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Case Report **Medicine**

Accelerated Extensive Lung Fibrosis Post–COVID-19 Immunization in an Asthmatic Patient

Wafaa Alshahrani[1*], Nadia M. Samad[2], Muhammad Rehan Malik[3], Abdullah Abdulwahed Eid[4]

[1]Pharm.D. Pharmaceutical Care Division, King Faisal Medical Complex, Taif, Saudi Arabia, Diploma in clinical Pharmacy, Notting Hill College, England
[2]Beaumont Hospital, Department of Emergency Medicine, Republic of Ireland, Xi'an Jiaotong University, School of Medicine, People's Republic of China
[3]Mater Misericordiae University Hospital, Department of Emergency Medicine, Republic of Ireland, Xi'an Jaitong University, School of Medicine, People's Republic of China.
[4]Consultant Pulmonologist, King Faisal Medical Complex, Taif, Saudi Arabia, PhD in Respiratory Medicine, Year 1999, Landough Hospital, College of Medicine, University of Wales, Cardiff-UK

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***Corresponding author:** Wafaa Alshahrani
Pharm.D. Pharmaceutical Care Division, King Faisal Medical Complex, Taif, Saudi Arabia, Diploma in clinical Pharmacy, Notting Hill College, England

Abstract

We describe a unique case of a 60-year-old asthmatic Saudi patient who developed acute respiratory distress syndrome (ARDS) and accelerated lung fibrosis after the administration of the second dose of the COVID-19 mRNA vaccine. This patient presented to the emergency room with a four-day history of fever, shortness of breath, and cough. His hospitalization was complicated by non-ST segment elevation myocardial infarction, non-sustained ventricular tachycardia, and a lowered Glasgow Coma Scale. He was intubated at a P/F ratio of 73 mmHg and a peak inspiratory pressure of 46 cmH_2O. His antibiotics had to be modified, as he had QT prolongation. Additional anti-pseudomonal, anti-anaerobe, and anti-fungal coverings were empirically given, which were later switched to colistin based on the results of a sputum culture. On ICU day 17, the patient went into cardiac arrest due to severe ARDS and septic shock. Despite attempts at resuscitation, he was unable to be revived.

Keywords: COVID-19, COVID-19 Vaccines, Acute Respiratory Distress Syndrome, Interstitial Pneumonitis, Adverse Drug Reaction.

1. INTRODUCTION

The first human coronavirus was identified in 1965 as the cause of the common cold. The following decade saw the discovery of a group of human and animal viruses, which were named coronaviruses after their crown-like appearance. To date, seven coronaviruses have been found to infect humans, including 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS), SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS), and SARS-CoV-2 (COVID-19).

The World Health Organization (WHO) declared the SARS-CoV-2 infection a Public Health Emergency of International Concern on January 30, 2020, and a pandemic on March 11, 2020. At present, the SARS-CoV2 virus itself has different variants labelled by the WHO based on their genetic lineage. As of October 21, 2022, a total of 623 million confirmed global cases and 6.55 million deaths have been reported by the WHO.

Common symptoms of COVID-19 include fever, dry cough, fatigue, and myalgia. The respiratory system is the most affected system, but other organs and systems (e.g., cardiovascular system, digestive system, and central nervous system) may also be affected.

The WHO has recommended several vaccines, after meeting certain criteria for safety and efficacy, to achieve herd immunity and control the pandemic. The

development of COVID-19 vaccines has been accelerated through government funding and the collaborative efforts of medical and scientific institutions, as well as the pharmaceutical industry. The three vaccines that are in use in Saudi Arabia for immunization against COVID-19 are ChAdOx1 nCoV-19 (Oxford/AstraZeneca), mRNA-1273 (Moderna), and BNT162b2 (Pfizer/BioNTech). However, the evidence needed to analyze the effects of these vaccines thoroughly, is still being collected and investigated.

2. CASE PRESENTATION

A 60-year-old male—a known case of bronchial asthma, a non-smoker, and with newly diagnosed but well-controlled hypertension on amlodipine—presented to the emergency room with a four-day history of fever, shortness of breath, and cough. His symptoms started within 12 h of receiving the second dose of the COVID-19 vaccine. He had a prior admission earlier in February 2021 for empyema in the left lower lobe, which was treated conservatively with intravenous (IV) antibiotics.

Later, in April 2021, he was admitted to the intensive care unit (ICU) after testing positive for COVID-19 and receiving standard antiviral, steroid, and antibiotic therapies. He was discharged with a tapering prednisolone dose and long-term O_2 therapy at home. His last positive polymerase chain reaction (PCR) was on May 3rd, 2021.

He was vaccinated with the first dose of the COVID-19 mRNA vaccine in September 2021 and the second dose in October 2021. He was not found to be diabetic or have any other history of cardiovascular disease or connective tissue disease. There was no change in his living environment or exposure to chemicals or organic particles.

On admission, his vitals were as follows: a body temperature of 38 °C, a pulse rate of 151/min, a respiratory rate of 32/min, and 70% O_2 saturation on room air. His systematic survey was unremarkable except for bilateral crackles heard over the lung fields, which eventually became more severe on the left side. He was given BiPAP therapy for 4 h to improve oxygenation and was admitted as a COVID-19 patient. Initial blood investigations revealed hemoglobin=164 g/L, white cell count=38.75 x 10^9/L (81.5% neutrophils, 0.03% eosinophils, 10.10% lymphocytes), platelets=264 x 10^9/L, international normalized ratio=1.45, erythrocyte sedimentation rate=38 mm/h, PRO-BNP (brain natriuretic peptide)=665.80 pg/mL, serum ferritin=339 ng/mL, lactate dehydrogenase=488 U/L, creatinine phosphokinase=20 U/L, blood group=A+ (positive), blood urea nitrogen=41 mg/dL, creatinine=0.67 mg/dL, aspartate aminotransferase=19 IU/L, and alanine aminotransferase=16 IU/L. A chest radiograph revealed bilateral reticular opacities (Figure 1).

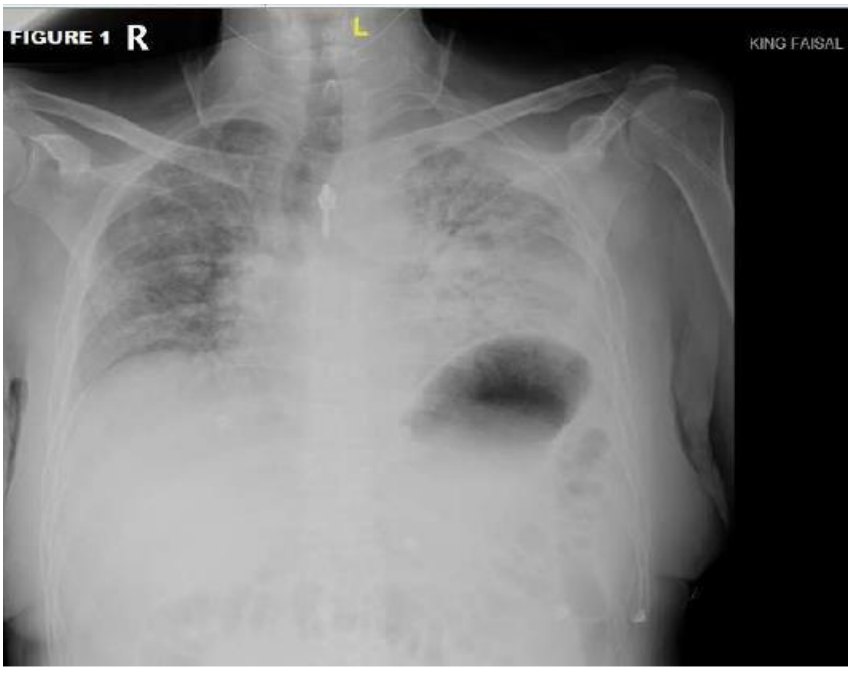

Figure 1: Chest radiography with bilateral reticular opacities

The patient was intubated and mechanically ventilated within the first 24 h of hospital admission. A computed tomography (CT) pulmonary angiogram was negative for pulmonary embolism, showing increased ground-glass opacity with diffuse bilateral lung infiltration and lung fibrosis (Figure 2).

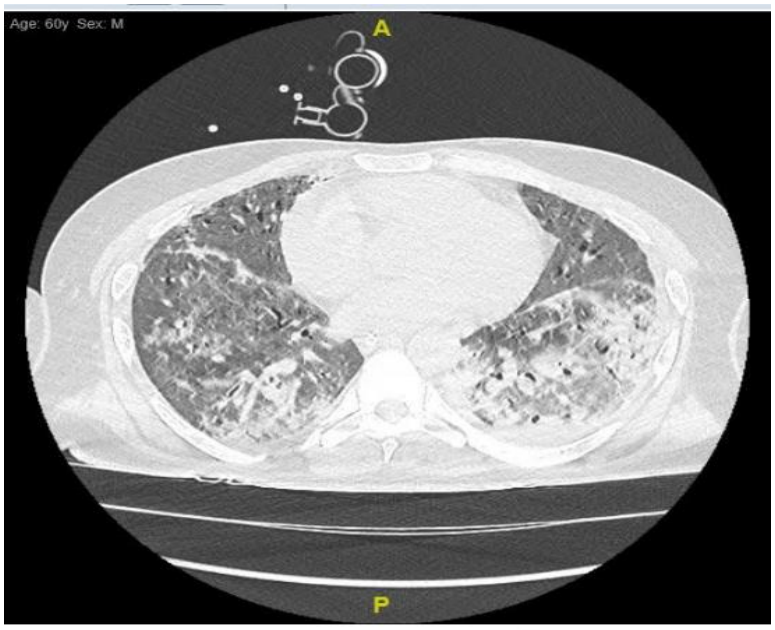

Figure 2: Computed tomography pulmonary angiogram showing increased ground-glass opacity with diffuse bilateral lung infiltration and lung fibrosis

The patient was treated for community-acquired pneumonia (CAP) and septic shock. Pan-cultures came back positive for *Streptococcus pneumoniae* in his blood. Two nCoV-19 PCRs of nasopharyngeal swabs done two days apart showed that he was COVID-19 negative. He also tested negative for influenza viruses (H1N1, MERS-CoV). Four days after ICU admission, his radiological findings worsened on culture-based antibiotics and high ventilatory support, and he developed deteriorating cardiac enzymes and required dopamine support for bradycardia (Figure 3).

On ICU day 7, sedation was stopped for neurological assessment, which showed a reduced Glasgow Coma Scale (GCS) of $E_1V_TM_3$; an urgent brain CT scan was done, which was unremarkable and did not explain the reason for the low GCS. Sedation had to be resumed due to ventilator dysynchrony and tachycardia.

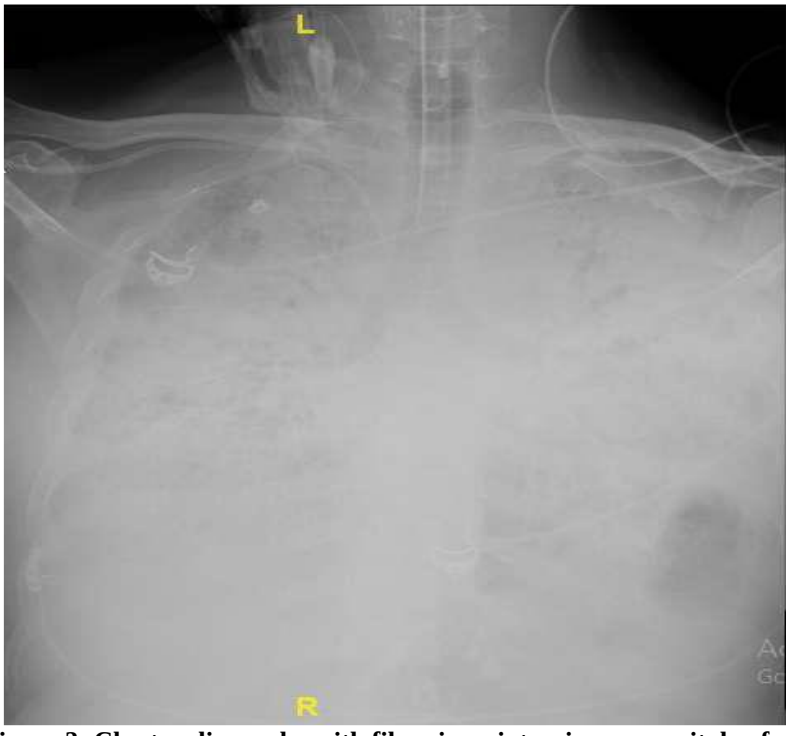

Figure 3: Chest radiography with fibrosis on intensive care unit day four

On ICU day eight, the patient developed non-sustained ventricular tachycardia and non-ST segment elevation myocardial infarction. He also developed a mild pleural effusion. An echocardiogram showed an ejection fraction of 60%, and the patient was negative for pulmonary hypertension and pericardial effusion. Tracheostomy was planned due to difficult weaning with extensive lung fibrosis but had to be postponed as the patient was on dual antiplatelet therapy and deep vein thrombosis prophylaxis. The patient's GCS improved to $E_4V_TM_5$ on ICU day 10, and a tracheostomy was planned again after stopping antiplatelet therapy for five days.

On ICU day 11, the patient developed ventilator-associated pneumonia (VAP) with multidrug-resistant *Acinetobacter*, and the tracheostomy had to be postponed again. The patient resumed antiplatelet therapy along with culture-based IV Colistin. He started developing severe respiratory acidosis with CO_2 retention and hypoxia, as well as drug-induced acute kidney injury.

Although the initial working diagnosis for this patient was CAP complicated by VAP, we also considered the reasons for his accelerated progression into acute respiratory distress syndrome (ARDS) post-vaccination. We first hypothesized that the patient's condition was due to an inflammatory process triggered by a response to immunization or interstitial lung damage caused by his earlier COVID-19 infection three months ago, leading to a post-COVID syndrome. He also had known asthma and an incidence of empyema earlier in the year, which could be contributing factors to the disease progression. We ruled out a pulmonary embolism after negative spiral CT scan. We also included H1N1 influenza infection in the workup, but the results were also negative.

Our initial management of the patient's CAP included broad-spectrum antibiotic coverage based on our hospital's antibiogram. We added oseltamivir empirically until influenza results could be received and later stopped on negative results. We prescribed IV dexamethasone 6 mg once daily for five days starting from the day of admission. He was intubated at a P/F ratio of 73 mmHg, with a peak inspiratory pressure of 46 cmH_2O, and managed as per Ministry of Health protocol [1, 2]. His antibiotics had to be adjusted because he developed QT prolongation, and he was on dopamine support for bradycardia. Additional anti-pseudomonal, anaerobe, and anti-fungal cover were added empirically; later, they were switched to colistin based on sputum culture results. On ICU day 17, the patient developed sudden cardiac arrest secondary to extensive ARDS and septic shock and could not be revived despite resuscitation measures.

3. DISCUSSION

The pathophysiology of pulmonary disease caused by SARS-CoV-2 is very similar to that described for SARS-CoV-1 and MERS-CoV; the associated lung injury has been linked to an aggressive inflammatory response. The pathological basis of the disease appears to be damage to infected lung cells (i.e., type II pneumocytes and capillary endothelial cells), which leads to compromised pulmonary gas exchange (i.e., hypoxemia) and a considerable plasma exudate in the alveolar spaces. When the SARS-CoV-2 virus invades the host, it is first recognized by the angiotensin-converting enzyme 2 (ACE2) receptor on respiratory epithelial cells, allowing viral entry. Following viral replication within the cells, the virus is released and met by the host's innate immune system.

The local production of extremely high levels of many inflammatory cytokines, chemokines, and free radicals causes severe damage to the lungs and other organs. SARS-CoV-2 mainly spreads through the respiratory tract, with lymphopenia and cytokine storms occurring in the blood of subjects with severe disease. These observations suggest the existence of immunological dysregulation and altered cytokine networks as an accompanying event during a severe illness caused by this virus [3].

Recovery from many viral infectious diseases is followed by infection-induced immunologic protection against reinfection. This phenomenon is widely observed in many respiratory viral infections, including influenza and endemic coronaviruses, for which acquired immunity also wanes over time, making individuals susceptible to reinfection [4].

The current COVID-19 vaccines function by mimicking the above-mentioned mechanism of immune activation and consequently strengthening whatever residual response is left in the body post–disease remission. Therefore, the Centers for Disease Control and Prevention continues to recommend COVID-19 vaccination for all eligible people, including those who have been previously infected with SARS-CoV-2 [5].

The safety of mRNA-based vaccines, which are widely used globally, has been established through phase II/III trials. Nevertheless, some rare or late-onset adverse effects could be identified only after the vaccine has been widely administered to the general population [6].

Our hypothesis for the uncommon, accelerated deterioration in our patient, despite all treatment maneuvers, is that he developed a robust immune reaction to the second dose of the mRNA vaccine along with the super-added streptococcal infection, leading to ARDS and irreversible interstitial lung disease. Unfortunately, we could not procure a picture of his earlier post-COVID lung parenchyma, which could also have contributed to rapid deterioration and an immune trigger despite the absence of the viral pathogen itself.

A comparative analysis of similar vaccine-induced interstitial lung diseases revealed 10 reported cases of drug-induced interstitial lung disease (ILD) secondary to influenza vaccines [7–9], suggesting a shared mechanism of lung injury that is not specific to the molecular composition of the vaccine. The first case of COVID-19 vaccine–related ILD was reported in August 2021 [10], following which similar cases have been reported post–COVID-19 vaccination [11–14]. All the patients had a similar presentation of pneumonitis post-vaccination with similar risk factors of older age and asthma, and showed dramatic improvement with corticosteroid therapy. Pharmacovigilance data published by the WHO, VigiAccess, showed 24 respirator-dependent cases among COVID-19 vaccine–related adverse events. According to Vaccine Adverse Event Reporting System data, among people who received the Pfizer-BioNTech vaccine, reactions reported to the V-safe system were more frequent after receipt of the second dose than that after the first dose [15].

The mechanism of drug-induced ILD is not well understood and has many clinical patterns ranging from benign infiltrates to life-threatening ARDS [16, 17], The two most common mechanisms investigated are cytotoxic and immune-mediated lung injury. Immune-mediated ILD may be T-cell-mediated and can be detected in peripheral blood smears of affected patients [18].

Another fact that cannot be disregarded is the patient's age and prior history of asthma, which allows for the possibility of an activated allergic response masked by the steroids he was already on. In early safety monitoring of the Pfizer-BioNTech COVID-19 vaccine, 21 cases of anaphylaxis were reported following 1,893,360 first doses of the vaccine. Many individuals who experienced possible anaphylaxis response to the mRNA vaccines had a history of allergy to various other allergens [19]. This association may be due to the patient's or vaccine provider's heightened anticipation or appreciation of possible allergic symptoms. The binding of the viral S-protein to ACE2 induces the production of anti-glycan antibodies, similar to naturally occurring ABO antibodies. These natural immunoglobulin M concentrations seem to mirror some of the patterns of clinical severity in COVID-19. Finally, immunization with vaccines encoding the virus N-protein induced an eosinophilic response in animals [20].

4. CONCLUSION

The likelihood of drug-induced ILD should be considered in cases of unexplained acute respiratory failure. The benefits of COVID-19 vaccination in the general population outweigh the risks. However, a particular risk group of older, asthmatic, and previously COVID-19–infected individuals should be monitored more closely with immunological assays to quantify anti-spike IgG concentrations pre- and post-vaccination. There should be close outpatient follow-up of COVID-19–recovered patients, and any re-hospitalizations should be flagged as markers for the need for post-COVID rehabilitation. Pulmonary function tests should be done before the vaccination of high-risk groups. We recommend the widespread availability of both drug-induced lymphocyte stimulation tests and the leukocyte migration test to detect drug-induced T-cell sensitization. Additionally, if sensitized T-lymphocytes are found following the initial dosage, we advise against using mRNA vaccines as booster doses and instead suggest trying other vaccinations with alternative immunological trigger mechanisms.

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