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An autopsy case of COVID-19-like acute respiratory distress syndrome after mRNA-1273 SARS-CoV-2 vaccination.

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ABSTRACT

We report the first case with COVID-19-like acute respiratory distress syndrome after mRNA-1273 SARS-CoV-2 vaccination. An 88-year-old woman developed dyspnea several hours after vaccination with the second dose of mRNA-1273. She was hospitalized on day nine due to worsening dyspnea. Chest computed tomography showed bilateral ground-glass opacities and consolidations, mainly in the peripheral lung areas. Repeat polymerase chain reaction tests for SARS-CoV-2 were negative, although the serum level of antibodies against spike protein was extremely elevated. Her condition did not improve with high-dose corticosteroids and high-flow nasal cannula oxygen therapy; she died on day 18. Autopsy findings revealed very early-phase diffuse alveolar damage in the whole lung without other lung diseases. The clinical and pathological findings suggested vaccine-induced acute respiratory distress syndrome. Serological and pathological tests might be useful to differentiate the disease from COVID-19.

Introduction

The messenger RNA (mRNA)-based vaccines, BNT162b2 and mRNA-1273, were developed against the SARS-CoV-2; their efficacy and safety have been reported (Baden et al., 2021; Polack et al., 2020; Tang et al., 2021). About 75% of Japan's population has received two shots of a COVID-19 vaccine; 83% received BNT162b2 and 17% received mRNA-1273 as of November 11, 2021 (Prime Minister's Office of Japan, 2021). In Japan, 23,279 possible adverse events have been reported, with 966 fatal cases as of October 3, 2021 (Ministry of Health, Labour and Welfare of Japan, 2021). Here, we report a case of acute respiratory distress syndrome (ARDS) that had strong similarities with COVID-19 after mRNA-1273 vaccination.

Case

An 88-year-old Japanese woman received the first dose of the mRNA-1273 vaccine and experienced cold, dyspnea, fatigue, headache, cough, and abnormal sense of taste one to 2 weeks after vaccination; however, symptoms resolved spontaneously. She experienced dyspnea, fatigue, and loss of sense of smell and taste several hours after the second dose of mRNA-1273 vaccination (day 0), which was administered 28 days after the first dose. These symptoms persisted, and dyspnea worsened on day 9, resulting in a hospital admission. Her medical history revealed intake of the following maintenance medications for the past year: amlodipine, pravastatin, montelukast, dihydrocodeine, DL-methylephedrine, chlorpheniramine, zolpidem, and mecobalamin for hypertension, dyslipidemia, asthma, peripheral neuropathy, and insomnia, re-

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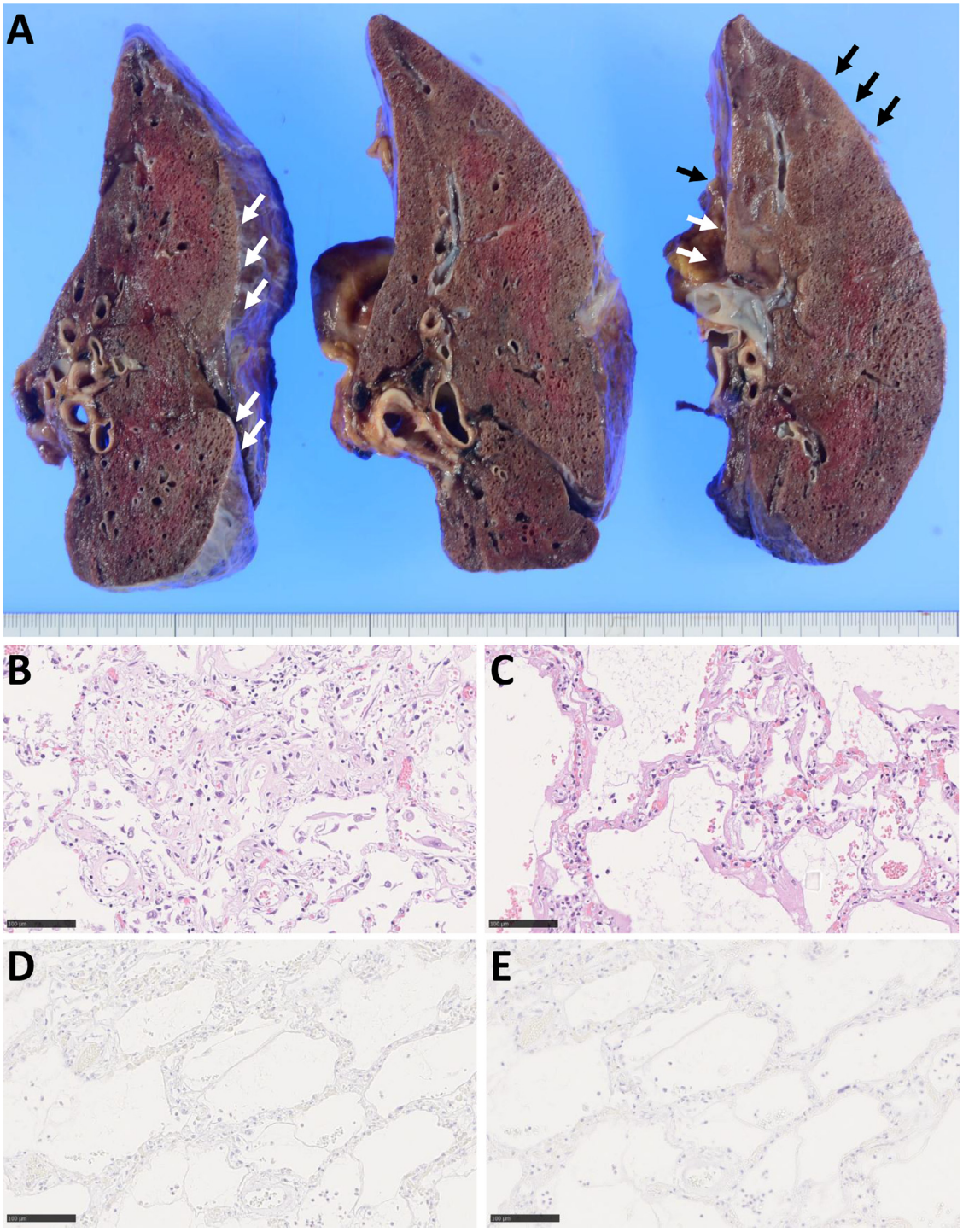

Figure 1. Pathological findings by autopsy
Gross appearance of the cut lung surfaces (left lobe) revealed gray whitish areas (arrows) and brownish-red areas (A). In the gray-white firm areas, pneumocytes, macrophages, and myofibroblastic cell proliferation were observed (B). In the brownish-red areas, hyaline membranes on the alveolar septa were found (C). The lesions were entirely immunohistochemically negative for both SARS-CoV-2 spike (D) and nucleocapsid protein (E). Antibodies for the spike protein (clone 1A9, Abcam, Cambridge, MA) and nucleocapsid protein (clone 001, Abcam) were used.

spectively. She had a hysterectomy for uterine fibroids and no history of COVID-19. She did not have any allergies and had never smoked. Physical examination showed tachypnea (38 breaths per minute), percutaneous oxygen saturation 92% with oxygen therapy at 10 L/min, febrile status (38.1 °C), fine crackles on both lung fields, and no edema in the extremities. Laboratory tests revealed the following: arterial partial pressure of oxygen (PaO_2), 112 mm Hg; lactate dehydrogenase, 452 U/L; C-reactive protein, 7.4 mg/dL; white blood cell count, 9,470 /μL; neutrophils, 8,400 /μL; lymphocytes, 653 /μL; d-dimer, 2.19 μg/mL; brain natriuretic peptide, 7.3 pg/mL; and Krebs von den Lungen-6, 1,194 U/mL (Supplementary Table 1). Day 9 levels of SARS-CoV-2 nucleocapsid (N) and spike (S) proteins serum immunoglobulin G (IgG) were 0.02 S/C and 114,585 AU/mL, respectively. Chest x-ray and computed tomography re-

vealed multifocal dilated bronchi, ground-glass opacities, and consolidations, mainly in the peripheral area of both lungs (Supplementary Figure 1). SARS-CoV-2 polymerase chain reaction (PCR) and rapid antigen testing with nasopharyngeal swabs were negative. We administered pulse steroid therapy (methylprednisolone, 500 mg/day on days 9–11), heparin (10,000 U/day), and ceftriaxone (2 g/day; Supplementary Figure 2). Hypoxia progressed without proportional signs of respiratory distress, and high-flow nasal cannula oxygen therapy was initiated on day 12; however, her oxygen levels did not improve. On day 14, we increased the methylprednisolone dose from 80 mg/day to 500 mg/day. She experienced dyspnea and did not wish for tracheal intubation; therefore, we initiated sedation with morphine on day 15. The patient died from respiratory failure on day 18. Her sputum culture revealed normal flora, serologic markers for *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* were negative, a *Legionella* urinary antigen test was negative, and sputum and pharyngeal swab multiplex PCR was negative with the Seeplex RV15 Onestep ACE Detection assay kit (Seegene, Inc., Seoul, Republic of Korea) for adenovirus, coronavirus 229E/NL63, parainfluenza virus 1/2/3/4, bocavirus 1/2/3/4, enterovirus, influenza A/B virus, metapneumovirus, coronavirus OC43, respiratory syncytial viruses A/B, and human rhinovirus A/B/C.

Autopsy was performed 88 hours postmortem because she died on a holiday and her body was placed in a cool room for 3 days. Both lungs were edematous and heavy. The cut surfaces felt solid and firm and appeared partially glittering, gray-white, brownish-red in color, with partially viscous exudate (Fig. 1A). Histologically, the gray-white firm areas were in the proliferative stage of diffuse alveolar damage with pneumocytes, macrophages, and myofibroblastic cell proliferation (Fig. 1B). The brownish-red areas were in the exudative stage with the presence of hyaline membranes (Fig. 1C). The lesions were entirely immunohistochemically negative for both the SARS-CoV-2 spike (Fig. 1D) and N protein (Fig. 1E). An enzyme-linked immunosorbent assay and western blot for the S protein of the lung lysate also showed negative results (data not shown). PCR confirmed that SARS-CoV-2 was not present in the lung and other organs, including the heart, liver, spleen, and kidney. We did not find any significant pathological changes, such as thrombosis and myocarditis, in any of the organs examined (Supplementary Table 2).

Discussion

To the best of our knowledge, this is the first report of an autopsy case of ARDS after mRNA-1273 vaccination. Her clinical presentation and pathological findings were similar to those of COVID-19; however, SARS-CoV-2 was not detected in the specimens, respiratory or otherwise. We tested SARS-CoV-2 PCR with nasopharyngeal swabs on day 9 and 12 and with bronchial fluid and lung specimens after death; all of which were negative.

Assessing the likelihood of a causal association between the events and the vaccine is a key issue of this case. This patient met the Berlin definition criteria for ARDS (Ranieri et al., 2012) and the Brighton collaboration case definition for ARDS as an adverse event after vaccination (Serazin et al., 2021). The causality algorithm of the World Health Organization (WHO) eligibility diagnosis classified this case's death as "probably related with vaccine administration" (Pomara et al., 2021). It was not classified as "confirmed" because there was no published evidence that confirmed the relationship (Sessa et al., 2021). With regard to the acute lung disease, there was no strong evidence for causes other than the vaccine, and there was a known causal association with the vaccine. The ARDS occurred within the time window of increased risk. Therefore, the lung disease was classified as "consistent with causal association to immunization (vaccine product-related reaction)" according to the other algorithm (World Health Organization, 2019). Taking all factors into account, this is regarded as the first probable case with COVID-19 vaccine-induced ARDS resulting in death.

Three hypotheses could be considered for the mechanisms of ARDS. First, the patient could have been infected with SARS-CoV-2 without detection of the virus. However, this is unlikely because we have detected SARS-CoV-2 with PCR in the lungs and other organs in more than 20 autopsy cases of COVID-19, performed at an approximately similar interval after symptom onset. In addition, anti-N IgG was not detected on day 18 despite the extremely high level of anti-S IgG detected. Anti-N IgG has been detected in 183 of 186 COVID-19 cases (98.4%) at 18 days after symptom onset at our hospital (Unpublished results). The level of anti-N IgG is strongly correlated with that of anti-S IgG in both acute and convalescent COVID-19 cases (Rydyznski et al., 2020). Furthermore, T cell responses against S protein, but not N protein, were detected in this patient on day 10 (data not shown). On the basis of these findings, it is unlikely that SARS-CoV-2 infection occurred in this patient. The second hypothesis is that the mRNA-1273 vaccine caused the development of ARDS. Two cases have been reported regarding drug-induced interstitial lung disease after mRNA vaccination (BNT162b2) (Park et al., 2022; Yoshifuji et al., 2022). In both cases, the patients were Asian men who developed interstitial pneumonia one or 4 days after BNT162b2 vaccination. Systemic corticosteroid therapy was administered and the patients recovered. The level of anti-S IgG in our patient was extremely high, whereas the highest titer in 63 of 104 individuals who were administered two doses of mRNA-1273/BNT162b2 vaccines in our hospital was 53,294/78,950 AU/mL (unpublished results; Yoshimura et al., 2021). This suggests that her body mounted a tremendous humoral immune response after vaccination. On the other hand, S protein was not detected in her lungs with various assays, and immune complex deposition of S protein and anti-S antibodies in the lung was less likely to occur. Another unlikely mechanism is that the S protein that was locally translated from mRNA in the vaccine traveled to the lung and induced inflammation. In this case, the S protein synthesized around the local injection site might have provoked hyperinflammation in the lungs simply through a systemic immune response. The third and last hypothesis is that an occult lung disease became overt after being triggered by the vaccination. However, this is unlikely because whole lung pathological findings revealed no other diseases, such as idiopathic pulmonary fibrosis. Her comorbidities and regular medicines, which had not been changed for a year, were unlikely to cause the ARDS.

In conclusion, the mRNA-1273 vaccine induced ARDS, which was confirmed by clinical and pathological findings. However, we should understand that COVID-19 vaccination is an important tool in stopping the pandemic and rarely causes severe pulmonary adverse events.

Conflict of Interest

Department of Infectious Disease and Respiratory Medicine of Yokohama Municipal Citizen's Hospital, to which Yukihiro Yoshimura, Hiroaki Sasaki, Nobuyuki Miyata, Kazuhito Miyazaki, and Natsuo Tachikawa belong, have received research funding from three companies, Gilead Sciences, Inc., Eli Lilly Japan K.K, and Ono Pharmaceutical Co., Ltd. in the last two years.

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Ethical Approval

Written informed consent for publication was obtained from the patient's family. We complied with the policy of the journal on ethical consent.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.04.057.

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