Early View

Research letter

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Acute Exacerbation of Idiopathic Pulmonary Fibrosis after SARS-CoV-2 Vaccination

Tomohiro Bando¹, Reoto Takei¹, Yoshikazu Mutoh², Hajime Sasano¹, Yasuhiko Yamano¹, Toshiki Yokoyama¹, Toshiaki Matsuda¹, Kensuke Kataoka¹, Tomoki Kimura¹, and Yasuhiro Kondoh¹

Affiliations

¹Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, Japan

²Department of Infectious Diseases, Tosei General Hospital, Seto, Japan

Correspondence

Yasuhiro Kondoh

Department of Respiratory Medicine and Allergy, Tosei General Hospital

160 Nishioiwake-cho, Seto, Aichi 489-8642, Japan

TEL: +81-561-82-5101, FAX: +81-561-82-9139.

E-mail: kondoh@tosei.or.jp

Take Home Message

Although the association between acute exacerbation of interstitial lung disease and vaccination is not yet clarified, this is the first case report describing the possibility that SARS-CoV-2 vaccination may trigger acute exacerbation.

Author's contributions

All authors fulfill the criteria of authorship. TB, RT, YM and YK wrote the original manuscript. All authors contributed to revisions of the manuscript, provided final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread worldwide and coronavirus disease 2019 remains a top health concern. Several SARS-CoV-2 vaccines have been produced and are playing great roles in the prevention of infection and worsening to a severe state, and in improving mortality [1]. However, some concerns about adverse effects related to SARS-CoV-2 vaccination have been raised. Recently, various adverse effects have been reported, but there is little data on adverse effects on the lungs [2].

We treated a patient with fibrotic interstitial lung disease (f-ILD) who needed hospitalization for acute respiratory failure and newly arising bilateral ground-glass opacities (GGO) on chest high-resolution computed tomography (HRCT) within nine days after his second mRNA SARS-CoV-2 vaccination. A full inpatient evaluation was performed and the patient was diagnosed with acute exacerbation (AE) of f-ILD (AE-f-ILD), raising a question on the relationship between SARS-CoV-2 vaccination and AE. Since recent studies have reported high mortality among f-ILD patients with SARS-CoV-2 infection [3, 4], this case has potential clinical significance and we present the clinical course below with some discussion.

An 84-year-old male was previously diagnosed with f-ILD (Figure 1A) and regularly followed at another hospital from October 2020. He was not receiving any medication. He had a former smoking history of 34 pack-years, and no significant past medical history. In mid-May 2021, he received his first BNT162b2 vaccine (BioNTech/Pfizer), which produced no adverse effects. In June 2021, he received his second vaccine and

gradually developed malaise and loss of appetite from the day following the vaccination. The symptoms persisted without improvement for nine days after he received the second vaccine, and he visited a nearby hospital. His chest HRCT revealed diffuse GGO with basal and subpleural honeycomb and reticulation (Figure 1B), and he was referred to our hospital.

On admission, his vital signs were a temperature of 38.4 degrees Celsius, respiratory rate of 20 breaths per minute, and peripheral oxygen saturation of 91% in ambient air. Physical examination revealed bilateral fine crackles and no signs of heart murmur, leg edema, or clubbed fingers. Arterial blood gas analysis on admission revealed hypoxemia and respiratory alkalosis (pH 7.493, PaCO₂ 33.5 mmHg, PaO₂ 56.4 mmHg, HCO₃⁻ 25.7 mmol/L). Laboratory findings were as follows: white blood cells 9300 cells/mL (neutrophils 82.3 %, lymphocytes 6.9 %, eosinophils 3.0 %), C-reactive protein (CRP) 4.09 mg/dL, lactate dehydrogenase 591 U/L, KL-6 1837 U/mL, SP-D 693 ng/mL, and procalcitonin 0.111 ng/mL. The remaining serological tests were all unremarkable, including various factors related to connective tissue disease (rheumatoid factor, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, anti-ARS antibody and others). SARS-CoV-2 antigen test and PCR were both negative. His sputum culture revealed no significant bacteria.

We began treatment with antibiotics to observe his initial response. However, despite antibiotic treatment for seven days, the bilateral GGO spread and his respiratory failure remained, requiring supplemental oxygen of 1L/min with a nasal canula. His CRP level remained high and KL-6 was elevated to 2042 U/mL on day 11 after admission, which led us to perform bronchoalveolar lavage (BAL) on day 12. The BAL fluid analysis was 14.0% neutrophils, 36.5% lymphocytes and 5.5% eosinophils. Cultures of BAL fluid

showed no evidence of bacterial infection. Since his previous chest HRCT showed subpleural reticulation and honeycomb compatible with idiopathic pulmonary fibrosis (IPF), we diagnosed his condition as AE-IPF.

Treatment with intravenous corticosteroids (two cycles of methylprednisolone 1000 mg/day for three days followed by 1 mg/kg/day) was initiated, after which methylprednisolone was gradually titrated from 60 mg to 10 mg, by 10 mg each every three or four days. After steroid pulse treatment, the GGO on chest HRCT improved but subpleural reticulation remained and progressed (Figure 1C). His respiratory condition stabilized without supplemental oxygen. After two weeks of rehabilitation, he was discharged to a care medical facility while receiving 10 mg of oral corticosteroids on the 71st day from admission.

We treated a patient with ILD who had acute respiratory failure and new GGO soon after receiving the SARS-CoV-2 vaccine. Even though he did not undergo a full evaluation for ILD when it was revealed at his former hospital, we retrospectively diagnosed him with IPF. This case met the criteria of AE defined in an international working group report [5]. We diagnosed the condition as AE-IPF, of which the AE could have been triggered by SARS-CoV-2 vaccination. The etiology of AE-ILD remains unknown, but causes such as bacterial/viral infection, certain procedures or surgeries, and drug toxicity have been reported to trigger the pathogenesis of AE [6]. Some vaccinations have also been reported to be a potential cause of AE. Previous case reports showed possible triggering of AE of IPF by influenza A vaccination [7] [8]. A case of AE of connective tissue disease-associated f-ILD resulting from an influenza

vaccine was also reported [9]. These three cases were diagnosed as f-ILD (two IPF and one CTD-ILD) before vaccination. Their HRCT showed bilateral GGO and they had respiratory failure several days after vaccination. All of them were treated with corticosteroid pulse therapy and their respiratory condition and CT findings improved after initial treatment. Although the relationship between ILD and vaccination has not been fully elucidated, these findings suggest that vaccination could trigger AE-ILD. No firm conclusion can be reached from this small number of case reports, but those earlier cases and our case share a similar clinical course and radiological features. Therefore, it is reasonable to conclude that our patient experienced AE-IPF triggered by SARS-CoV-2 vaccination.

No previous study on AE-f-ILD triggered by SARS-CoV-2 vaccine has been reported. Park et al. has reported a case of SARS-CoV-2 vaccine-related ILD [10], and the WHO global pharmacovigilance database (VigiAccess) showed 464 cases of suspected ILD, 87 cases of suspected organizing pneumonia, eight cases of acute lung injury and two cases of acute interstitial pneumonitis and idiopathic interstitial pneumonia from the BNT162b2 vaccine. However, no AE-f-ILD cases were seen [11], nor was AE-f-ILD reported in a clinical trial [2]. Therefore, to our knowledge, this is the first report of AE-f-ILD that could have been triggered by SARS-CoV-2 vaccination.

The pathogenesis of AE triggered by vaccination remains unclear. SARS-CoV-2 vaccination has been revealed to induce T cell responses reflected in production of some cytokines, such as interferon-gamma and interleukin-2 [12]. Since a high percentage of the population that receives SARS-CoV-2 vaccination experiences fatigue and fever as side effects, some sort of immune response likely occurs in the body, possibly provoking AE in f-ILD patients. However, AE-f-ILD occurs with a certain probability in

patients with f-ILD, with an incidence rate reported to be around 5-10% per year [5] [6].

In this case, we cannot prove whether this event just happened to overlap with the timing of vaccination, or was triggered by the vaccination itself. Further study of the possible association between SARS-CoV-2 vaccination and AE is needed, by evaluating numbers of vaccinated patients with ILD and the incidence of AE among those patients.

In conclusion, this is the first case report describing AE-f-ILD after SARS-CoV-2 vaccination. Unquestionably, vaccination is a very effective method of preventing SARS-CoV-2 infection and has more benefits than risk. However, little is known about whether vaccination itself could cause AE-f-ILD, and further investigation of the relation between vaccination and AE is needed.

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Case: 84 years old male

Figure 1: HRCT and chest X-ray photo findings with simple clinical course. 1A (taken eight months prior to admission) shows subpleural reticulation and honeycomb structure compatible with fibrotic interstitial lung disease. 1B shows chest images on admission. Newly developed bilateral and diffuse GGO and underlying subpleural honeycomb and reticulation are seen in his HRCT. 1C shows chest images before discharge. GGO has improved. Below, his simple clinical course is shown. Numbers show clinical days from second vaccination. GGO; ground-glass opacities, HRCT; high-resolution computed tomography, BAL; bronchoalveolar lavage, mPSL; methylprednisolone