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Case Report

Case report: Acute exacerbation of interstitial pneumonia related to messenger RNA COVID-19 vaccination

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ABSTRACT

Messenger RNA (mRNA) vaccines that protect against COVID-19 are widely used in many countries owing to their high efficacy and safety profiles. Recently, few severe adverse events, such as anaphylaxis and myocarditis, were reported in healthy individuals. The safety of mRNA COVID-19 vaccines has not been adequately studied in patients with interstitial lung disease. We report 2 cases of acute exacerbation of preexisting interstitial pneumonia associated with mRNA COVID-19 vaccination. In both cases, lung disease was stable before the vaccination. Initial responses to steroid therapy were unfavorable, and intravenous cyclophosphamide was administered in both cases. Both patients were diagnosed with vaccine-related exacerbation of interstitial pneumonia based on laboratory results, radiologic features, and the observed clinical course, which lacked other causative events. We suggest that clinicians should note the possibility of acute exacerbation of pneumonia after mRNA COVID-19 vaccination and carefully monitor patients with interstitial lung disease.

Introduction

Patients with respiratory comorbidities are at increased risk of severe COVID-19 (Aveyard et al., 2021, Drake et al., 2020); hence, these individuals are primary candidates for vaccination against the disease. In a phase 2/3 trial, which included 1,478 patients with chronic pulmonary disease, the short-term safety of the BNT162b2 messenger RNA (mRNA) vaccine was established (Polack et al., 2020). Recently, few severe adverse events associated with vaccination, such as anaphylaxis (Shimabukuro et al., 2021) and myocarditis (Bozkurt et al., 2021, Montgomery et al., 2021), were reported in a healthy population. The rare occurrence of adverse events requires further investigation. Little is known about the safety of the mRNA COVID-19 vaccine in patients with interstitial lung disease. We report 2 cases of acute exacerbation of preexisting interstitial pneumonia related to mRNA COVID-19 vaccination.

Case Presentation

Case 1

An 83-year-old man with a 13-day history of high fever and dyspnea was referred to our hospital. He received his first dose of the BNT162b2 mRNA vaccine 1 day before the onset of these symptoms. Three days later, his family doctor prescribed levofloxacin, but his condition worsened. Two years before admission, the patient was diagnosed with idiopathic interstitial pneumonia. He had no respiratory symptoms and his radiologic findings were stable before vaccination (Figure 1A). He was a previous smoker and had a history of hypertension and atrial fibrillation that had remained unchanged and were treated with candesartan and edoxaban. He reported no new chemical exposure.

On admission, the patient's body temperature was 37.5°C and he was tachypneic, with 93% peripheral oxygen saturation in

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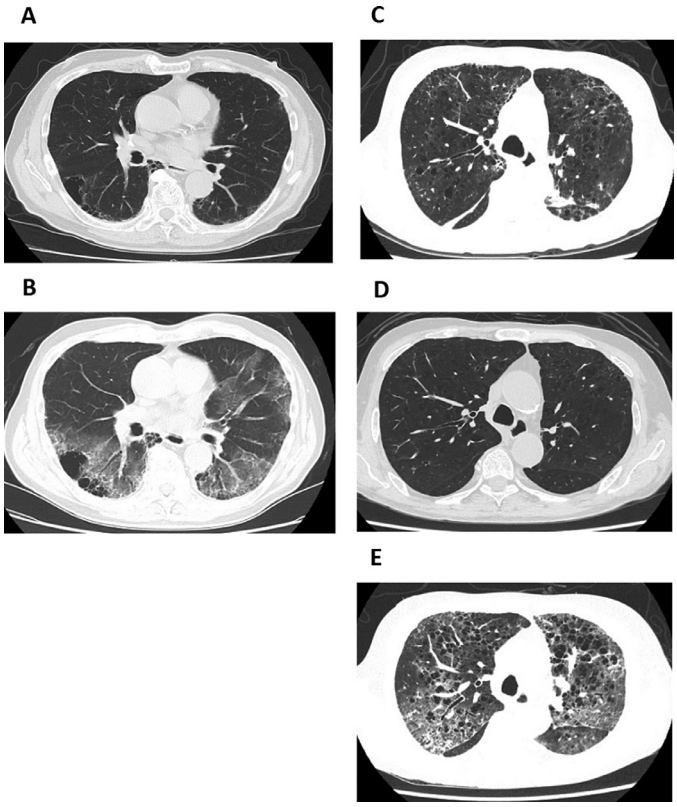

Figure 1. Computed tomography (CT) findings of the cases. (A) A CT scan of case 1, performed 3 months before admission. Slight cystic changes and fibrosis that had been stable for 2 years is shown. (B) Imaging findings on admission revealing diffuse ground-grass opacities extending over both lung fields are shown. (C) Peripherally oriented ground-glass opacities detected during the first acute exacerbation episode of case 2 are shown. (D) Radiologic findings 5 months before admission revealed no detectable radiologic abnormalities despite the fact that the patient received no medications in the past year. (E) Ground-glass opacities and traction bronchiectasis extending superior on both the upper lobes on admission to the emergency department are shown.

room air. Blood tests revealed elevated C-reactive protein (CRP) (24.5 mg/dL), ferritin (1,976 ng/mL), Krebs von den Lungen-6 (KL-6) (1,457 U/mL), and pulmonary surfactant protein-D (SP-D) (427 ng/mL) levels. White blood cell count was 9,300/uL and the differential count was neutrophils 87.6%, lymphocytes 5.0%, and eosinophils 2.6%. Procalcitonin was within normal levels (0.135 ng/mL). Serologic tests for autoimmune markers were negative. Chest radiography and computed tomography (CT) showed bilateral diffuse ground-glass opacities (Figure 1B). Sputum and blood cultures for bacteria, fungi, and mycobacteria were negative and polymerase chain reaction (PCR) test for SARS-CoV-2, using a pharyngeal swab was negative.

Because antibiotics failed to improve symptoms, the patient was considered unlikely to have an infection at that time. He was diagnosed with interstitial pneumonia exacerbation related to mRNA vaccination based on his clinical course, laboratory results, and radiologic findings. Pulsed corticosteroid therapy was initiated, with little effect. Another pulsed corticosteroid dose was administered in addition to intravenous cyclophosphamide (IVCY). The patient's respiratory distress eventually improved, and oxygen therapy was discontinued 4 weeks after IVCY administration.

Case 2

A 65-year-old man presented to the emergency department with low-grade fever and shortness of breath. He received a second BNT162b2 mRNA vaccine 14 days before admission, which resulted in a low-grade fever the next day. No systemic reaction was noted after his first vaccination. Six days after his second vaccination, the patient visited his family doctor because of prolonged low-grade fever and dyspnea. Levofloxacin was prescribed to treat the abnormalities observed in his chest radiograph. SARS-CoV-2 PCR test using a pharyngeal swab was negative. However, the patient's symptoms continued to deteriorate.

Two years before admission, the patient was diagnosed with acute exacerbation of interstitial pneumonia and was treated with oral prednisolone (Figure 1C). Steroid therapy was gradually tapered and withdrawn a year before admission. Subsequently, no relapse was observed (Figure 1D). He was a previous smoker with a history of very low-risk myelodysplastic syndrome. His hemoglobin level was relatively low but stable, and regular checkups were performed. He reported receiving no new medications or chemical exposure.

On admission, he was afebrile but his peripheral oxygen saturation was 90% on 5 L/min oxygen support. Chest radiography and CT revealed ground-glass opacities and traction bronchiectasis extending superior to both upper lobes (Figure 1E). Serum laboratory tests showed leukopenia (1,440 /μL), with a differential of 65.2% neutrophils, 18.8% lymphocytes, and 1.4% eosinophils; anemia that was more severe than typical for the patient (5.6 g/dL hemoglobin); and elevated CRP (6.18 mg/dL), ferritin (1,178 ng/mL), KL-6 (984 U/mL), and SP-D (1,610 ng/mL) levels. Serologic tests for autoimmune markers were negative. Another SARS-CoV-2 PCR test and sputum and blood cultures for pathogens were negative. Therefore, an infectious disease was considered unlikely to be the cause of the symptoms.

The patient was diagnosed with interstitial pneumonia exacerbation related to mRNA vaccination based on his clinical course, laboratory data, and radiologic findings. Pulsed corticosteroid therapy was initiated, with no respiratory symptom improvement. Repeated pulsed corticosteroid and IVCY therapies were initiated, which resulted in gradual recovery of the patient in a month.

Discussion

To the best of our knowledge, this is the first report of acute exacerbation of preexisting interstitial pneumonia after mRNA COVID-19 vaccination. In the United States, 108 cases of interstitial lung disease in association with COVID-19 vaccination have been identified (the Centers for Disease Control and Prevention and the Food and Drug Administration, 2021). However, detailed information is unavailable, and the presence or absence of a preexisting lung disease is unknown.

Hibino et al reported 9 cases of interstitial pneumonia associated with the influenza vaccine (Hibino and Kondo, 2017). In that report, 2 patients had preexisting interstitial pneumonia, and all cases were resolved after corticosteroid administration. The mean interval between symptom onset and vaccination was 2 days, which was comparable with our cases. Park et al reported a case of BNT162b2 mRNA vaccine–related interstitial lung disease without a history of pulmonary disease (Park et al., 2022). The acute symptom onset after vaccination and chest CT findings in that case are similar to those in our cases. The patient was responsive to steroid therapy, as with influenza vaccine-related interstitial pneumonia, whereas our patients were not. This difference may be due to the different vaccines the patients received or because our patients had preexisting interstitial pneumonia. We are unable to establish the reason for the difference because we reviewed only a few cases.

The etiology of mRNA vaccine-related exacerbation of interstitial pneumonia remains unknown. We speculated that the immune system contributes to the exacerbation of interstitial pneumonia. Notably, in our case, we could treat the patients using strong im-

munosuppressive therapy, which confirms this idea. Recently, it was reported that an innate inflammatory response could be induced by the mRNA or by SARS-CoV-2 spike protein (Caso et al., 2020, Lu et al., 2021, Zhao et al., 2021). It has also been reported that cross-reactivity of spike proteins with lung surfactants and related proteins may induce pulmonary inflammation (Kanduc and Shoenfeld, 2020).

To achieve safer COVID-19 vaccination in patients with interstitial lung disease, more studies are needed to determine the reason for the exacerbation of the disease's symptoms and to identify patients at risk of experiencing adverse events.

In conclusion, we encountered 2 cases of acute interstitial pneumonia exacerbation related to COVID-19 mRNA vaccination. Interstitial lung disease is considered a risk factor for severe COVID-19 (Aveyard et al., 2021, Drake et al., 2020). The benefits of vaccination outweigh the risks associated with these rare adverse events. However, clinicians should note the possibility of acute exacerbation post-mRNA COVID-19 vaccination and carefully monitor patients with interstitial lung diseases after vaccination.

Declaration of Competing Interest

Authors declare no conflict of interests.

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Ethical Approval Statement

Informed consent was obtained from the patients for the publication of this case report and accompanying image.

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