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### Clinical characteristics of patients with COVID-19 vaccine-related pneumonitis: a case series and literature review

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### Clinical characteristics of patients with COVID-19 vaccine-related pneumonitis: a case series and literature review



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**Background/Aims:** Pulmonary toxicities of coronavirus disease 2019 (COVID-19) vaccination are exceedingly rare. However, there are a few reported cases after mRNA vaccination, especially from Asian countries. The purpose of this study was to report the clinical characteristics of patients with COVID-19 vaccine-related pneumonitis (CV-P) and to review cases reported in the literature.

Methods: We performed a prospective, observational case series analysis.

**Results:** Eleven patients with a median age of 80 years were enrolled. Ten patients developed CV-P after BNT162b2-mRNA vaccination and one after ChAdOx1 nCoV-19 vaccination. We identified various patterns of CV-P, including transient infiltration, life-threatening acute respiratory distress syndrome, and aggravation of underlying interstitial lung disease. Most patients showed favorable outcomes with good responses to corticosteroid therapy.

**Conclusions:** Identifying the mechanism of CV-P requires further investigation; however, radiological and laboratory findings in our case series support inflammatory dysregulation in the lung parenchyma after vaccination. Clinicians should consider CV-P in patients with atypical lung infiltration, no specific etiologies, and recent COVID-19 vaccination.

Keywords: COVID-19; Vaccines; Drug-related side effects and adverse reactions; Pneumonitis; Lung diseases, interstitial

#### **INTRODUCTION**

Various vaccines for coronavirus disease 2019 (COVID-19) are being developed, with some being used under emergency approval. However, most COVID-19 vaccine trials enrolled a limited number of elderly participants and patients with chronic lung diseases. Hence, ensuring the effectiveness and safety of vaccination in these populations is challenging [1]. As novel vaccines are administered worldwide, very rare but potentially serious adverse events (AEs) have been reported.

Cases of myocarditis after COVID-19 vaccination have been continuously reported in safety surveillance and published literature. Through large healthcare data analysis, the BNT162b2-mRNA vaccine was associated with a risk of myocarditis [2,3]. In contrast, vaccine-induced immune thrombotic thrombocytopenia is more relevant to adenoviral vector-based vaccines, and a convincing pathogenesis has been revealed [4-6]. However, pre-approval trials have not identified these rare AEs. Clinical trials with a limited number of participants who meet the inclusion criteria lack the power to identify these AEs [7-9]. Although scarce, the significance of AEs cannot be underestimated as a massive amount of vaccination has been conducted and might continue.

Vaccine-related lung toxicity is rare and not well known, although reports of pneumonitis after influenza vaccinations have been published, mainly in Asian countries [10]. Moreover, it may be misdiagnosed as infectious pneumonia unless suspected and not easily identified as skin AEs [11]. In mild cases, the lung parenchymal lesions could not be identified by simple chest radiography but only by computed tomography (CT) [12]. Therefore, the true prevalence of AEs is difficult to estimate. However, we recently reported a case of COVID-19 vaccine-related pneumonitis (CV-P) in an elderly patient (patient #1) [13]. Herein, we describe other Korean cases of CV-P with different clinical and radiological features and review the literature.

#### **METHODS**

We diagnosed CV-P using the clinical criteria for drug-induced pneumonitis suggested by Camus et al. [14] and the radiological criteria suggested by the Fleischner Society [12,14]. Our working definition of CV-P is shown in Table 1 and Supplementary Table 1. Patients without underlying interstitial lung disease (ILD) were classified with de novo CV-P and differentiated from patients with pre-existing ILD. As with the diagnostic process of drug-related pneumonitis, the diagnosis was reached by excluding other diseases by evaluating various possible differential diagnoses. COVID-19 polymerase chain reaction (PCR) testing (Real-Q 2019-nCoV Detection kit, BioSewoom, Seoul, Korea) was performed to confirm severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [13] using nasopharyngeal swabs, sputum, or bronchoalveolar lavage (BAL) fluid. To exclude infectious pneumonia, conventional cultures, respiratory



bacterial multiplex PCR tests (Allplex PneumoBacter Assay, Seegene, Seoul, Korea), and seasonal respiratory virus multiplex PCR tests (Real-Q RV Detection kit, BioSewoom) were performed. All microbiological tests performed for differential diagnosis are summarized in Supplementary Table 2. Bronchoscopy was recommended and performed with patients' informed consent after considering the risk-benefit ratio. Echocardiography was performed in all patients without underlying ILD.

South Korea introduced the BNT162b2-mRNA vaccine program for the elderly (age  $\geq$  75 years) in April 2021; the vaccines were administered on a large scale within a short period. Since then, vaccination programs with both BNT162b2-mRNA and ChAdOx1 nCoV-19 vaccines have been extended to include younger individuals. Physicians diagnosing or treating COVID-19 vaccine-related AEs are obligated to report them to the Korea Disease Control and Prevention Agency that publishes weekly national reports on vaccine-related AEs [15]. We compared this data with that of the Public Health Agency of Canada that has a similar surveillance system and publishes weekly AE reports [16].

The study institution is the only tertiary referral hospital covering three adjacent cities (Anyang, Gunpo, and Uiwang: population, 0.98 million). The observed incidence of CV-P was calculated using the number of patients diagnosed and the number of vaccinees administered in the three cities until the date of presentation of the last diagnosed patient. The Institutional Review Board approved this study (HAL-LYM2021-08-006). We obtained written informed consent from the patients for publication of their clinical features and radiological images.

#### RESULTS

#### **Baseline characteristics and diagnosis**

Eleven patients with CV-P were enrolled (median age, 80 years; five male and six female patients). Ten patients received the BNT162b2-mRNA vaccine (first dose: six patients), and one received the first dose of ChAdOx1 nCoV-19. No patients had been infected by SARS-CoV-2 previously or at presentation or had a history of vaccine-related AEs (Tables 2 and 3). According to the chest CT pattern, four of the eight patients with de novo CV-P were subcategorized as having organizing pneumonia and four as having diffuse alveolar damage (DAD). We confirmed the absence of underlying ILD using radiological images previously obtained for health check-ups or other medical reasons (CT, 3/8; radiograph, 8/8). Three patients had pre-existing ILD: hypersensitivity pneumonitis (HP), airspace enlargement with fibrosis, and idiopathic pulmonary fibrosis (IPF). We identified newly aggravated parenchymal lesions (increased ground-glass opacity or consolidation) through comparison with stable background ILD findings. All three patients were clinically and radiologically stable without anti-inflammatory drugs or anti-fibrotic agents before vaccination. The radiological findings of representative cases are shown in Fig. 1. Radiological images before and after CV-P of all patients except patient #1 are shown in Supplementary Figs. 1-10.

### *De novo* CV-P and aggravation of pre-existing ILD

We compared the clinical features of patients who developed *de novo* pneumonitis after vaccination (n = 8) with that of those with pre-existing ILD (n = 3) (Table 2). The me-

#### Table 1. Working definition of COVID-19 vaccine-related pneumonitis

New-onset respiratory symptoms after COVID-19 vaccination meeting all of the following criteria:

- A: Singularity of the agent and temporal eligibility: onset of symptoms and parenchymal opacities on chest computed tomography (CT) must be temporally associated with only COVID-19 vaccination
- B: Chest CT abnormalities<sup>a</sup>: new occurrence or increased severity of interstitial lung disease (nonspecific interstitial pneumonia, organizing pneumonia, hypersensitivity pneumonitis, simple pulmonary eosinophilia, diffuse alveolar damage [acute respiratory distress syndrome pattern])
- C: Exclusion of other diagnoses: COVID-19, infectious pneumonia, embolism, aspiration, inhalations, cardiac failure or fluid overload, sepsis, trauma, and transfusion-related adverse reactions.

Bronchoalveolar lavage is recommended when possible. Lung biopsy is not mandatory but could be performed to exclude other diagnoses.

COVID-19, coronavirus disease 2019.

<sup>a</sup>The definitions of CT patterns of COVID-19 vaccine-related pneumonitis are described in Supplementary Table 1.



Table 2. Clinical characteristics of patients with CV-P according to de novo CV-P and aggravated pre-existing interstiti	al
lung disease	

Characteristic	Total (n = 11)	De novo CV-P (n = 8)	Pre-existing ILD (n = 3)
Demographics			
Age, yr	80 (51–83)	78 (50–84)	80
Male sex	5 (45)	3 (38)	2 (67)
Current or past smoker	4 (36)	2 (25)	2 (67)
Vaccine doses received <sup>a</sup>	m1: 6, m2: 4, a1: 1	m1: 4, m2: 3, a1: 1	m1: 2, m2: 1
Symptom onset, day <sup>b</sup>	9 (4–13)	9 (6–13)	7
Comorbid disease			
Connective tissue disease	0	0	0
Asthma	0	0	0
Diabetes mellitus	6 (55)	5 (63)	1 (33)
Chronic kidney disease	1 (9)	1 (13)	0
Hypertension	6 (55)	4 (50)	2 (67)
Cardiovascular disease	1 (9)	1 (13)	0
Symptoms			
Cough	10 (91)	7 (88)	3 (100)
Sputum production	9 (82)	6 (75)	3 (100)
Shortness of breath	10 (91)	8 (100)	2 (67)
Temperature > 38°C	5 (45)	5 (63)	0
Initial laboratory findings			
$WBC > 11,000/mm^3$	2/11 (18)	1/8 (13)	1/3 (33)
Blood eosinophil > 5%	3/11 (27)	2/8 (25)	1/3 (33)
CRP, mg/dL	7.5 (0.6–13.6)	11.4 (5.2–13.7)	0.2
Procalcitonin > 0.5 ng/mL	0/9 (0)	0/8 (0)	0/1 (0)
Creatinine > 1.2 mg/dL	2/11 (18)	2/8 (25)	0/3 (0)
ALT > 40 IU/L	3/11 (27)	3/8 (38)	0/3 (0)
BNP > 100 pg/mL	1/8 (13)	1/7 (14)	0/1 (0)
Troponin I > 15.6 pg/mL	1/8 (13)	1/7 (14)	0/1 (0)
FeNO > 25 ppb	0/3 (0)	0/1 (0)	0/2 (0)
Bronchoalveolar lavage	5 (45)	5 (63)	0
Autoantibodies			
Antinuclear antibodies	4/11 (36)	3/8 (38)	1/3 (33)
Anti-Ro/SSA	2/11 (18)	2/8 (25)	0/3 (0)
Anti-La/SSB	0/11 (0)	0/8 (0)	0/3 (0)
Rheumatoid factor	1/11 (9)	1/8 (13)	0/3 (0)
Anti-CCP	0/11 (0)	0/8 (0)	0/3 (0)
Case management			
Oxygen supply, FiO <sub>2</sub> %	48 (21–80)	65 (44–80)	21
Hospitalization	8 (73)	7 (88)	1 (33)
Systemic steroid treatment	11 (100)	8 (100)	3 (100)
Steroid dose, mg/day <sup>c</sup>	32 (8–70)	57 (28–80)	8
Steroid tapering or withhold	10/11 (91)	7/8 (88)	3/3 (100)
Follow-up, mo	5.2 (3.9-8.0)	4.5 (3.2–7.8)	7.4
Death	1 (9)	1 (13)	0

Values are presented as median (interquartile range) or number (%).

CV-P, COVID-19 vaccine-related pneumonitis; ILD, interstitial lung disease; WBC, white blood cell; CRP, C-reactive protein; ALT, alanine aminotransferase; BNP, brain natriuretic peptide; FeNO, fractional exhaled nitric oxide (before systemic steroid); Anti-CCP, anti-cyclic citrullinated peptide antibody.

<sup>a</sup>m: BNT162b2-mRNA, a: ChAdOx1 nCoV-19.

<sup>b</sup>Time from most recent vaccination to symptom onset.

<sup>c</sup>Initial steroid dose of methylprednisolone equivalent.

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Table 3. Demographic characteristics, sympt	coms, evalu	uations, and	d clinical co	urses of 11	patients						
Characteristic	Pt #1	Pt #2	Pt #3	Pt #4	Pt #5	Pt #6	Pt #7	Pt #8	Pt #9	Pt #10	Pt #11
Age, yr	86	83	85	48	82	73	51	44	80	82	80
Sex	Male	Female	Female	Male	Female	Male	Female	Female	Female	Male	Male
Vaccine (doses) received <sup>a</sup>	m1	m2	m1	a-m1	m2	a1	m1	m2	m2	m1	m1
Time from most recent vaccination to symp- tom onset, day	-	13	Ø	6	13	6	4	25	7	12	4
Underlying interstitial lung disease	Z	z	z	z	z	z	z	z	ЧH	AEF	ΙΡF
Radiologic patterns on chest CT	OP	OP	OP	OP	DAD	DAD	DAD	DAD	A/E	A/E	A/E
SARS-CoV-2 PCR test, negative <sup>b</sup>	≻	≻	≻	≻	≻	≻	≻	≻	≻	≻	≻
Current or past smoker	Z	Z	z	≻	z	≻	z	Z	z	≻	$\succ$
Comorbid disease											
Connective tissue disease	Z	z	z	z	z	z	z	z	z	z	Z
Asthma	Z	Z	z	Z	Z	Z	z	Z	Z	Z	Z
Diabetes mellitus	≻	≻	≻	z	Z	≻	z	≻	z	≻	Z
Chronic kidney disease	≻	Z	Z	Z	Z	Z	Z	Z	Z	Z	Z
Hypertension	≻	Z	≻	z	≻	≻	z	z	≻	z	≻
Cardiovascular disease	Z	Z	≻	z	Z	Z	z	Z	z	Z	Z
Symptoms											
Cough	Z	≻	≻	≻	≻	≻	≻	≻	≻	≻	≻
Sputum production	Z	≻	$\succ$	Z	≻	≻	≻	≻	≻	≻	$\succ$
Shortness of breath	≻	≻	≻	≻	≻	≻	≻	≻	Z	≻	≻
Temperature > 38°C	≻	Z	z	≻	≻	≻	z	≻	Z	Z	z
Initial laboratory findings											
White cell count, /mm <sup>3</sup>	11.6	10.2	8.4	7.0	9.1	9.7	6.0	8.7	4.7	6.7	16.9
Blood eosinophil, %	4.1	1.9	3.3	7.1	0.4	2.0	8.5	1.6	5.2	1.5	2.3
C-reactive protein, mg/dL	11.4	13.6	2.9	14.9	1.0	11.3	7.5	13.8	0.2	0.0	0.6
Procalcitonin, ng/mL	0.32	0.01	0.06	0.33	0.15	0.22	0.08	0.08	NP	NP	0.03
Creatinine, mg/dL	1.85	0.65	0.75	0.86	0.61	1.78	0.72	09.0	0.71	0.72	0.78
Alanine aminotransferase, IU/L	11	12	12	57	70	37	64	18	22	12	21
Brain natriuretic peptide, pg/mL	88	32	NP	139	29	16	24	10	NP	NP	-
Troponin I, pg/mL	15.2	< 10	NP	11.4	28.4 <sup>c</sup>	< 10	< 10	< 10	NP	NP	10.5
FeNO, ppb, before systemic steroids	NP	NP	NP	NP	NP	24	NP	NP	6	NP	18





Characteristic	Pt #1	Pt #2	Pt #3	Pt #4	Pt #5	Pt #6	Pt #7	Pt #8	Pt #9	Pt #10	Pt #11
Bronchoalveolar lavage	NP	≻	NP	≻	NP	≻	≻	≻	NP	NP	NP
Autoantibodies, positive											
Antinuclear antibodies <sup>d</sup>	z	Z	≻	z	≻	≻	z	z	≻	Z	Z
Anti-Ro/SSA antibody	z	z	z	z	≻	≻	z	z	z	z	z
Anti-La/SSB antibody	z	z	z	z	z	z	z	z	z	z	z
Rheumatoid factor	z	z	Z	z	z	≻	z	z	z	z	z
Anti-citrullinated peptide antibody	z	z	z	z	z	z	Z	Z	Z	Z	z
Case management											
Oxygen supply, FiO <sub>2</sub> , %	50	40	NP	48	100	80	80	80	NP	NP	45
Hospitalization	≻	≻	z	≻	≻	≻	≻	≻	z	z	≻
Systemic steroid treatment	≻	≻	≻	≻	≻	≻	≻	≻	≻	≻	≻
Steroid dose, mg/day (MPD equivalent)	63	24	12	32	125	70	06	50	œ	Ø	8
Steroid tapering or withhold	≻	≻	≻	≻	z	≻	≻	≻	≻	≻	≻
Time from onset to last follow-up, mo	11.7	8.0	7.6	3.9	1.1	4.6	2.5	4.3	7.4	5.2	9.6
Death	z	Z	Z	z	≻	z	Z	Z	Z	Z	z
<sup>3</sup> t, patient; HP, hypersensitivity pneumonitis; $^{\rm A}$ nonia; DAD, diffuse alveolar damage; A/E, ag	vEF, airspac	e enlargem or exacerba	ent with fik tion; SARS-	orosis; IPF, i CoV-2, sev	diopathic p ere acute re	ulmonary fil espiratory sy	brosis; CT, c /ndrome co	computed t ronavirus 2	omography ; PCR, poly	; OP, organ merase cha	izing pneu- in reaction;

<sup>a</sup>m: BNT162b2-mRNA vaccine, a: ChAdOx1 nCoV-19. a-m: The first dose was ChAdOx1 nCoV-19, and the second dose was the BNT162b2-mRNA vaccine. This is due to a NP, not performed; FeNO, fractional exhaled nitric oxide; MPD, methylprednisolone.

<sup>b</sup>Real-time PCR coronavirus disease 2019 (COVID-19) test was performed (Real-Q 2019-nCoV Detection kit, BioSewoom, Seoul, Korea). temporary change in the age criteria for ChAdOX1 nCoV-19 in Korea, not for patient's medical reasons.

Initial electrocardiography showed T-wave inversion on lateral precordial leads. Echocardiography showed normal function and wall motion. Clinically, the case had no edema or cardiogenic congestive features. Cardiac magnetic resonance imaging was not performed.

Patient #3: antinuclear antibody (ANA) titer 1:1,280; Patient #5: ANA titer 1:80, anti-Ro/SSA antibody 30.0 units/mL (normal < 7 units/mL); Patient #6: cytoplasmic ANA titer 1:640, ANA titre 1:80, and anti-Ro/SSA antibody 115.0 units/mL; and Patient #9: ANA, 3+ (fluorescence intensity)



**Figure 1.** Computed tomography findings of patients with coronavirus disease 2019 (COVID-19) vaccine-related pneumonitis (CV-P). (A) Patient #2: 83-year-old woman (second dose of BNT162b2-mRNA). (B) Patient #6: 73-year-old man (first dose of ChAdOx1 nCoV-19). (C) Patient #5: 82-year-old woman (second dose of BNT162b2-mRNA vaccine). Computed tomography (CT) revealed symmetrical ground-glass opacification with spontaneous pneumomediastinum and pneumothorax. (D) Patient #7: 51-year-old woman (first dose of BNT162b2-mRNA) (E) Patient #9: 80-year-old woman (second dose of BNT162b2-mRNA) CT image revealed centrilobular nodules (arrow), ground-glass opacity (GGOs, arrow), and a mosaic pattern of hypersensitivity pneumonitis (asterisks). (F) Patient #11: 80-year-old man (first dose of BNT162b2-mRNA). After vaccination, new bilateral GGOs (arrowheads) were superimposed on reticular opacities and honey-combing with spontaneous pneumothorax.

dian time from the most recent vaccination to symptom onset was 9 days in patients with *de novo* CV-P and 7 days in those with pre-existing ILD. All patients with *de novo* CV-P had dyspnea. Aggravation of cough and sputum production were the main symptoms of patients with pre-existing ILD. Fever (> 38°C) occurred in five of the eight patients with *de novo* CV-P; however, none developed fever in the pre-existing ILD group. The median C-reactive protein level was 3.8 mg/dL, showing a moderate increase in most cases. No patients had procalcitonin levels > 0.5 ng/mL. Echocardiography in all eight patients with *de novo* CV-P demonstrated normal left ventricular systolic function and wall motion. In the *de novo* group, antinuclear antibody was positive in three out of eight cases, and anti-SSA/Ro antibody was positive in two cases.

#### Management and prognosis

Systemic corticosteroids were administered after diagnosis in all patients, and the attending physician determined the starting dose. In the *de novo* patient group, the methylprednisolone equivalent dose was started at a median value of 57 mg/day. All patients with underlying pre-existing ILD were treated with methylprednisolone 8 mg/day. One patient with acute respiratory distress syndrome (ARDS) died despite appropriate treatment (Patient #5: DAD pattern) (Fig. 1C). All other patients responded well to corticosteroids, and improvement was maintained without sequelae during follow-up.



#### **Observed incidence**

Our observed incidence of CV-P was 1.37 per 100,000 (11/804,318 with at least one dose of COVID-19 vaccine in the three cities until November 27, 2021).

#### A representative case presentation and radiological features

Patient #2 (Fig. 1A): An 83-year-old woman who received the second dose of BNT162b2-mRNA vaccine presented with an organizing pneumonia pattern of CV-P. Chest CT revealed multifocal patchy consolidations, ground-glass opacifications (GGOs), and mild interlobar septal thickening in both lungs (14 days after the second dose). BAL fluid analysis revealed neutrophils (Np) 24%, lymphocytes (Lp) 32%, eosinophils (Eo) 32%, and macrophages (Mq) 12% (Supplementary Table 3). All microbiological tests in BAL specimens were negative. Intravenous methylprednisolone was initiated at 24 mg/day, and the patient had a rapid response to treatment.

Patient #6 (Fig. 1B): ARDS (DAD pattern) occurred in a 73-year-old man who received the first dose of ChAdOx1 nCoV-19 vaccine. Chest CT revealed extensive bilateral GGOs with consolidations. There were no abnormal findings in the lung parenchyma on chest CT performed 10 months prior. BAL fluid analysis revealed Np 29%, Lp 32%, Eo 2%, and Mq 37%. The interstitial lesions gradually improved with steroid treatment.

Patient #7 (Fig. 1D): A rapidly progressive DAD pattern was observed after primary BNT162b2-mRNA vaccination in a 51-year-old woman. Chest CT showed diffuse bilateral GGOs, centrilobular nodules, bronchovascular bundles, and interlobular septal thickening, but no cardiomegaly (8 days after vaccination). Small bilateral pleural effusions were present, but not shown in the current figure. BAL fluid analysis revealed Np 0%, Lp 92%, Eo 7%, and Mq 1%. Methylprednisolone was initiated at 90 mg/day; rapid clinical and radiological improvement was observed.

Patient #9 (Fig. 1E): An 80-year-old woman was diagnosed with HP following mold exposure 2 years prior. She changed her living accommodations and received corticosteroid therapy for 3 months resulting in complete remission, and was relapse-free after discontinuation of steroids. Cough with sputum production developed 7 days after BNT162b2-mRNA vaccination, and chest CT showed recurrence of centrilobular nodules, GGOs, and a mosaic pattern of HP. She improved with steroid treatment and is without recurrence even after discontinuation of steroids.

Patient #11 (Fig. 1F): Acute exacerbation of IPF was observed in an 80-year-old man who received BNT162b2-mR-NA vaccine (first dose). He discontinued pirfenidone 1 year before vaccination due to adverse skin reactions and anorexia. Four days after COVID-19 vaccination, chest CT revealed new bilateral GGOs superimposed on reticular opacities and honeycombing with spontaneous pneumothorax. The patient improved with steroid treatment and chest tube management and was discharged with no acute exacerbation thereafter.

#### Differential diagnosis process

We evaluated the differential diagnoses and potential other triggers of ILD. Various laboratory tests were performed to rule out infectious lung disease; all of the results were negative (Supplementary Table 2). The following clinical features support the diagnosis of CV-P. No patients had upper respiratory symptoms, such as a runny nose and sore throat. suggestive of viral infection. In macroscopic bronchoscopy findings, there was no purulent secretion or diffuse bronchitis, suggestive of infectious etiologies. Cell differential counts of BAL fluid in five cases showed lymphocytic or eosinophilic inflammatory patterns. The procalcitonin level was low compared to extensive radiologic lesions. Since most patients improved rapidly with steroid treatment, it was strongly suggested to be an inflammatory lesion rather than an infection. From an epidemiologic point of view, the incidence of seasonal respiratory viral infections significantly decreased in Korea during the COVID-19 pandemic [17,18].

Autoantibody tests were performed to differentiate rheumatic diseases (Supplementary Table 2). Patients who tested positive for any autoantibodies consulted with a rheumatologist; however, none were suspected or met the diagnostic criteria for autoimmune disease. None of the patients showed dry eye, dry mouth, arthritis, or Raynaud's phenomenon. During the outpatient follow-up after the discontinuation of steroids, no additional clinical findings suitable for rheumatic diseases were observed. No patients were exposed to novel environments, inhaled antigens, or inorganic particulate matter. Patients with underlying conditions were taking medications with no recent changes. Patients maintained these medications during and after the course of CV-P (Supplementary Table 4). In addition, there were no other triggers of ILD exacerbation, such as aspiration events or surgical procedures.

#### DISCUSSION

In all patients, the only newly administered agent before CV-P onset was the COVID-19 vaccine, which shows a clear temporal relationship. Other diseases causing lung infiltration were methodically ruled out [10]. We identified various manifestations of CV-P ranging from transient pulmonary infiltrates with mild symptoms to life-threatening ARDS, as well as aggravation of underlying ILD. The findings of the present cases are similar to those of previously reported cases of pneumonitis associated with influenza vaccines and novel cancer therapies [8,9], suggesting that pathogenic mechanisms might vary.

Although the pathophysiology in the current cases remains unclear, there are several noteworthy findings. First, we found lymphocytic alveolitis (32%-92%), either pure or associated with eosinophilic inflammation (2%-32%), from the BAL fluid in five patients with de novo CV-P. As a potential mechanism, an aberrant innate immune response to a vaccine molecule (e.g., mRNA) may be considered in individuals with a specific immunogenetic predisposition [19]. Another mechanism is molecular mimicry, in which the antibody against the spike protein of SARS-CoV-2 has cross-reactivity with human tissue antigens [20]. The rate of antinuclear antibody positivity reported herein was higher than what is expected among the general population [21]. Although this finding could be incidental, a heightened immune response after vaccination in patients with potential autoimmune diathesis may play a role. Autoantibodies are being evaluated as potential mechanisms for various AEs following COVID-19 vaccination, including myocarditis, thrombosis with thrombocytopenia syndrome, and glomerulonephritis [3,22,23].

Second, three patients with underlying ILD developed CV-P. In previous studies, pre-existing ILD was a risk factor for drug-induced lung toxicity, including that of immune checkpoint inhibitors [12,24]. CV-P with pre-existing ILD was milder than a typical ILD exacerbation in terms of symptoms, laboratory findings, and radiological extent. Additionally, these patients improved with lower doses of corticosteroids than those with *de novo* CV-P. However, this could be due to selection bias, as patients with underlying ILD might undergo imaging evaluation more frequently, even with milder symptoms.

Fig. 2 shows the national data of reported AEs after the BNT162b2-mRNA vaccinations in South Korea and Canada.

As both reports are based on passive surveillance, there is a significant likelihood of under-reporting and biases; nevertheless, the frequency of reporting ARDS in South Korea is much higher than that in Canada. Differences in ethnicity should be considered; however, the differences might also be because the vaccine was first administered to the elderly in South Korea. Old age has been reported as a risk factor for drug-related pneumonitis [24]. However, these hypotheses and causality cannot be proven by our limited report. Therefore, active surveillance through prospective cohorts in different populations is necessary for evaluating the incidence, prognosis, and risk factors for CV-P.

We found 12 cases of CV-P in previously published reports through a review of the literature (Table 4) [25-33]. Eleven patients developed CV-P after receiving the BNT162b2-mR-NA vaccine and one after receiving the first dose of the Ch-AdOx1 nCoV-19 vaccine. The median age of these patients was 65 years, and 11 were male. The date of symptom onset was median 2 days after the most recent vaccination. Among the cases, seven were smokers, and four had underlying ILD. Fever and shortness of breath were the most common symptoms. The cell differential counts of BAL fluid reported in five cases showed a lymphocytic or eosinophilic inflammatory pattern. Although two patients spontaneously improved without medication, all other cases were treated with corticosteroids. The outcome of all reported cases was favorable. There were no unique diagnostic findings in these reported cases, but the clinical features and imaging findings are similar to our current case series. Most patients show bilateral GGO infiltration with or without interlobular thickening. The symptoms and pulmonary parenchymal lesions did not respond to antibiotics; however, they respond-



**Figure 2.** The number of reported specific adverse events per 100,000 vaccine doses following BNT162b2-mRNA vaccination in South Korea (by October 3, 2021) and in Canada (by October 4, 2021). ARDS, acute respiratory distress syndrome; TTS, thrombosis with thrombocytopenia syndrome.

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Characteristic	Case #1	Case #2	Case #3	Case #4	Case #5	Case #6	Case #7	Case #8	Case #9	Case #10	Case #11	Case #12
Case reporting country	Japan	Japan	Japan	Japan	Japan	Japan	Spain	Australia	Japan	Japan	United States	Morocco
Age, yr	99	85	62	99	65	60	37	55	83	65	40	66
Sex	Male	Male	Male	Male	Male	Male	Male	Female	Male	Male	Male	Male
Vaccine (doses) received <sup>a</sup>	m1	m1	m2	m2	m1	m2	m2	m2	m1	m2	m2	a1
Time from most recent vaccination to symptom onset, day	<del>.                                    </del>	4	2	Ъ	M	2	<del>~ -</del>	4	<del>.                                    </del>	9	<del>.                                    </del>	-
Underlying interstitial lung disease	DIP	ILA	z	z	z	z	Unknown	Unknown	đ	Ш	Unknown	Unknown
Current or past smoker	≻	≻	z	Unknown	≻	≻	Unknown	Unknown	≻	≻	≻	Unknown
Symptoms												
Cough	z	z	z	≻	≻	z	≻	≻	z	z	≻	Z
Sputum production	Z	Z	z	Z	z	z	Z	Z	z	Z	≻	Z
Shortness of breath	Z	≻	Z	≻	≻	≻	≻	≻	≻	≻	≻	≻
Fever	$\succ$	z	≻	≻	≻	≻	≻	≻	$\succ$	≻	≻	≻
Bronchoalveolar lavage	≻	≻	NA	NA	≻	≻	≻	NA	AN	NA	NA	NA
CT features and lesion distribution												
Radiologic patterns	NSIP	NSIP	ОР	DAD	DAD	DAD	DAD	OP	NSIP	DAD	OP	ОР
Bilateral distribution	≻	≻	≻	≻	≻	≻	≻	≻	≻	≻	≻	≻
Diffuse distribution	≻	Z	Z	≻	≻	≻	≻	z	z	≻	z	Z
Multifocal distribution	z	≻	≻	Z	z	z	Z	≻	≻	Z	≻	≻
Subpleural distribution	z	≻	≻	Z	z	z	z	z	z	z	z	Z
Consolidation	≻	Z	≻	Z	z	≻	z	≻	≻	≻	z	≻
Ground-glass opacity	≻	≻	Z	≻	≻	≻	≻	≻	≻	≻	≻	≻
Interstitial thickening	≻	≻	z	≻	≻	≻	≻	z	≻	≻	z	z
Case management												
Systemic steroid treatment	z	≻	≻	≻	≻	≻	z	≻	≻	≻	≻	≻
Steroid dose, mg/day (MPD equivalent)	None	1,000	16	1,000	1,000	1,000	None	20	Pulse <sup>b</sup>	Pulse <sup>b</sup>	40	240
Death	Z	Z	Z	Z	Z	Z	Z	Z	Z	Z	Z	Z
Case #1-#3, Shimizu et al. [25]; Case #4, H	Kono et al.	[26]; Case #	≠5, Matsuza	aki et al. [27	']; Case #6	Yoshifuji e	t al. [28]; Cā	ase #7, Piqu€	eras et al. [2	29]; Case #	8, Stoyano	/ et al. [30];
Case #9 and #10, Amiya et al. [31]; Case	e #11, Wang	g et al. [32];	Case #12	Miqdadi et	al. [33].							
COVID-19, coronavirus disease 2019; DII	IP, desquan	native inters	stitial pneu	monia; ILA	, interstitia	l lung abn	ormality; Ill	P, idiopathic	: interstitia	l pneumor	iia; NA, nc	t available;
CT, computed tomography; NSIP, nonspe	ecific inters	stitial pneun	nonia; OP,	organizing	pneumonia	i; DAD, dif	fuse alveol	ar damage;	MPD, meth	nylprednisc	lone.	

<sup>b</sup>lnitial responses to steroid therapy were unfavorable. Both patients received another pulsed steroid and cyclophosphamide.

<sup>a</sup>m: BNT162b2-mRNA vaccine, a: ChAdOx1 nCoV-19.



ed to systemic corticosteroids. In particular, it is characteristic that most CV-P cases developed after BNT162b2-mRNA vaccination.

The limitations of this study are as follows. First, we could not directly prove the definitive pathophysiology of CV-P. However, we reached the diagnosis through extensive differential diagnosis processes and multidisciplinary discussion. We also hypothesized a pathologic mechanism and identified a therapeutic response that was non-specific but commensurate with our hypothesis. Second, the possibility of idiopathic exacerbations of pre-existing ILD could not be absolutely ruled out. In general, acute exacerbations of ILD may be triggered or idiopathic. In patients classified as idiopathic, it is not clear whether there is an undiscovered intrinsic factor or inciting event (external factor) has not been found [34]. We meticulously ruled out other possible triggers. All CV-P cases being stable without additional measures after complete steroid treatment might be indirect evidence that the vaccines have been the trigger. In the patient with de novo CV-P, we confirmed that there was no underlying ILD through previous chest radiologic images. Third, although extensive evaluations were performed on most patients to differentiate infections, not all identical tests were performed on all patients; the tests were selected according to the attending physician's judgment. In patients who missed specific tests, we determined that the corresponding infection was unlikely by evaluating other clinical parameters (symptoms, laboratory tests, radiologic tests, and clinical course).

In conclusion, although rare, reports of pneumonitis related to the new COVID-19 vaccine continue to increase and should be defined as an 'AE of special interest' with continuous safety monitoring. Clinicians should have a high index of suspicion in patients who develop atypical pneumonitis after vaccination without any specific etiologies. However, COVID-19 vaccination, including booster doses, must be continued as the expected benefits far outweigh the risks. For safe administration of these vaccines, further investigation to elucidate the association of these vaccines with lung toxicity is required.

#### **KEY MESSAGE**

- We identified various patterns of coronavirus disease 2019 (COVID-19) vaccine-related pneumonitis (CV-P), including transient infiltration, life-threatening acute respiratory distress syndrome, and aggravation of underlying interstitial lung disease.
- Most patients with CV-P showed favorable outcomes with good responses to systemic corticosteroid
- The potential pulmonary toxicities of COVID-19 vaccines are very rare; however, clinicians should consider the differential diagnosis for patients with atypical lung infiltration without specific etiologies.

#### **Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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#### Supplementary Table 1. Chest CT patterns of COVID-19 vaccine-related pneumonitis.

Radiologic pattern of CV-P	Relevant chest CT abnormalities
Nonspecific interstitial pneumonia (NSIP)	Bilateral patchy or diffuse ground-glass opacity (GGO) with lower lung zone predominance. Later findings of fibrosis (reticular opacities and traction bronchiectasis).
Organizing pneumonia (OP)	Airspace consolidation with peribronchovascular and/or peripheral distribution. GGO and nod- ular opacities observed frequently.
Diffuse alveolar damage (DAD)	Bilateral areas of GGO and airspace consolidation in the dependent lung. Some sparing of individual lobules (geographic appearance). The extent of GGO increases with disease progression. Later findings of fibrosis (traction bronchiectasis and decreased lung volumes).
Hypersensitivity pneumonitis (HP)	Diffusely distributed GGO and mosaic attenuation. Ill-defined centrilobular nodules and air-trapping on expiratory images.

The radiologic pattern of CV-P was classified according to the definition of the interstitial lung disease pattern presented by the following organizations (2008 Fleischner Society: glossary of terms for thoracic Imaging; 2013 American Thoracic Society/European Respiratory Society: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias; 2021 Fleischner Society: chest CT diagnosis and clinical management of drug-related pneumonitis in patients receiving molecular targeting agents and immune checkpoint inhibitors).

CT, computed tomography; COVID-19, coronavirus disease 2019; CV-P, COVID-19 vaccine-related pneumonitis.



#### Supplementary Table 2. Microbiological and auto-antibodies investigations

	Tested patients
Microbiological tests <sup>a</sup>	
Sputum culture	11/11
Bacterial multiplex PCR assays <sup>b</sup> (sputum or BAL fluid)	8/11
Respiratory virus multiplex PCR assays <sup>c</sup> (nasopharyngeal swabs, sputum, or BAL fluid)	8/11
BAL fluid or tracheal aspirate culture	6/11
Cytomegalovirus PCR assay (BAL fluid or tracheal aspirate)	6/11
Acid-fast bacillus smear, culture, and PCR assay	9/11
Serum anti-Mycoplasma pneumoniae IgM	7/11
Serum anti-Chlamydophila pneumoniae IgM	7/11
Urine Legionella pneumophila antigen assay	5/11
Urine Streptococcus pneumoniae antigen assay	6/11
Pneumocystis carinii PCR assay (BAL fluid)	5/11
Auto-antibodies tests	
Antinuclear antibodies	11/11
Anti-Ro/SSA antibody	11/11
Anti-La/SSB antibody	11/11
Rheumatoid factor	11/11
Anti-citrullinated peptide antibody	11/11
Anti-dsDNA antibody	9/11
Anti-Sm antibody	8/11
Anti-U1RNP antibody	8/11
Anti-Scl-70 antibody	8/11
ANCA, anti-proteinase 3 antibody	9/11
ANCA, anti-myeloperoxidase antibody	9/11
Anti-Jo-1 antibody	8/11

PCR, polymerase chain reaction; BAL, bronchoalveolar lavage; IgM, immunoglobulin M; dsDNA, double-stranded DNA; ANCA, anti-neutrophil cytoplasmic antibodies.

<sup>a</sup>In all patients, the results of all microbiological tests were negative.

<sup>b</sup>Bacterial multiplex PCR assays: Bordetella pertussis, Bordetella parapertussis, Chlamydophila pneumoniae, Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae, Streptococcus pneumonia.

<sup>c</sup>Adenovirus, human bocavirus, human rhinovirus, human coronavirus (229E, OC43), influenza virus (Flu A, Flu B), parainfluenza virus (PIV 1 ,2, 3), respiratory syncytial virus (RSV A, RSV B), and metapneumovirus.



#### Supplementary Table 3. Bronchoalveolar lavage total and differential cell counts (%) in five patients with COVID-19 vaccine-related pneumonitis

	Patient #2	Patient #4	Patient #6	Patient #7	Patient #8
Total WBC count, /µL	778	Not performed	344	2,373	1,344
Neutrophils, %	24	4	29	0	4
Lymphocytes, %	32	49	32	92	53
Eosinophils, %	32	29	2	7	9
Macrophages, %	12	18	37	1	34

There were no findings of alveolar hemorrhage in any BAL specimens.

COVID-19, coronavirus disease 2019; WBC, white blood cell.

Supplementa	ry Table 4. Mec	dication lists for	r underlying co	onditions befor	e COVID-19 va	ccination				
Pt #1	Pt #2	Pt #3	Pt #4	Pt #5	Pt #6	Pt #7	Pt #8	Pt #9	Pt #10	Pt #11
Atorvastatin	Glimepiride	Simvastatin	None	Rosuvastatin	Mirabegron	None	Atorvastatin	Telmisartan	Thioctic acid	Atorvastatin
Amlodipine	Choline- alfoscerate	Choline-alfos- cerate		Amlodipine	Tamsulosin		Gemigliptin	Amlodipine	Pregabalin	Amlodipine
Furosemide		Carvedilol		Nebivolol	Metformin		Metformin	Paroxetine	Glimepiride	Valsartan
Linagliptin		Clonazepam					Insulin aspart	Lorazepam	Metformin	Ginko
Metformin		Metformin					Insulin degludec		Acetylcysteine	Ebastine
Clopidogrel		Clopidogrel							Desloratadine	Levodro- propizine
		Betahistine mesylate								Terazosin
										Thiazide
										Clopidogrel
										Olodaterol/ tiotropium

COVID-19, coronavirus disease 2019; Pt, patient.

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**Supplementary Figure 1.** Radiologic findings of patient #2 before and after coronavirus disease 2019 (COVID-19) vaccination (second dose of BNT162b2-mRNA vaccine). (A) Three years prior to onset. (B, C) COVID-19 vaccine-related pneumonitis (CV-P). (D) Four months after CV-P.





**Supplementary Figure 2.** Radiologic findings of patient #3 before and after coronavirus disease 2019 (COVID-19) vaccination (first dose of BNT162b2-mRNA vaccine). (A) Four years prior to onset. (B, C) COVID-19 vaccine-related pneumonitis (CV-P). (D) Five months after CV-P.



**Supplementary Figure 3.** Radiologic findings of patient #4 before and after coronavirus disease 2019 (COVID-19) vaccination (first dose of BNT162b2-mRNA vaccine). (A) Eleven days after vaccination. (B, C) Fifteen days after vaccination COVID-19 vaccine-related pneumonitis (CV-P). (D) Five weeks after CV-P.





**Supplementary Figure 4.** Radiologic findings of patient #5 before and after coronavirus disease 2019 (COVID-19) vaccination (second dose of BNT162b2-mRNA vaccine). (A) Six years prior to onset. (B, C) COVID-19 vaccine-related pneumonitis (CV-P). (D) Five weeks after onset.



**Supplementary Figure 5.** Radiologic findings of patient #6 before and after coronavirus disease 2019 (COVID-19) vaccination (first dose of ChAdOx1 nCoV-19 vaccine). (A) Ten months prior to onset. (B) Three months prior to onset. (C) COVID-19 vaccine-related pneumonitis (CV-P). (D) Two months after CV-P.





**Supplementary Figure 6.** Radiologic findings of patient #7 before and after coronavirus disease 2019 (COVID-19) vaccination (first dose of BNT162b2-mRNA vaccine). (A) Sixteen months prior to onset. (B, C) COVID-19 vaccine-related pneumonitis (CV-P). (D) One month after CV-P.



**Supplementary Figure 7.** Radiologic findings of patient #8 before and after coronavirus disease 2019 (COVID-19) vaccination (second dose of BNT162b2-mRNA vaccine). (A) One year prior to onset. (B, C) COVID-19 vaccine-related pneumonitis (CV-P). (D) Two weeks after CV-P.





**Supplementary Figure 8.** Radiologic findings of patient #9 before and after coronavirus disease 2019 (COVID-19) vaccination (second dose of BNT162b2-mRNA vaccine). (A) Seven months prior to onset. (B, C) COVID-19 vaccine-related pneumonitis (CV-P). (D) Four months after CV-P.



**Supplementary Figure 9.** Radiologic findings of patient #10 before and after coronavirus disease 2019 (COVID-19) vaccination (first dose of BNT162b2-mRNA vaccine). (A, B) Seven months prior to onset. (C) COVID-19 vaccine-related pneumonitis (CV-P). (D) One month after CV-P.





**Supplementary Figure 10.** Radiologic findings of patient #11 before and after coronavirus disease 2019 (COVID-19) vaccination (first dose of BNT162b2-mRNA vaccine). (A) Seven months prior to onset. (B) Three weeks prior to onset. (C, D) COVID-19 vaccine-related pneumonitis (CV-P).