onset of pulmonary alveolar proteinosis.

© 2013 The Japanese Respiratory Society. Published by Elsevier B.V. All rights reserved.

1. Introduction

The Great East Japan Earthquake deeply impacted respiratory health care in the affected areas. During the acute phase of the disaster, in addition to an increase in the number of

patients with “tsunami lung” caused by near-drowning, there was also an increase in the number of patients with common respiratory diseases such as pneumonia and acute exacerbations of COPD and bronchial asthma [1]. During the sub-acute phase of the disaster, patients presented with

Abbreviations: PAP, pulmonary alveolar proteinosis; GM-CSF, granulocyte macrophage colony-stimulating factor; COPD, chronic obstructive pulmonary disease; CT, computed tomography; HRCT, high-resolution computed tomography; BALF, bronchoalveolar lavage fluid; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; CEA, carcinoembryonic antigen; TBLB, transbronchial lung biopsy

*Corresponding author. Tel.: +81 22 717 8534; fax: +81 22 717 8549.

E-mail address: hisata@idac.tohoku.ac.jp (S. Hisata).

allergic lung inflammation, including hypersensitivity pneumonitis and organizing pneumonia. These respiratory conditions occurred not only in the victims of the tsunami but also in the workers engaged to clean up the debris, which contained rubble from buildings and industrial waste material from the sea [2].

Previous studies have shown that dust exposure may be related to the pathogenesis of PAP. Exposure to dust has been reported as a cause of secondary PAP, in which serum GM-CSF autoantibodies are considered negative, but this has not been fully confirmed [3]. Further, recent studies have raised the hypothesis that an inhaled agent may instead be the trigger of the development of autoimmune PAP, characterized by positive GM-CSF autoantibodies [4]. To our knowledge, no increase in the incidence of PAP after natural disasters or the World Trade Center attacks has been reported [5]. However, specific materials contained in the debris from disasters can induce PAP

Here, we report a case of PAP that developed after exposure to dust following the Great East Japan Earthquake.

2. Case presentation

A 63-year-old Japanese woman was referred to our institute for worsening lung infiltrates, dyspnea, and hypoxia. She had never smoked and had a past history of hypertension.

Although she was not otherwise injured her house was completely destroyed in the large tsunami triggered by the Great East Japan Earthquake on March 11 of 2011. After the

earthquake, she repeatedly retrieved personal effects from the rubble without wearing a mask. Since large amounts of sludge and burned embers were scattered throughout the area, she was exposed to various kinds of inhaled dust. Three weeks after the earthquake, she developed dry cough and her chest X-ray showed bilateral reticular shadows (Fig. 1Aa). The computed tomography (CT) of her chest showed diffusely-distributed ground glass opacity in the subpleural area (Fig. 1Ab). At the previous hospital, analysis of her bronchoalveolar lavage fluid (BALF) revealed lymphocytosis (lymphocytes: 89.0%, CD4/CD8: 3.6) without turbidity and a transbronchial lung biopsy (TBLB) did not indicate PAP. However, upon re-evaluation, we detected particles within the lung (Fig. 2A), and an electron probe X-ray microanalysis revealed the deposition of silicon, oxygen, and aluminum, while other specific elements were not detected (data not shown). On clinical suspicion of idiopathic interstitial pneumonias, she was treated with prednisolone, cyclosporin, and methylprednisolone pulse therapy. Eight months later, she was referred to our University Hospital as the treatment was not fully effective.

On admission, her blood pressure was 137/98 mm Hg; pulse, 105 beats/min; and body temperature, 36.8 °C. Chest examination revealed slight bilateral inspiratory crackles, and a chest X-ray showed a significant loss of lung volume (Fig. 1Ba). High-resolution computed tomography (HRCT) of the chest showed diffuse ground-glass opacities with superimposed interlobular septal thickening and intralobular lines (Fig. 1Bb). Five weeks after admission, pulmonary function testing showed that the patient had a severe, restrictive pattern (vital capacity, 1.17L; 52.7% predicted) with reduced

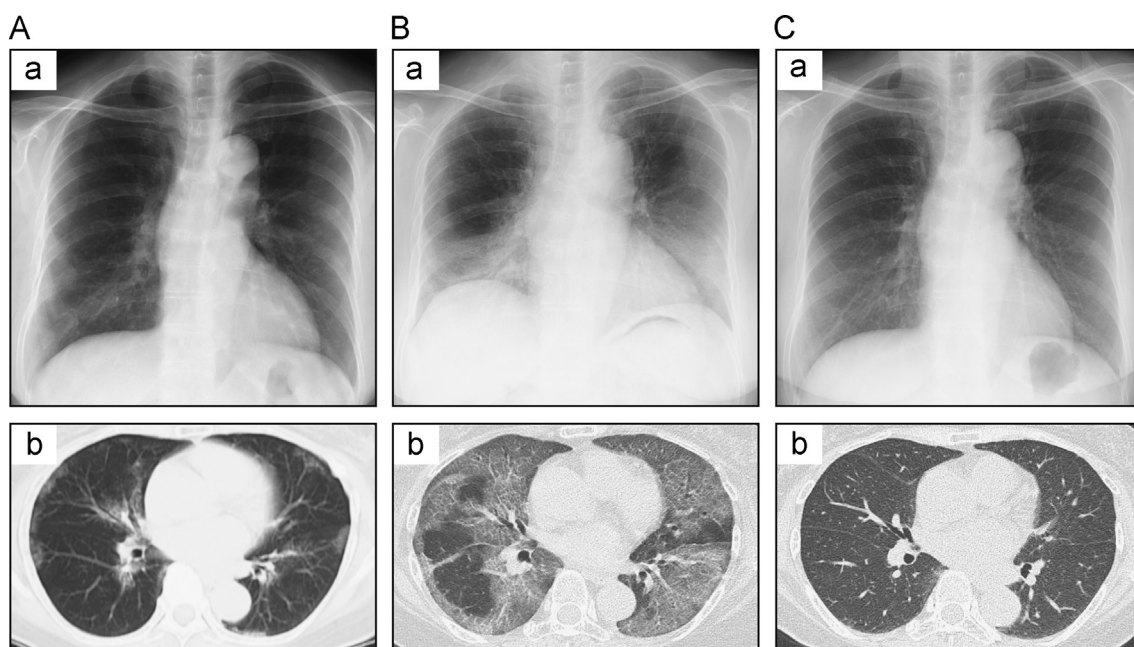


Fig. 1 – X-ray (a) and computed tomography (b) of the chest (A) at the initial visit in the previous hospital (April 2011), showing limited ground glass opacity in the subpleural area; (B) at 3 weeks after admission to our hospital (January 2012), showing significant loss of lung volume and a wide range of ground-glass opacities with superimposed interlobular septal thickening and intralobular lines; (C) at 6 months after the whole lung lavage (August 2012), showing improvements in the lung volume and ground glass opacities.

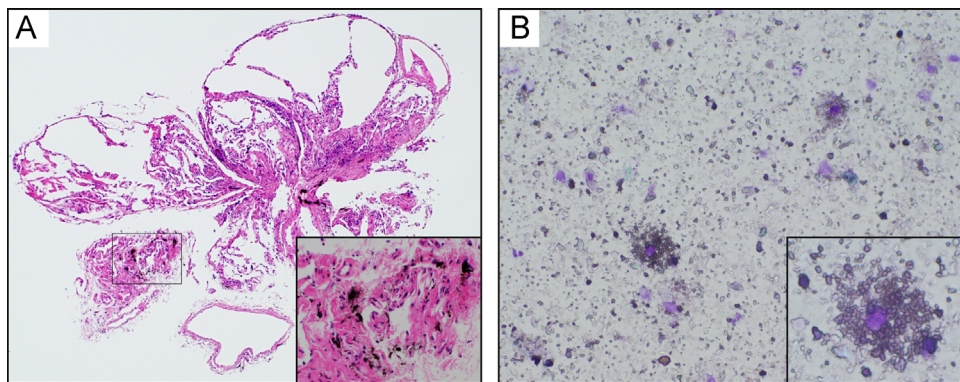


Fig. 2 – Pathological findings. (A) Hematoxylin-Eosin staining of patient's lung tissue obtained in April 2011, by transbronchial lung biopsy at the previous hospital, showing dark brown particles without typical findings as protein alveolar proteinosis ($\times 20$); lower right box: partial enlargement of black box ($\times 200$). (B) Appearance of bronchoalveolar lavage fluid obtained in January 2012 at our hospital, showing large foamy macrophages and amorphous materials ($\times 100$); lower right box: enlargement of a foamy macrophage. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

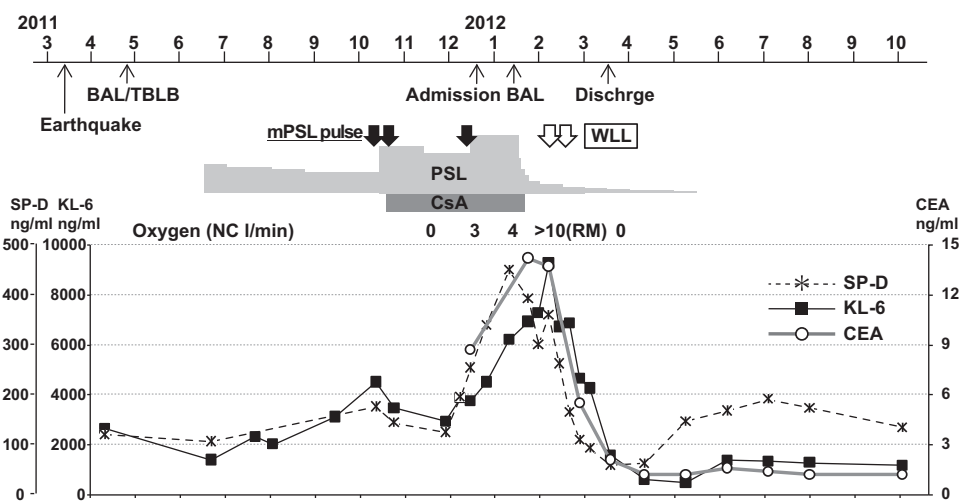


Fig. 3 – The patient's clinical course is outlined and clearly shows improving clinical parameters following admission to our hospital and the whole lung lavage procedure. WLL: whole lung lavage; PSL: prednisolone; mPSL: methylprednisolone; CsA: cyclosporin A; NC: nasal cannula; RM: reservoir face mask. Cut off: SP-D < 109 ng/mL, KL-6 < 435 U/mL, and CEA < 5.0 ng/mL.

carbon monoxide diffusing capacity (38.2% predicted). The patient's serum levels of Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) were elevated to 3752 U/mL and 254 ng/mL, respectively (Supplementary Table S1).

At first, steroid and immunosuppressive therapy had been continued, because an acute exacerbation of interstitial pneumonia could not be excluded. However, the patient was re-evaluated in response to the HRCT imaging as described above. Her BALF showed a milky appearance with large foamy macrophages and amorphous materials (Fig. 2B). TBLB could not be performed owing to severe hypoxia. Her serum was negative for GM-CSF autoantibody.

Under the diagnosis of PAP, the doses of prednisolone and cyclosporine were gradually decreased. Even after the discontinuation of these agents, her hypoxia progressed at a relatively rapid rate, and 5 days before whole lung lavage, her

alveolar–arterial oxygen gradient was 71.8 Torr. Under extracorporeal membrane oxygenation, she underwent bilateral whole lung lavage at 2-week intervals (Fig. 3). Subsequently, her hypoxia, infiltration observed on HRCT, and levels of serum biomarkers (KL-6, SP-D, CEA) dramatically improved (Fig. 1Ca, Cb; Fig. 3). After 1 year, despite having slightly elevated levels of serum biomarker, she had no further respiratory symptoms.

3. Discussion

In this report, we describe a case of PAP that developed after the tsunami triggered by the Great East Japan Earthquake. To the best of our knowledge, no cases of PAP have been reported in association with other major tsunami disasters [6]

or following the World Trade Center attacks [5]; however a case of PAP was reported after the Great Hanshin Earthquake in Japan [7]. Although we observed only a single case, we believe that inhalation of materials within the dust deposited by the tsunami can induce PAP.

In this case, we believe that, in spite of the negative findings of bronchoscopy, it would have been reasonable to diagnose PAP at the patient's initial visit. First, the patient had symptoms after exposure to large amounts of dust over several weeks. At the initial visit, analysis of the patient's BALF excluded infectious or malignant diseases, the CT-image showed subpleural ground glass opacities, consistent with the features of PAP [8] and the infiltrates continued to expand despite steroid therapy. Second, 5 weeks after the tsunami her lung-specimen showed plenty of deposits. Since she had never smoked, the presence of these particles suggested that she had been exposed to large amounts of dust. The clinical symptoms resolved almost entirely after whole lung lavage therapy was performed. After admission to our hospital, the sub-acute exacerbation could have been precipitated by the prednisolone or cyclosporin treatment, as has been previously reported [9].

Previous studies have shown that secondary PAP can occur as a consequence of underlying conditions (such as hematologic or autoimmune diseases), infections, or exposure to inhaled dust including silica, titanium, aluminum, cement, and tin [3]. However, the presence of serum GM-CSF autoantibodies was not confirmed in most of the reported cases. In a large cohort of Japanese patients, secondary PAP without GM-CSF autoantibodies was limited to those with hematologic or autoimmune comorbidities [10]. In contrast, 26% of patients with autoimmune PAP had a history of dust exposure [11]. Furthermore, a case of autoimmune PAP associated with exposure to indium-tin oxide has been reported [12]. These studies have raised the hypothesis that an inhaled agent may be the trigger for the development of autoimmune PAP [4]. In the case presented here, the serum level of GM-CSF autoantibodies barely exceeded the cutoff (0.9 µg/mL in December 2012, cut off <0.5 µg/mL) 1 year after the initial visit to our hospital, while autoantibodies could not be detected in the active phase of PAP (Supplementary Table S2). *In vitro* studies revealed that the serum from this patient had an inhibitory effect on GM-CSF signaling (Supplementary Fig. S1). Accordingly, in this case we propose that a low titer of GM-CSF autoantibodies might be associated with the development of PAP. However, there are limitations to this interpretation. First, our *in vitro* studies cannot clarify whether this inhibitory effect on GM-CSF signaling is due to the presence of GM-CSF autoantibodies. We cannot exclude the possibility that other factors in the serum inhibited GM-CSF signaling and thus caused PAP. Second, during the active phase of PAP the patient was negative for GM-CSF autoantibody, and as such there is a discrepancy between the titer of autoantibody and the activity of PAP. The level of serum immunoglobulin G decreased to 383 mg/dL at the initial visit to our hospital (Supplementary Table S2), suggesting that large amounts of steroid and immunosuppressive agents could lower the level of autoantibodies. Furthermore, the effect of immunosuppression on the pathogenesis of PAP has not been determined.

The contribution of element comprising particle deposition within the lung to the development of PAP is not fully understood, although an association between PAP and iron

accumulation in alveolar macrophages has been reported [13]. In our elemental analysis of the patient's lung specimen, the ratio of silicon, oxygen, and aluminum was high, which indicates silica and aluminum oxide, while iron was also detected. Although silicon and aluminum are also found in the normal lung, silica and aluminum have been reported to cause the onset of PAP [3]. Therefore, the amount of an inhaled agent may be an important factor in the development of PAP.

In conclusion, we present a unique case of PAP that developed after exposure to dust following the tsunami triggered by the Great East Japan Earthquake. In the future, monitoring the incidence of PAP following disasters, as well as assessing the air for hazardous substances in affected areas, will be required.

Conflict of interest

The authors have no potential conflict of interest related to the manuscript.

Acknowledgments

The authors gratefully acknowledge Mr. Brent K. Bell for reading the manuscript.

This work was supported in part by grants from the Ministry of Health, Labor and Welfare of Japan (H24-Nanchitou-Nan-Ippan-035).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.resinv.2013.04.005>.

REFERENCES

- [1] Yamanda S, Hanagama M, Kobayashi S, et al. The impact of the 2011 Great East Japan Earthquake on hospitalisation for respiratory disease in a rapidly aging society: a retrospective descriptive and cross-sectional study at the disaster base hospital in Ishinomaki. *BMJ* 2013 Jan 3;3(1). pii: e000865.
- [2] Nukiwa T. An overview of respiratory medicine during the Tsunami Disaster at Tohoku, Japan, on March 11, 2011. *Respir Invest* 2012;50:124–8.
- [3] Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med* 2002;166:215–35.
- [4] Costabel U, Nakata K. Pulmonary alveolar proteinosis associated with dust inhalation: not secondary but autoimmune? *Am J Respir Crit Care Med* 2010;181:427–8.
- [5] Perlman SE, Friedman S, Galea S, et al. Short-term and medium-term health effects of 9/11. *Lancet* 2011;378:925–34.
- [6] Guha-Sapir D, van Panhuis WG. Health impact of the 2004 Andaman Nicobar earthquake and tsunami in Indonesia. *Prehosp Disaster Med* 2009;24:493–9.
- [7] Tsuchiya Takaaki, Nishimura Yoshihiro, Kotani Yoshikazu, et al. Secondary pulmonary alveolar proteinosis in a patient

- engaged in building demolition work. *Nihon Kogyoku Gakkai Zasshi* 1999;37:219–23.
- [8] Satoh H, Tazawa R, Sakakibara T, et al. Bilateral peripheral infiltrates refractory to immunosuppressants were diagnosed as autoimmune pulmonary alveolar proteinosis and improved by inhalation of granulocyte/macrophage-colony stimulating factor. *Intern Med* 2012;51:1737–42.
- [9] Samuels MP, Warner JO. Pulmonary alveolar lipoproteinosis complicating juvenile dermatomyositis. *Thorax* 1988;43:939–40.
- [10] Ishii H, Tazawa R, Kaneko C, et al. Clinical features of secondary pulmonary alveolar proteinosis: pre-mortem cases in Japan. *Eur Respir J* 2011;37:465–8.
- [11] 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* 2008;177:752–62.
- [12] Cummings KJ, Donat WE, Etensohn DB, et al. Pulmonary alveolar proteinosis in workers at an indium processing facility. *Am J Respir Crit Care Med* 2010;181:458–64.
- [13] Shimizu Y, Matsuzaki S, Dobashi K, et al. Elemental analysis of lung tissue particles and intracellular iron content of alveolar macrophages in pulmonary alveolar proteinosis. *Respir Res* 2011;12:88.