COVID-19 vaccine-related interstitial lung disease: a case study

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Herd immunity through extensive and rapid vaccination rather than natural immunity acquired by infection is necessary to control a global pandemic like COVID-19. The development of COVID-19 vaccines has been accelerated through government funding and the collaborative efforts of the medical–scientific institutions and the pharmaceutical industry.1 2

In South Korea, the ChAdOx1 nCoV-19 (Oxford/AstraZeneca) and BNT162b2 (Pfizer/BioNTech) vaccines have received emergency approval and are being used. Although the safety and efficacy of these vaccines were established through interim analysis in global clinical trials, long-term data and reports of rare adverse reactions remain inadequate.1 2 We report a case of interstitial lung disease (ILD) after COVID-19 vaccination and review the literature on influenza vaccine-related ILDs. This review is favourable as influenza vaccines are widely administered annually among the elderly, and several vaccine-related ILDs have been reported.

DR HWAN IL KIM
In early April 2021, an 86-year-old man presented to the emergency department with a 1-day history of weakness, dyspnoea and fever. He had no cough, expectoration, nasal discharge or sore throat. One day before symptom onset, he had received a COVID-19 mRNA vaccine. He had hypertension, diabetes and chronic renal disease, which were well controlled with medications (atorvastatin, amlodipine, furosemide, linagliptin, metformin and clopidogrel). He was a non-smoker with no history of cardiovascular, pulmonary, allergic or connective tissue disease (CTD). He took an influenza vaccine annually with no adverse events and had no history of adverse events with other vaccines or drugs. He denied any recent changes in his living environment and exposure to chemicals or organic particles. On admission, his body temperature was 38.2°C, and peripheral oxygen saturation was 80% on room air. He had no rash, oedema or clubbing, but bilateral crackles were found on auscultation. The partial pressure of oxygen (PaO2) was maintained at 248 (50% FiO2; PaO2, 124.2 mm Hg; PaCO2, 21.2 mm Hg) with high-flow nasal cannula oxygen therapy. An electrocardiograph showed sinus tachycardia without ST changes. Blood investigations revealed the following: haemoglobin, 136 g/L; white cell count, 11.60×109/L (neutrophils, 82.8%; eosinophils, 4.1%; lymphocytes, 5.8%); platelets, 340×109/L; International Normalized Ratio (INR), 1.04; D-dimer, 0.55 μg/mL; blood urea nitrogen, 22.7 mg/dL; creatinine, 1.85 mg/dL; aspartate aminotransferase, 18 IU/L; and alanine aminotransferase, 11 IU/L. Chest radiograph revealed bilateral reticular opacities. Empirical antibiotics were administered for 3 days considering a diagnosis of pneumonia; however, the symptoms and chest radiograph findings worsened. Chest CT revealed bilateral diffuse ground-glass opacities (GGO) with focal consolidations, centrilobular micronodules and interlobular septal thickening (figure 1A,B). The C reactive protein level increased to 11.43 mg/dL. The brain natriuretic peptide level (88 pg/mL) was within the reference range, and serum procalcitonin (0.32 ng/mL) was slightly elevated.

DR SUNGHOON PARK
The results of COVID-19 PCR testing (Real-Q 2019-nCoV Detection kit; BioSewoom, Seoul, Korea) of nasopharyngeal swabs and sputum samples were negative, initially and after 3 days. Test results of the induced sputum samples were negative for other pathogens (seasonal respiratory virus multiplex PCR testing (Real-Q RV Detection kit, BioSewoom), bacterial culture, acid–fast bacillus smear, tuberculous PCR testing and respiratory bacterial multiplex PCR testing (Allplex PneumoBacter Assay; Seegene, Seoul, Korea)). He was seronegative for rheumatoid factor and anticitrullinated peptide, antineutrophil cytoplasmic, antinuclear, anti-dsDNA, anti-Sm, anti-U1RNP, anti-Scl-70, anti-Ro and anti-La antibodies. IgE, IgG, IgA and IgM concentrations were within the normal range, and 62 allergen-specific IgE antibodies using AdvanSure AlloScreen (LG Life Science, Seoul, Korea) were negative. Bronchoscopic bronchoalveolar lavage and lung biopsy could not be performed because of the patient’s refusal. COVID-19 vaccine-related ILD was diagnosed based on the clinical course, radiological features and laboratory results. We discontinued antibiotic therapy and initiated intravenous methylprednisolone at 1 mg/kg/day. His symptoms and chest radiography findings rapidly improved the following day. After 3 days, the steroid dose was reduced. Thirteen days later, he was discharged. Subsequently, the steroid dose was gradually tapered and discontinued with no relapse. The onset was acute after vaccination, and the clinical course was transient with rapid improvement by steroid treatment.

A SARS-CoV-2 serological antibody test performed 16 days after vaccination showed that both IgM and IgG were negative (STANDARD Q COVID-19 IgM/IgG Plus Test; SD Biosensor, Korea). The test was conducted to reconfirm whether the patient had a previously undiagnosed COVID-19 before vaccination and to rule out the hypothesis that a
past SARS-CoV-2 infection may have elicited a robust antibody response after vaccination. Moreover, high-dose steroids might prevent adequate antibody formation after vaccination. However, to date, there are no commercial antibody tests approved for the evaluation of immunity following COVID-19 vaccinations, including the tests we conducted.

**DR YONG IL HWANG**

Drug-induced interstitial lung disease (DILD) has a wide spectrum of clinical presentation, from transient lung infiltration to acute respiratory distress syndrome, and is a diagnosis of exclusion. The 'identification' and 'singularity' criteria proposed by Camus et al. were met, because other than the routine medications for hypertension and diabetes, COVID-19 mRNA vaccine was the only drug administered before the onset of ILD. The 'temporal eligibility' criteria were met as the patient had no respiratory symptoms or fever, and ILD with severe hypoxia occurred on the day after vaccination. The rechallenge test is necessary only when no alternative treatment is available; therefore, the patient was advised not to take the second dose of the vaccine. Lastly, the 'exclusion of other conditions' criterion was met as infections and CTDs were ruled out based on the radiological findings and microbiological and serological test results. Bronchoalveolar lavage and lung biopsy were not performed. However, their results are usually non-specific for the diagnosis of DILD.

**DR SEUNG HUN JANG AND DR IN JAE LEE**

We found 10 published case reports of influenza vaccine-related ILD. The clinical characteristics of influenza vaccine-related ILD cases were similar to those of the current case in the following respects (Figure 1c). Symptom onset was acute and occurred at a median of 2 days after vaccination, and fever appeared in most patients. In all cases where chest CT findings can be referred to, bilateral distribution and GGO were confirmed. All patients
recovered, and most responded well to steroid therapy. Interestingly, 8 of 10 patients were Asian, underlying ILD in two cases. Although publication bias is a significant limitation, these might be risk factors for influenza vaccine-related ILD. There was a vaccine safety committee’s report of acute deterioration of underlying ILD after influenza vaccinations from the Japanese Ministry of Health, Labour and Welfare (19 cases from 22.8 million doses of H1N1 vaccine in 2009–2010, Japan). However, the evaluation of risk factors for adverse reactions should be analysed through prospective studies that can proactively evaluate every vaccinated individual and not through case series or reports from passive safety surveillance. Moreover, for rare adverse reactions and delayed-onset events, large healthcare databases with standardised definitions and appropriate statistic models are necessary (active safety surveillance).

Between 14 December 2020 and 6 June 2021, 905.89 million people received at least one dose of the COVID-19 vaccine worldwide. We reviewed the WHO global pharmacovigilance database (through VigiAccess, summary statistics from VigiBase) to identify individual cases of suspected COVID-19 vaccine-related ILD. Eighty-four cases of ILD (single diagnosis code) had been reported until 6 June 2021. Additional cases of COVID-19 vaccine-related adverse events registered included 135 cases of pneumonitis, 88 of acute respiratory distress syndrome, 9 of pulmonary alveolar haemorrhage, 9 of organising pneumonia, 6 of hypersensitivity pneumonitis, 4 of alveolitis, 2 of eosinophilic pneumonia and 1 case each of acute interstitial pneumonitis, immune-mediated lung disease and pulmonary vasculitis. However, a significant limitation of this database is that the information came from various sources, and the causal relationship between a suspected adverse effect and the drug is inconsistent.

**DR JOO-HEE KIM**

Various candidate vaccines against COVID-19, such as inactivated vaccines, viral vector vaccines, nucleic acid (DNA or mRNA-based) vaccines and protein subunit vaccines, are in different stages of development and clinical trials. Two mRNA-based vaccines being used worldwide under an emergency authorisation, BNT162b2 and mRNA-1273 (Moderna), showed 95% and 94.1% efficacy, respectively, in the primary analysis of phase II/III trials. Both vaccines showed similar reactogenicity profiles. The most common local reaction was pain at the injection site (BNT162b2, 71%; mRNA-1273, 74% among older participants after the first dose), which resolved within 2–3 days. Redness and swelling at the injection site were infrequent (approximately 6%). Systemic reactions were more common in young individuals and after the second dose than the first dose. With both vaccines, fatigue was reported by approximately one-third of the elderly subjects after the first dose. Fever occurred in 16% and 17.4% of young individuals after the second dose of the BNT162b2 and mRNA-1273, respectively. The rate of treatment-related serious adverse events was 0.02% (4/21621) and 0.02% (6/15181) with BNT162b2 and mRNA-1273, respectively. No vaccine-related ILD was reported in either clinical trial.

**DR KI-SUCK JUNG AND DR JI YOUNG PARK**

The safety of the mRNA-based vaccines currently in use has been confirmed through phase II/III trials. However, extremely rare or late-onset adverse events might be identified only after the vaccine has been widely administered to the general population. After the national vaccination programme, anaphylaxis and thrombotic events have been reported, although further analysis is necessary to determine their relevance. In countries such as South Korea, where vaccine availability is limited, elderly subjects are being prioritised for vaccination after healthcare workers. However, older adults usually have pre-existing comorbidities and are less tolerant of adverse events. A comprehensive review with a long-term follow-up about the safety of COVID-19 vaccines in older adults is lacking. This report suggests that healthcare professionals monitoring the adverse events should be vigilant for COVID-19 vaccine-related ILD, for a prompt diagnosis and timely treatment. Although vaccine-related ILD should be listed as an adverse reaction of the COVID-19 vaccine, we emphasise that the risk:benefit ratio remains firmly in favour of vaccination.

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