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Respiratory Medicine Case Reports

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Interstitial lung disease after receiving the mRNA-based COVID-19 vaccine tozinameran

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A B S T R A C T

Tozinameran, a messenger ribonucleic acid (mRNA)-based coronavirus disease 19 (COVID-19) vaccine, has a favorable safety profile and is highly efficacious in preventing COVID-19. Adverse reactions such as pain at the vaccination site, fever, malaise, headache, rash, and anaphylaxis have been commonly reported for mRNA-based COVID-19 vaccines. We report a case involving a 71-year-old Japanese woman who developed interstitial lung disease (ILD) after receiving an mRNA-based COVID-19 vaccine. We also review case reports of COVID-19 mRNA vaccine-associated ILD. Dyspnea or hypoxia that develops within 1–3 days after COVID-19 mRNA vaccination should be differentiated from ILD. Further studies to elucidate mechanisms and risk factors of rare adverse reactions such as ILD are warranted.

1. Introduction

Tozinameran, a messenger ribonucleic acid (mRNA)-based coronavirus disease 2019 (COVID-19) vaccine, has a favorable safety profile and is highly efficacious in preventing COVID-19 [1]. Adverse reactions such as pain at the vaccination site, fever, malaise, headache, rash, and anaphylaxis have been commonly reported for mRNA-based COVID-19 vaccines [2]. Although the safety and efficacy of COVID-19 mRNA vaccines were demonstrated in global clinical trials, long-term data, and detailed reports of infrequently observed adverse reactions remains insufficient. Interstitial lung disease (ILD) has not been reported as an adverse reaction in global clinical trials of COVID-19 mRNA vaccines, including both tozinameran and spikevax [1–3]. Herein, we report a case involving a 71-year-old Japanese woman who developed ILD after receiving a mRNA-based COVID-19 vaccine. We also reviewed case reports of COVID-19 mRNA vaccine-associated ILD.

2. Case report

The patient, who had no history of COVID-19, received the first dose of the mRNA-based COVID-19 vaccine, tozinameran (Pfizer/BioNTech). Two days after vaccination, the patient was afebrile but had dyspnea on exertion. Due to her symptoms, the patient visited her primary physician six days after vaccination. Her oxygen saturation (SpO₂) level at rest was 91% and fluticasone propionate/formoterol fumarate hydrate (pressurized metered-dose inhaler) was prescribed. She visited her previous doctor eight days after vaccination because her symptoms persisted. At that time, her SpO₂ was 93%. She had no history of smoking or allergies. She had a history of bronchiectasis and cerebral infarction, and took ambroxol hydrochloride, aspirin, pravastatin sodium, alfacalcidol, lomerizine hydrochloride, and herbal medicine containing skullcap. The patient reported no recent changes to her living environment or exposure to chemicals or organic particles. The following laboratory test results were obtained: white blood cells, 6700/μL (neutrophils, 48.4%; eosinophils, 11.1%; basophils, 0.9%; lymphocytes, 26.8%; monocytes, 12.8%); hemoglobin, 12.4 g/dL; platelet, 308

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<https://doi.org/10.1016/j.rmcr.2022.101618>

Received 1 December 2021; Received in revised form 16 February 2022; Accepted 17 February 2022

Available online 20 February 2022

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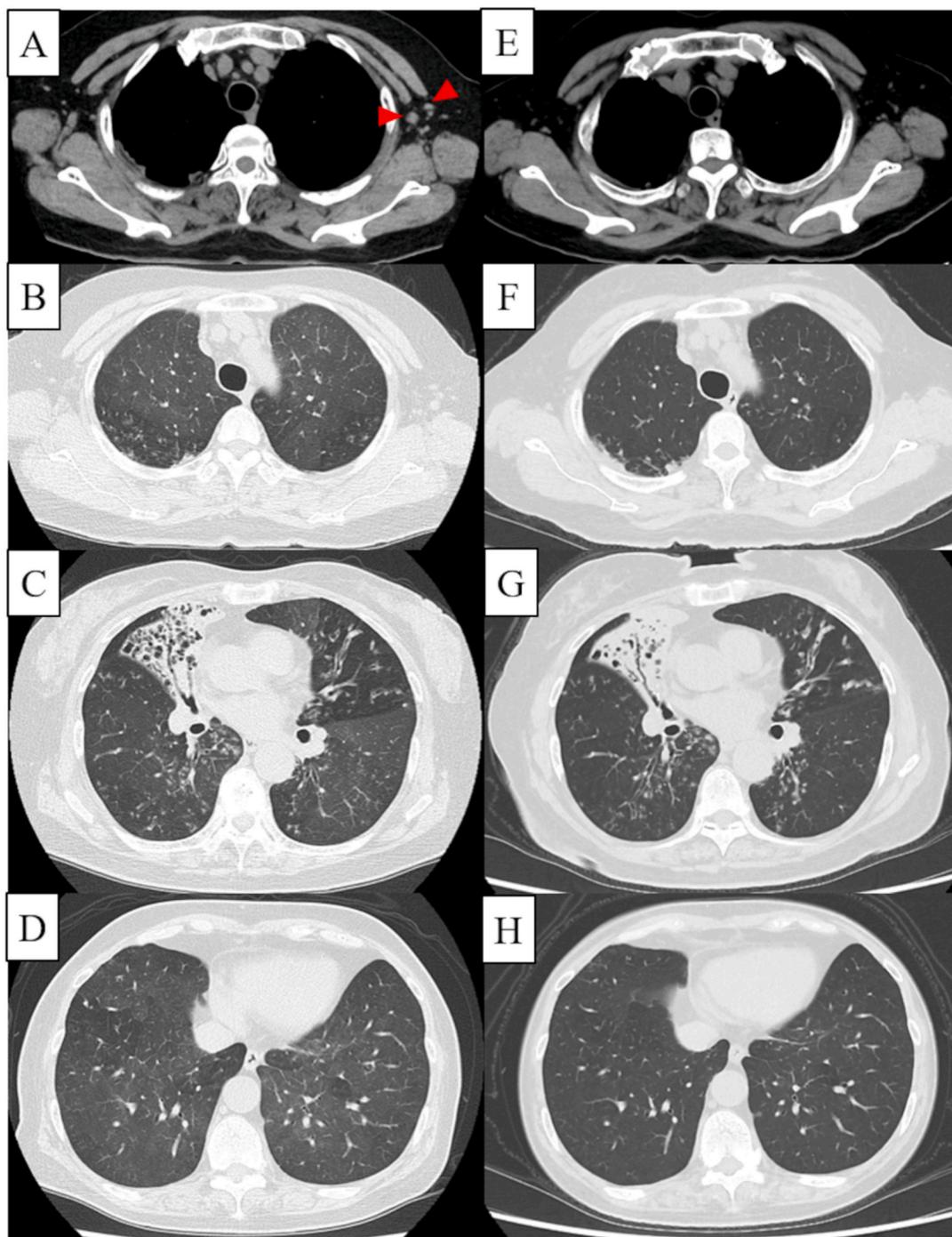


Fig. 1. Chest computed tomography (CT) eight days post-vaccination showing left axillary lymphadenopathies (red arrows) (A), ground-glass opacities (GGOs), mosaic attenuation (B–D), and bronchiectasis in both lungs. Thirty-three days after vaccination, left axial lymphadenopathies and GGOs disappearance were observed (E–H). High-resolution CT eight and 33 days post-vaccination revealed GGOs with mosaic attenuation (I) and GGOs disappearance, respectively (J). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

$\times 10^3/\mu\text{L}$; serum blood urea nitrogen, 19.5 mg/dL; creatinine, 0.57 mg/dL; aspartate aminotransferase, 24 U/L; alanine aminotransferase, 18 U/L; lactate dehydrogenase, 233 U/L; albumin, 3.4 g/dL; C-reactive protein, 1.49 mg/dL; Krebs von den Lungen-6 (KL-6), 1932 U/mL (normal range, 0–499.9 U/mL); Immunoglobulin E, 27 IU/mL; rheumatoid factor, 34 IU/mL; plasma prothrombin time, 74%; D-dimer, 0.5 $\mu\text{g}/\text{mL}$; brain natriuretic peptide, 10.6 pg/mL; and β -D-glucan, 9.0 pg/mL (normal range, 0–20 pg/mL). She was

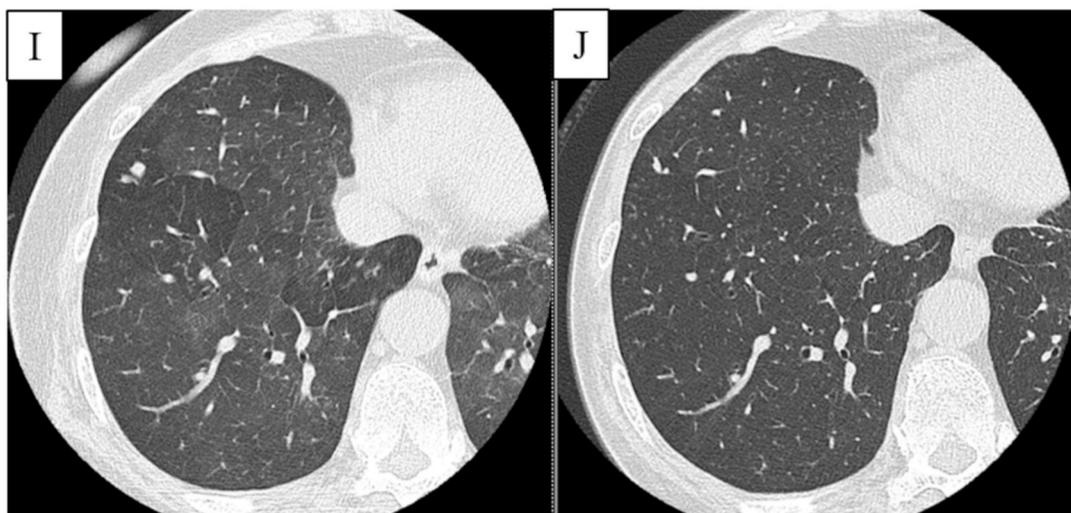


Fig. 1. (continued).

seronegative for antinuclear, anti-neutrophil cytoplasmic, anti-cyclic citrullinated peptide, anti-aminoacyl transfers RNA synthetase, and anti-*Trichosporon asahii* antibodies. She was also negative for severe acute respiratory syndrome coronavirus 2, via a polymerase chain reaction test using a nasopharyngeal swab. Chest CT revealed the presence of left axillary lymphadenopathies on the same side as the vaccination, bronchiectasis in middle and lingual lobes, ground-glass opacities (GGOs), and mosaic attenuation in both lungs suggestive of hypersensitivity pneumonia (Fig. 1A–D, J). GGOs and mosaic attenuation in both lungs were not seen on chest CT taken eight weeks before vaccination for routine follow-up of bronchiectasis (Supplement Fig. 1A–C).

She was referred to our hospital for further examination and bronchoscopy was performed 14 days after the vaccination. On admission, her oxygen saturation level, 94%; respiratory rate, 18 breath/minute; body temperature, 36.5 °C; heart rate, 83 beat/minute; blood pressure, 90/55 mmHg; and physical examination results were normal. Chest computed tomography (CT) showed GGOs had reduced but remained. Bronchoalveolar lavage (BAL) fluid recovered from the right B8 bronchus was determined to contain 134×10^4 cells/mL, with a composition of 4.0% neutrophils, 1.1% eosinophils, 37.4% macrophages, and 57.5% lymphocytes, and a cluster of differentiation (CD)4/CD8 ratio of 0.56. *Escherichia coli* and *Mycobacterium intracellulare* were detected in airway mucus cultures. Gram and Ziehl-Neelsen staining of organisms of the BAL fluid was both negative, revealing that they likely colonized the bronchiectasis. A transbronchial lung biopsy was not performed because the patient was taking aspirin. The clinical course, CT findings, and predominance of lymphocytes in BAL fluid indicated a diagnosis of drug-induced ILD with a hypersensitivity pneumonia pattern, which was associated with mRNA vaccination for COVID-19.

Thereafter, the patient's symptoms gradually improved without antibiotics or systemic corticosteroids, and her oxygen saturation level recovered to 96%, 19 days after vaccination. A follow-up chest CT that was performed 33 days after the vaccination showed that left axial lymphadenopathies and GGOs had disappeared (Fig. 1E–H, J). The serum KL-6 levels decreased to 455 U/mL. The patient declined a second tozinameran dose.

3. Discussion

In Japan, vaccination of the population against COVID-19 began on February 17, 2021. Over the next eight months, more than 90 million people had received at least one dose of the vaccine. According to a post-marketing survey of tozinameran conducted in Japan, 63 cases of ILD, 7 organizing pneumonia, 7 acute respiratory distress syndrome, 4 eosinophilic pneumonia, 4 pulmonary fibrosis, 2 pneumonitis, and 1 case of alveolitis were reported as suspected adverse reactions after the administration of an estimated 101,809,021 vaccine doses [4]. Post-marketing survey can provide important information on adverse reactions that were not known at the clinical trial, but it is insufficient to examine the details of individual cases. Only a few COVID-19 mRNA vaccine-associated ILDs have been reported in the literature [5–7].

This case did not prove a causal relationship between the COVID-19 mRNA vaccine and ILD. However, the patient met the criteria for drug-induced ILD, as defined by Caums et al. [8]. There was no evidence of active infection, connective tissue disease, or usual hypersensitivity pneumonia caused by the inhalation of chemicals or organic particles. An assessment of BAL fluid revealed lymphocyte predominance (>50%) with a low CD4/CD8 ratio, findings consistent with cellular pneumonia, as classified by Costabel et al. [9], which is common in drug-induced ILD with a hypersensitivity pneumonia pattern [10]. The patient had taken herbal medicine containing skullcap for 3 months and the other drugs for more than 6 months before the onset of ILD. The patient stopped taking herbal medicine because there are reports of drug-induced ILD caused by skullcap [11]. However, symptom onset in this case occurred two days after COVID-19 mRNA vaccination and the patient's respiratory condition and chest CT findings of ILD tended to improve spontaneously without the use of antibiotics and systemic corticosteroids before stopping herbal medicine. Furthermore, all three cases of ILD induced by COVID-19 mRNA vaccines were reported to have developed within 1–3 days after vaccination [Table 1].

Table 1
The characteristics of case reports of COVID-19 mRNA vaccine-associated ILD and the present case.

	Ref. 5	Ref. 6	Ref. 7	Our case
Age/Sex	86y/man	60y/man	65y/man	71y/woman
Vaccine	tozinameran	tozinameran	tozinameran	tozinameran
Dose	1st	2nd	1st	1st
Onset	1 day	2 days	3 days	2 days
Symptoms	dyspnea, fever	dyspnea, fever	dyspnea, cough, fever	dyspnea
Smoking	–	+	+	–
Allergy	–	–	–	–
Comorbidities	HT, DM, CKD	ACO, HT	OMI, HL, HT	bronchiectasis, CI
KL-6 (U/mL)	NA	800	214	1932
CRP (mg/dL)	11.43	10.87	5.49	1.49
WBC (/μL)	11600	12400	16200	6700
Neutrophils	82.8%	88.3%	78.2%	48.4%
Lymphocytes	5.8%	5.6%	9.7%	26.8%
Eosinophils	4.1%	2%	5.9%	11.1%
BAL fluid				
Neutrophils	NA	21.9%	78%	4%
Lymphocytes	NA	31.3%	14%	57.5%
CD4/8 ratio	NA	1.26	0.62	0.56
Eosinophils	NA	0%	7%	1.1%
DLST for vaccine	NA	negative	negative	NA
CT findings	GGO, consolidations, centrilobular micronodules, interlobular septal thickening	GGO, interlobar septal thickening, bronchial wall thickening	GGO with a crazy-paving pattern, interlobular septal thickening	GGO, mosaic attenuation
Treatment	Corticosteroid	Corticosteroid	Corticosteroid	–
Prognosis	alive	alive	alive	alive

HT, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; ACO, asthma chronic obstructive pulmonary disease overlap; OMI, old myocardial infarction; HL, hyperlipidemia; CI, cerebral infarction; NA, not assessed.

These data suggested a causal relationship between ILD and the COVID-19 mRNA vaccine in this case.

Although the mechanisms of drug-induced ILD are often unknown, direct, dose-dependent toxicity or immune-mediated mechanisms have been proposed [12]. These two mechanisms are likely to be modified by a variety of host and environmental factors including genetic predisposition, age, underlying pathological conditions in the lungs, and interactions with concomitant drugs [10]. Drug lymphocyte stimulation test (DLST) is often used to detect drug-sensitized T cells. However, because of its low sensitivity, even a negative result does not rule out drug-induced ILD [8], and DLST may not be useful for diagnosis in COVID-19 mRNA vaccine-associated ILD [Table 1]. In this case, BAL fluid findings of lymphocyte predominance suggest immune-mediated mechanisms, and old age and pre-existing lung disease (bronchiectasis) might be risk factors for ILD after vaccination. In addition, although the literature is limited, most reports of influenza vaccine-associated ILD are from Asia [5]. This introduces a potential bias, as the frequency of vaccine-associated ILD may differ among races. The clinical course of drug-induced ILD with hypersensitivity pneumonia pattern is usually good and resolves with drug discontinuation or corticosteroid treatment [10]. All three cases of COVID-19 mRNA vaccine-associated ILD were reported to have required corticosteroid treatment [Table 1], however; COVID-19 mRNA vaccine-associated ILD with a hypersensitivity pneumonia pattern may resolve spontaneously, as in this case, and may be underestimated as an adverse reaction.

In summary, dyspnea or hypoxia that develops within 1–3 days after COVID-19 mRNA vaccination should be differentiated from ILD. Further studies to elucidate mechanisms and risk factors of rare adverse reactions such as ILD are warranted.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2022.101618>.

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