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Case Report

Acute exacerbation of idiopathic pulmonary fibrosis after bivalent {tozinameran and famtozinameran} mRNA COVID-19 vaccination

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ABSTRACT

An 82-year-old man diagnosed with interstitial lung disease through computed tomography (CT) 1 year prior received a bivalent (tozinameran and famtozinameran) mRNA COVID-19 vaccine. He developed respiratory symptoms 1.5 months later, and chest high-resolution CT revealed new ground-glass opacities showing traction bronchiectasis. Transbronchial lung cryobiopsy revealed organizing acute lung injury and fibrosis with architectural destruction. The patient was diagnosed with an acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF). The bivalent mRNA COVID-19 vaccination was determined as the cause of the AE-IPF based on detailed medical history and examination findings. High-dose corticosteroid therapy improved the patient's symptoms and radiological findings.

1. Introduction

Acute exacerbation of interstitial lung disease (AE-ILD) is a condition in which new ground-glass opacities (GGOs) or consolidations appear in bilateral lung fields. Rapid progression of respiratory failure is observed during the chronic course of fibrotic interstitial pneumonia, especially idiopathic pulmonary fibrosis (IPF) [1–3]. The pathological features of AE-IPF are mainly a diffuse alveolar damage pattern and occasionally mixed findings of an organizing pneumonia pattern, known as acute lung injury (ALI) [4]. COVID-19 is now prevalent worldwide, and a few cases of AE-ILD triggered by COVID-19 have been reported [5]. COVID-19 vaccination has been proven highly effective in preventing the onset of SARS-CoV-2 infection and may reduce the incidence of COVID-19–triggered AE-ILD [6]. However, a rare case of AE-IPF following conventional monovalent mRNA COVID-19 vaccination has been reported [7–10]. Bivalent vaccines, tozinameran and famtozinameran, against omicron strains of COVID-19 became available in Japan in September 2022 and are expected to be more effective in preventing severe disease, infection, and disease onset against omicron strains of COVID-19 than conventional monovalent vaccines. Tozinameran and famtozinameran are bivalent vaccines containing mRNA (i.e., the blueprint for the spike protein) components of both conventional and omicron strains. No cases of AE-ILD after inoculation

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with tozinameran and famtozinameran have been reported. We herein present a case of AE-IPF with a comparatively slow course after inoculation with tozinameran and famtozinameran.

2. Case presentation

The patient was an 82-year-old Japanese man with a smoking history of 10 pack-years. He had undergone laparoscopic-assisted robotic distal gastrectomy for gastric cancer using Billroth II reconstruction 1 year previously. When he underwent surgery, computed tomography (CT) revealed abnormal findings in his chest, suggestive of ILD, for which he did not receive any treatment (Fig. 1A). He was vaccinated with the BNT162b2 and mRNA-1273 vaccines twice, for a total of four doses, but he had no specific exacerbation of respiratory symptoms. After these vaccinations, he was inoculated with a bivalent mRNA COVID-19 vaccine in mid-November 2022. Chest and abdominal CTs were performed in mid-December 2022, which revealed that the patient's ILD worsened. He had dyspnea on exertion, cough, and anorexia since early January 2023. He was suspected of having ILD exacerbation (Fig. 1B) and was referred to our department in early February.

On admission, his vital signs were as follows: temperature, 36.6 °C; respiratory rate, 15 breaths/minute; peripheral oxygen saturation, 96 % in room air. Physical examination revealed bilateral fine crackles, but no signs of heart murmur, leg edema, or clubbed fingers were observed. Laboratory findings were as follows: white blood cells, 7400 cells/mL (neutrophils, 73.5 %; lymphocytes, 20 %; eosinophils, 2.7 %); C-reactive protein, 0.75 mg/dL; lactate dehydrogenase, 219 U/L; Krebs von den Lungen, 770 U/mL; surfactant protein D, 255 ng/mL. The remaining serological tests were unremarkable, including various factors related to connective tissue disease (rheumatoid factor, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, and anti-aminoacyl tRNA synthetase antibody). Both SARS-CoV-2 antigen and polymerase chain reaction tests were negative. Chest high-resolution CT (HRCT) revealed basal and subpleural reticulations and new GGOs showing traction bronchiectasis, predominantly in the bilateral lower lobes (Fig. 1B).

He had extensive GGOs and fibrosis on chest HRCT but did not have hypoxemia. We used the HRCT findings of extensive GGOs as basis for an alternative diagnosis according to IPF diagnosis guidelines [11], but we also considered AE-IPF. Bronchoscopy was necessary to determine the cause of the GGOs and fibrosis observed on chest HRCT, and performing bronchoscopy in his condition was feasible. He consented to the examination and underwent bronchoalveolar lavage (BAL) from the left B4 and transbronchial lung cryobiopsy (TBLC) from the left B9a. BAL fluid analysis showed macrophages (50.0 %), lymphocytes (47.4 %), neutrophils (1.0 %), and eosinophils (1.6 %). BAL fluid culture showed lymphocytosis, but no findings were suggestive of infection. TBLC revealed extensive alveolar epithelium swelling with alveolar lymphocyte infiltration and foamy alveolar macrophages, suggesting that the alveolar epithelial injury was caused by inflammation. Organizing pneumonia was also observed. Dense fibrosis with architectural destruction and fibroblastic foci was also observed, suggesting the presence of a usual interstitial pneumonia (UIP)–pattern fibrosis in the background (Fig. 2). We determined that the previously reported interstitial pneumonia was idiopathic pulmonary fibrosis and confirmed that the patient had AE-IPF. High-dose corticosteroid therapy (methylprednisolone 500 mg/day for 3 days) was initiated, followed by maintenance therapy with 35 mg/day prednisolone (PSL); the patient improved without any worsening of oxygenation or respiratory symptoms. He was discharged 10 days after admission, during which he was receiving 30 mg/day PSL. These treatments improved the patient's dyspnea on exertion and dry cough. Thereafter, the PSL dose was tapered to 5 mg every 2–4 weeks. Three months after high-dose corticosteroid therapy, HRCT revealed that the GGOs were reduced, but subpleural reticulation, which suggests IPF, remained (Fig. 1C).

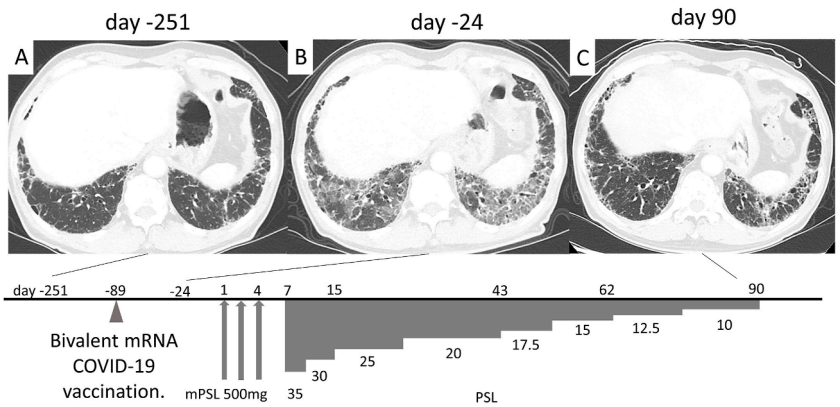

Fig. 1. Representative CT images before and after bivalent mRNA COVID-19 vaccination. (A) CT performed 5 months before bivalent mRNA COVID-19 vaccination revealed basal and subpleural reticulations. (B) CT performed 2 months after bivalent mRNA COVID-19 vaccination revealed new GGOs showing traction bronchiectasis predominantly in the bilateral lower lobes. (C) High-resolution CT revealed improvement of GGOs 3 months after high-dose steroid therapy, but the subpleural reticulation, which suggests idiopathic pulmonary fibrosis, remained. CT, computed tomography; GGOs, ground-glass opacities; mPSL, methylprednisolone; PSL, prednisolone.

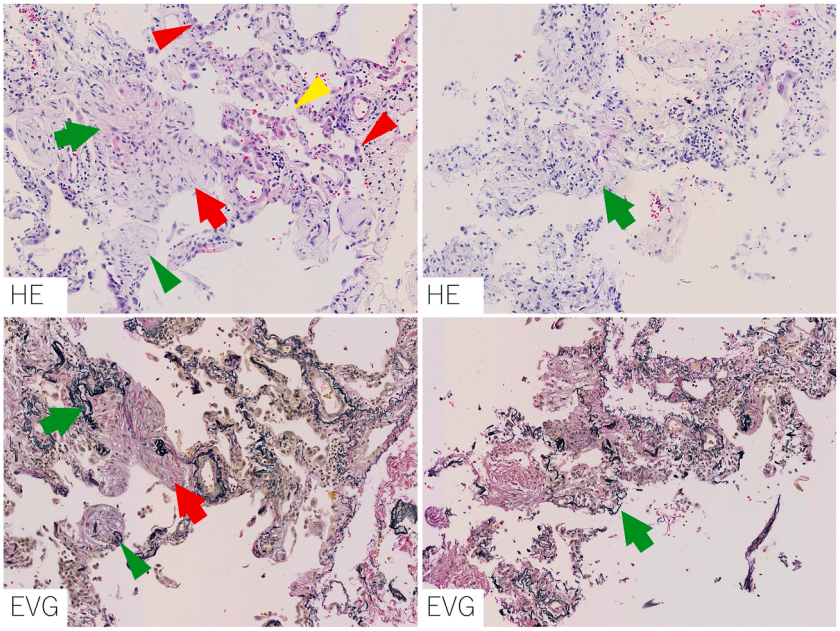

Fig. 2. Pathology determined by transbronchial lung cryobiopsy. Some dense fibrosis with architectural destruction (green arrow) and fibroblastic foci (red arrow), which are suggestive of a usual interstitial pneumonia pattern, are observed. Extensive alveola epithelium swelling (red arrowhead), foamy alveolar macrophages (yellow arrowhead), and organizing pneumonia (green arrowhead) were also observed, which suggest organizing acute lung injury. EVG, elastin van Gieson; HE, hematoxylin and eosin.

3. Discussion

AE-IPF is a serious condition triggered by an infection or other event that leads to rapid worsening of a patient's respiratory condition. Recently, several cases of AE-IPF caused by COVID-19 vaccine have been reported [7–10]. Bivalent vaccines against the omicron strains of COVID-19, tozinameran and famtozinameran have recently become available to many people. However, to our knowledge, no cases of AE-IPF caused by this bivalent vaccine have been reported. This is the first case report of AE-IPF caused by the bivalent mRNA COVID-19 vaccines tozinameran and famtozinameran.

Our patient developed AE-IPF, which is characterized by a slower course than that of previously reported cases. AE-IPF generally worsens respiratory symptoms within a few weeks [3]. Previously reported acute exacerbations triggered by the monovalent mRNA COVID-19 vaccination had a relatively acute course, with the onset of symptoms ranging from 1 day to 30 days [7–10]. However, in this case, the symptoms of AE-IPF appeared 1.5 months after bivalent mRNA COVID-19 vaccination, and it took approximately 3 months to start treatment. AE-ILD after bivalent mRNA COVID-19 vaccination may have a relatively slow course, as observed in this case.

The patient had already experienced acute exacerbation at the initial visit to our department; however, the presence of fibrotic lesions in the lung was based on a previous CT scan at our hospital. Lung pathology showed organizing acute lung injury and a UIP pattern of fibrosis compatible with AE-IPF [12]. The clinical course after high-dose steroid therapy is consistent with AE-IPF [13]. Identifying the triggers of AE-ILD is often difficult. We carefully investigated the causes of AE-ILD, but we could not identify any cause of AE-IPF other than COVID-19 vaccination. Finally, we diagnosed AE-IPF related on mRNA COVID-19 vaccination.

AE-ILD has a poor prognosis and is associated with a high mortality rate within 6–12 months [1]. Although evidence-based data are insufficient, in clinical practice, AE-ILD is often treated with high-dose corticosteroid therapy, which was administered to previously reported patients [7–10]. In our patient, high-dose corticosteroid therapy successfully treated the AE-IPF. Although the mechanism of mRNA vaccine-induced exacerbation of ILD remains unclear, recent reports suggest that an innate inflammatory response could be induced by mRNA or the SARS-CoV-2 spike protein [14,15]. Furthermore, a study reported that the cross-reactivity of spike proteins with lung surfactants and related proteins may induce pulmonary inflammation [16].

Immunization for vaccine-preventable diseases, including IPF, is widely supported for chronic lung disease [17]. The benefits of the vaccine are considered to outweigh the risk of adverse drug reactions in patients with IPF because AE-IPF triggered by mRNA COVID-19 vaccination is extremely rare. Previous studies have revealed that COVID-19 patients with preexisting, especially fibrotic, ILDs are at a very high risk of mortality; hence, they should be vaccinated [18,19]. However, if respiratory symptoms are observed after vaccination, patients should be immediately examined for the possibility of acute exacerbation. We should be especially aware of the possibility of a delayed onset of acute exacerbations following bivalent mRNA COVID-19 vaccination, as in the present case.

4. Conclusions

- We herein reported the first case of AE-IPF that was possibly triggered by bivalent mRNA COVID-19 vaccination.

- Some cases of AE-IPF caused by COVID-19 vaccination have a slow clinical course and may not be recognized as AE-IPF, as in our patient. Further investigations with more cases are required.

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Author contributions

All authors met the International Committee of Medical Journal Editors authorship criteria. KT wrote the manuscript. All authors contributed to the editing of the manuscript and approved the final version of the manuscript.

Declaration of generative AI in scientific writing

None.

Declaration of competing interest

None.

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