

Vaccine-induced interstitial lung disease: a rare reaction to COVID-19 vaccination

Alison M DeDent, Erica Farrand

After millions of deaths worldwide and months of widespread social and economic devastation, the first vaccine against SARS-CoV-2 (COVID-19) was given emergency use listing by the WHO.¹ Approved only 1 year after the virus was first identified in Wuhan, China, this historic achievement was the result of public and private institutional partnerships, as well as decades of foundational scientific research. Two of the earliest vaccines authorised for widespread use were the BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) messenger RNA (mRNA) vaccines, demonstrating 95% and 94.1% efficacy, respectively, in phase II/III clinical trials. Notably, both vaccines have strong safety profiles, with the most common adverse events including injection site reactions, fever, chills, fatigue, headache, and muscle and joint aches.²⁻³ Postauthorisation reports of severe reactions, including anaphylaxis, have been extremely rare, occurring in only 4.5 reported cases per million doses.⁴

In this issue of *Thorax*, Park and colleagues⁵ present the first published case of COVID-19 vaccine-related interstitial lung disease (ILD). An 86-year-old man developed an acute onset of fever, weakness, shortness of breath and hypoxaemia requiring high-flow nasal cannula 1 day after receiving a dose of a COVID-19 mRNA vaccine. He had no history of ILD, connective tissue disease, tobacco use or exposure to offending medications. CT of the chest showed bilateral, diffuse ground glass opacities, with areas of focal consolidation and centrilobular nodules. Evaluations for alternative aetiologies, including nasal and sputum testing for COVID-19 and other infectious diseases, an ECG, a brain natriuretic peptide test, and serological testing for connective tissue diseases, were normal or negative. The patient declined to undergo bronchoscopy or surgical lung biopsy. Based

on the time course and available information, he was diagnosed with drug-induced ILD and treated with high-dose methylprednisolone, with rapid improvement in his clinical condition and imaging. He was discharged on a steroid taper, and follow-up imaging nearly 3 months after discharge confirmed resolving ground glass opacities and consolidations without the development of fibrosis.

Drug-induced ILD is a rare disease, for which the true incidence and prevalence are unknown. The severity of illness can range from subclinical disease to severe acute respiratory distress syndrome, and it is a diagnosis of exclusion, with a differential that includes infection, haemorrhage, oedema and exacerbation of an underlying ILD. In the absence of an alternative diagnosis, drug-induced ILD should be suspected if a temporal association between symptom onset and an offending agent can be identified. The most common medications associated with drug toxicity of the lungs include chemotherapeutic agents, rheumatological medications (disease modifying antirheumatic drugs (DMARDs) and tumor necrosis factor (TNF)-alpha inhibitors), amiodarone and nitrofurantoin,⁶ although a complete list of medications that may cause pulmonary toxicity can be found on the website Pneumotox (www.pneumotox.com). Symptoms may include cough, shortness of breath, fever and hypoxaemia, and both imaging and histology findings are non-specific, often overlapping with other types of ILD. While more invasive testing, such as bronchoscopy and surgical lung biopsy, is often non-diagnostic, it may aid with the exclusion of alternative diagnoses and should be considered on an individual basis.⁷ Risk factors vary and are poorly understood; however, older age, underlying pulmonary disease and tobacco use have been most commonly reported. Treatment depends on the degree of disease severity, and high-quality evidence is lacking. Mild cases may resolve with medication discontinuation alone, while corticosteroids are often added to treat more severe cases.⁶

The pathogenesis of drug-induced ILD is incompletely understood, although both cytotoxic and immune-mediated pathways

of injury have been described. Cytotoxic injury may occur directly to pneumocytes or the alveolar capillary endothelium, and immune-mediated reactions occur through T cell regulation.⁷ Whether one or both of these pathways are involved in COVID-19 vaccine-induced ILD is unknown; however, reports of vaccine-induced ILD after influenza vaccination may suggest a shared mechanism of lung injury that is not specific to the molecular composition of the vaccine. While more studies are needed, the presence of lymphocyte sensitisation, demonstrated using in vitro drug lymphocyte stimulation testing after exposure to various types of vaccines, could possibly support a common immune-mediated mechanism of lung injury.⁷

There are important limitations for clinical practice that accompany published case reports. First, while reporting and recognising potential adverse events in the postauthorisation period are essential, a causal relationship cannot be established from a single case report. Further, these findings cannot be generalised to any specific risk group or population. While the authors note that other potential cases of ILD due to COVID-19 vaccination were identified in VigiBase, a drug safety database managed by the WHO,⁸ the accuracy of these reports must be interpreted with caution due to differences in international coding criteria, errors, lack of transparent diagnostic criteria, and lack of distinction between a new, acute ILD and the exacerbation of an existing ILD. Nevertheless, continuous monitoring of both patients and international drug safety databases for pulmonary toxicity from these vaccines is warranted.

In conclusion, clinicians should consider drug toxicity in their differential of any unexplained acute respiratory failure or ILD and should be aware of this reaction as COVID-19 vaccination efforts continue. However, the benefits of widespread COVID-19 vaccination in the general population continue to strongly outweigh the risks. COVID-19 vaccination is the most effective and safe method for preventing COVID-19-related serious events.

Twitter Erica Farrand @ericafarrandMD

Contributors AMD drafted the initial version of the manuscript, and AMD and EF participated in drafting all revisions. Both authors approved the final manuscript submitted for publication.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of California San Francisco, San Francisco, California, USA

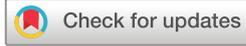
Correspondence to Dr Alison M DeDent, 513 Parnassus Ave, HSE 1314, Box 0111, University of California San Francisco, San Francisco, California CA 94143, USA; alison.dedent@ucsf.edu

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

© Author(s) (or their employer(s)) 2022. No commercial re-use. See rights and permissions. Published by BMJ.



To cite DeDent AM, Farrand E. *Thorax* 2022;**77**:9–10.

Accepted 24 August 2021

Published Online First 11 September 2021



► <http://dx.doi.org/10.1136/thoraxjnl-2021-217609>

Thorax 2022;**77**:9–10.

doi:10.1136/thoraxjnl-2021-217985

REFERENCES

1 "WHO issues its first emergency use validation for a COVID-19 vaccine and emphasizes need for equitable global access." WHO, 2020. Available: <https://www.who.int/news/item/31-12-2020-who-issues-its-first-emergency-use-validation-for-a-covid-19-vaccine-and-emphasizes-need-for-equitable-global-access> [Accessed 6 Aug 2021].

2 Polack FP, Thomas SJ, Kitchin N, *et al.* Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603–15. doi:10.1056/NEJMoa2034577

3 Baden LR, El Sahly HM, Essink B, *et al.* Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403–16.

4 Gee J, Marquez P, Su J, *et al.* First Month of COVID-19 Vaccine Safety Monitoring - United States, December 14, 2020-January 13, 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:283–8.

5 Park JY, Kim J-H, Lee IJ. COVID-19 vaccine-related interstitial lung disease: a case study. *Thorax* 2022;77:103–5.

6 Skeoch S, Weatherley N, Swift AJ, *et al.* Drug-Induced interstitial lung disease: a systematic review. *J Clin Med* 2018;7. doi:10.3390/jcm7100356. [Epub ahead of print: 15 Oct 2018].

7 Matsuno O. Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. *Respir Res* 2012;13:39.

8 Uppsala Monitoring Centre. "Vigibase." Available: <https://www.who-umc.org/vigibase/vigibase/> [Accessed 7 Aug 2021].