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Letter to the Editor

# Increase in autoimmune pulmonary alveolar proteinosis after the 2011 Fukushima disaster

*Dear Editor,*

The Great East Japan Earthquake and tsunami on March 11, 2011, resulted in the Fukushima nuclear power plant accident, which consequently led to a massive emission of radioactive substances. Although it is important to know how the disaster affects the victims' health status, the number of reports on lung diseases are limited.[1,2] We investigate the effect of the disaster on patients with pulmonary alveolar proteinosis (PAP), who were admitted to Fukushima Medical University Hospital, located 57 km away from the Fukushima Daiichi Nuclear Power Plant. Participants gave written informed consent and the Fukushima Medical University Ethics Committee approved this study.

PAP is a rare pulmonary disease characterized by abnormal accumulation of surfactant lipids and protein in the alveolar spaces resulting in impairment of gas exchange.[3] Signaling by granulocyte-macrophage colony-stimulating factor (GM-CSF), which is critical for surfactant homeostasis by alveolar macrophages in the lungs, is impaired in PAP. In the majority of patients with PAP, GM-CSF autoantibodies, which decrease GM-CSF bioactivity, were present in the serum and bronchoalveolar lavage (BAL) fluid, and PAP with the antibody is considered to be autoimmune PAP (aPAP).[4] Although detailed pathogenesis of PAP is still unknown, Hisata *et al.* reported a patient who developed PAP following dust exposure after the Great East Japan Earthquake.[5] This finding prompted us to investigate whether the Fukushima disaster increased the number of aPAP patients.

We reviewed patients with aPAP who had been admitted to our hospital retrospectively, and the prevalence of the patients before and after Fukushima disaster was evaluated. PAP was diagnosed by the characteristic findings of chest high resolution computed tomography, BAL fluid with milk-like appearance and pathologic and/or cytologic specimens obtained by a transbronchial lung biopsy. In patients with PAP, serum levels of GM-CSF autoantibody were analyzed, and patients with diseases known to cause PAP, such as hematological malignancy, were excluded. We next compared clinical characteristics, such as laboratory data and pulmonary function tests between the patients who developed aPAP, before and after the disaster.

In the four years prior to the disaster, the number of patients with aPAP was only one out of 387 patients with interstitial lung diseases. On the other hand, in the four years following the disaster, the number of aPAP patients was seven out of 386 interstitial lung disease patients, showing a significant increase (0.35 vs 1.85%, $p < 0.05$). The place of residence of the aPAP patients at the time of the earthquake was not regarded as an impacting factor for the disease. Because we had only one aPAP patient before the disaster, it is difficult to compare the exact difference in clinical characteristics of the aPAP patients before and after the disaster. However, it seems that the clinical condition of the aPAP patients who developed after the disaster was possibly more severe on admission, as such patients had lower partial arterial oxygen pressure and vital capacity % predicted and higher serum Krebs von den lungen-6, compared with the patient who was observed before the disaster (Table 1). On the other hand, the titer of the GM-CSF antibody measured on admission was not different between the patients who developed aPAP before and after the disaster (32.5 and 30.3 ± 5.6 ug/ml, respectively). With regard to the clinical course of the patients who developed aPAP after the disaster, five patients (71.4%) were clinically improved during follow-up. Because 42.5% of patients has been reported to be improved in a large Japanese cohort of 223 aPAP patients,[4] it may be possible that the clinical course was not severe in the patients who developed aPAP after the disaster.

In the Hisata *et al.* report of the 63-year-old Japanese woman who developed PAP from dust exposure after the Great East Japan Earthquake,[5] the patient visited a devastated neighborhood without a protective mask and repeatedly inhaled dust. Three weeks after the earthquake, she developed a dry cough and was diagnosed as having PAP. In addition, Tsuchiya *et al.*, reported a case in which a 41-year-old Japanese man had developed PAP after the Great Hanshin Earthquake in 1995.[6] He was involved in building demolition and also inhaled dust. Both reports suggest the possibility of dust exposure after a disaster being a cause of PAP development. In fact, the relationship between secondary PAP and exposure to dust, such as silica and aluminum, is widely believed.[3] In patients with secondary PAP, GM-CSF antibody is not usually detected in the serum and BAL fluid. In the case reported by Hisata *et al.*,[5] GM-CSF antibody was not detected in the serum, and an electron probe X-ray microanalysis of the lung biopsy samples showed a deposition of silica and aluminum. This case further suggests the relationship between secondary PAP and dust exposure. In our study, all patients with PAP were diagnosed as having aPAP, due to the findings of positive GM-CSF antibodies in the serum. Although the relationship between dust exposure and aPAP is not clarified,[7] Inoue *et al.* has reported that 26% of patients with aPAP had a history of dust exposure.[4] Furthermore, the presence of GM-CSF antibody was not confirmed in the majority of cases diagnosed as secondary PAP including the

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**Table 1**
Characteristics of patients with autoimmune pulmonary alveolar proteinosis before and after the disaster.

| | Total (n = 8) | Before the Disaster (n = 1) | After the Disaster (n = 7) |
|---|---|---|---|
| Age (yr) | 51.6 ± 7.4 | 21 | 55.9 ± 7.1 |
| Gender (M/F) | 5/3 | 1/0 | 4/3 |
| Smoking (C/F/N) | 1/2/5 | 0/1/0 | 1/1/5 |
| WBC (/mm$^3$) | 7757 ± 1093 | 5300 | 7680 ± 1259 |
| LDH (IU/L) | 302 ± 41.8 | 158 | 312 ± 46.8 |
| CRP (mg/dL) | 0.44 ± 0.25 | 0.03 | 0.50 ± 0.28 |
| ESR (mm/hr) | 9.5 ± 3.5 | 0 | 10.4 ± 3.7 |
| KL-6 (IU/L) | 7298 ± 3375 | 4470 | 7699 ± 3870 |
| SP-A (ng/mL) | 159.5 ± 38.0 | 70.0 | 168.1 ± 42.8 |
| SP-D (ng/mL) | 183.2 ± 38.2 | 169.9 | 182.1 ± 44.1 |
| CEA (ng/mL) | 20.7 ± 9.6 | 4.3 | 22.7 ± 10.8 |
| PaO2 (Torr) (room air) | 68.4 ± 3.7 | 82.2 | 66.8 ± 3.9 |
| VC (L) | 3.02 ± 0.37 | 4.99 | 2.69 ± 0.19 |
| %VC (%) | 85.4 ± 8.4 | 105.5 | 82.4 ± 9.1 |

Before the Disaster: from March 11, 2007 to March 10, 2011, After the Disaster: from March 11, 2011 to March 10, 2015. C/F/N, Current/Ex/Never smoker; WBC, white blood cells; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; KL-6, Krebs von den Lungen-6; SP-A, surfactant protein-A; SP-D, surfactant protein-D; CEA, carcinoembryonic antigen; $PaO_2$, arterial partial pressure of oxygen; VC, vital capacity. Mean ± SEM.

case that Tsuchiya *et al.* reported. In addition, Cummings *et al.* reported a case of aPAP after indium-tin oxide exposure,[8] and it has been recently demonstrated that 34.2% of patients with aPAP had a history of occupational inhalational exposure.[9] We also evaluated smoking history, because aPAP is reported to have some relation with smoking.[4,10] In seven patients who had developed aPAP after the disaster, five did not have smoking history and one had quitted smoking more than 30 years before the disaster. The remaining one patient had stopped smoking immediately after the disaster, but resumed smoking after one month. These results suggest that smoking did not affect the development of aPAP in most patients.

Our hospital is located inland of northern Fukushima Prefecture and did not experience a tsunami; however, many houses in the area suffered construction or interior damage, such as wall cracks and roof collapse. Although it is difficult to draw a conclusion, these facts also suggest the possibility that dust exposure may be the trigger of aPAP development.

In summary, a significant increase in the number of patients with aPAP was observed after the 2011 Fukushima Disaster. Although the pathogenesis of aPAP has not been fully clarified, the results of this study provide the further evidence on the relationship between aPAP and dust inhalation. In the future, further investigations such as analysis of gene–environment interaction are necessary.

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*Conflict of interest*
The authors have no conflict of interest to declare.

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