

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

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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.

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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.

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Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

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To cite DeDent AM, Farrand E. *Thorax* Epub ahead of print: [please include Day Month Year]. doi:10.1136/thoraxjnl-2021-217985

Accepted 24 August 2021



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

Thorax 2021;**0**:1–2.
doi:10.1136/thoraxjnl-2021-217985

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