

Altered mental status and pronounced febrile response after second mRNA-1273 (Moderna) COVID-19 vaccine administration in a patient with previously documented COVID-19 infection

Patrick Shamell Hilaire, Emmanuel Tito, Nirmal Muthukumarasamy, Mark Schauer

Internal Medicine, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, Michigan, USA

Correspondence to
Patrick Shamell Hilaire;
patrick.hilaire@med.wmich.edu

Accepted 10 August 2021

SUMMARY

A 54-year-old man who was previously found to be COVID-19 positive received two doses of mRNA-1273 (Moderna) vaccine 4 weeks apart, as recommended by the manufacturer. He was brought to the emergency department 1 day after second dose of the vaccine with altered mental status, headache and high fever. The patient was hospitalised for 2 days and managed with supportive care. He completely recovered with return of mental status to baseline and resolution of fever.

BACKGROUND

The ongoing COVID-19 pandemic has prompted the FDA to authorise the use of several vaccines without completing the usual lengthy robust trials in an effort to curb the spread of the virus and hasten a global recovery. Adverse effects of the mRNA-1273 (Moderna's COVID-19 vaccine) have been recorded and are particularly more severe with the second dose.¹ This vaccine was approved by the Food and Drug Administration (FDA) on 18 December 2020 under the Emergency Use Authorization clause. It is an mRNA vaccine that is delivered in a lipid nanoparticle to express a full-length spike protein, given intramuscularly in two doses ideally spaced 28 days apart.²

The goal of this report is to describe and document the hospital course and associated comorbidities of this patient who suffered from severe adverse effects requiring hospitalisation after completing his immunisation for the novel SARS-CoV-2.

CASE PRESENTATION

A 54-year-old man with a medical history of type 2 diabetes mellitus, atrial flutter, hypothyroidism, well-controlled seizure disorder and a remote history of traumatic brain injury presented to emergency department with fever and altered mental status after receiving his second dose of the COVID-19 vaccine. The patient received his first dose of mRNA-1273 COVID-19 vaccine in January 2021 which was 3 months after his minimally symptomatic COVID-19 infection. His second dose of vaccine was given in February 2021. He complained of headache a few hours following his second dose but was otherwise at baseline. The next morning his caretaker found him difficult to arouse and feverish. In the emergency department, the patient was unable to provide much history due

to significant lethargy. He was febrile (103.3°F), tachycardic (114/min) and hypertensive (145/71 mm Hg) with normal oxygen saturation on room air. On physical examination, the patient was alert but confused. He had residual left-sided weakness and cognitive deficit from his traumatic brain injury but does not have any new focal neurological deficits. The remainder of the physical examination was consistent with his baseline except for mild generalised abdominal tenderness.

The patient resided in an assisted care facility; at baseline, the patient was interactive and communicative. Four months prior to this admission, the patient had a positive-COVID-19 PCR during a preprocedure screen before ablation of atrial flutter.

INVESTIGATIONS

Initial labs showed leukocytosis (white cell count— $12.1 \times 10^9/L$), haemoglobin 109 g/L and normal platelet count. Blood glucose, electrolytes, renal function, liver enzymes and procalcitonin levels were normal. COVID-19 nasopharyngeal PCR was positive. His seizure medications valproate and carbamazepine levels were within therapeutic range. Lab findings included elevated C reactive protein of 157.4 (reference range <6 mg/L), erythrocyte sedimentation rate of 48 mm/hour (reference range <20 mm/hour), normal urinalysis, elevated creatine kinase of 1025 U/L (reference range <206 U/L), Thyroid Stimulating Hormone (TSH) of 4.81 μmL (reference range 0.27–4.2 μmL), Prothrombin Time (PT) of 37.7 (reference range 10.5–13 s) and International Normalized Ratio (INR) of 3.4 (patient taking warfarin).

Chest X-ray was normal. ECG showed normal sinus rhythm with no other acute changes. CT scan of the brain showed no acute changes to suggest infarct or haemorrhage. There were post-surgical changes involving right frontoparietal calvarium, encephalomalacia right frontoparietal temporal region and to a lesser extent left parietal region similar when compared with prior CT examinations.

DIFFERENTIAL DIAGNOSIS

The patient did not have a documented seizure episode and his seizure medications were in the therapeutic range. However, he could have had an unwitting seizure and postictal confusion secondary to fever. Absence of new focal neurological deficits



© BMJ Publishing Group Limited 2021. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Hilaire PS, Tito E, Muthukumarasamy N, et al. *BMJ Case Rep* 2021;**14**:e244119. doi:10.1136/bcr-2021-244119

and the CT findings rule out cerebrovascular accident. Meningoencephalitis was considered but lumbar puncture could not be done due to supratherapeutic INR secondary to warfarin. With the improvement in mental status and resolution of fever, infectious aetiology was deemed unlikely.

TREATMENT

The patient received supportive treatment with intravenous fluids and antipyretics. As the day progressed, the patient became more encephalopathic and reached a maximum temperature of 104.8°F axillary. He was therefore started on empiric treatment for meningoencephalitis with intravenous ceftriaxone, vancomycin, acyclovir and dexamethasone but these were discontinued after patient's mental status markedly improved overnight.

OUTCOME AND FOLLOW-UP

The patient was hospitalised for 2 days. His mental status started improving after the first hospital day. The patient had a maximum documented temperature of 104.8°F axillary during his inpatient stay and fever lasted for approximately up to 30 hours after vaccination. He was discharged after his mental status returned to baseline.

DISCUSSION

Vaccine Adverse Event Reporting System (VAERS) and v-safe are passive and active surveillance systems, respectively, used to monitor adverse effects of COVID-19 vaccines. The symptoms most frequently reported to VAERS were headache, fatigue and dizziness. After receiving the first dose of mRNA-1273 vaccine, headache, fatigue and dizziness were reported in 25.3%, 16.6% and 16.6% of patients in comparison to serious adverse reactions which were reported in 18.8% of patients.¹

In the randomised placebo-controlled phase III trials of mRNA-1273 vaccine, injection site and systemic adverse events were more common among younger participants (18–<65 years of age) than among older participants (≥65 years of age). No patients were reported to have confusion in the vaccine group as per the supplementary appendix data of the vaccine trial.² Our patient had febrile illness with headache and confusion and to our knowledge no similar adverse events were reported in the literature.

In vaccinees with previous SARS-CoV-2 infections, immunogenicity and adverse reactions of mRNA vaccines are important considerations. Vaccinees with previous SARS-CoV-2 infection have been shown to have higher antibody titers than infection naive individuals after mRNA COVID-19 vaccines.^{3–5} In a study by Krammer *et al*, the antibody titers of vaccinees with pre-existing immunity was 10–45 times higher after the first vaccine dose.³ Rios *et al* reported that previous COVID-19 infection increased the immunogenicity of mRNA vaccine in frail or disabled nursing home residents.⁴

As per the vaccine trial, solicited adverse events (including local and systemic reactions) during the first week after vaccination were less common in participants who were positive for SARS-CoV-2 infection at baseline than in those who were negative at baseline.² Vaccine recipients with pre-existing immunity had higher rates of systemic side effects than those without pre-existing immunity.^{3,5} In a study involving frail and disabled nursing home patients, 58% of the 134 study participants had previous COVID-19 infection. There was no serious adverse reaction or anaphylaxis reported in this study.⁴ Local

and systemic adverse events were more common after the second dose as well as being longer lasting and more severe.^{2,5} Henceforth it is unclear if prior SARS-CoV-2 infection predisposes to serious adverse reactions, but second dose of mRNA vaccine certainly has more frequent adverse reactions.

Our patient had positive-COVID-19 PCR 4 months prior to this admission with minimal symptoms. His repeat COVID-19 PCR during this admission remained positive. It is uncertain if this is due to continued presence of viral particles or reinfection. Previous COVID-19 infection and the second dose of vaccine could have played a role in causing him serious adverse reaction needing hospital admission. His medical history of traumatic brain injury and cognitive deficit likely contributed to the clinical picture.

In the constant tug of war between vaccination rates and continuing waves of COVID-19 due to new variants, improving vaccine acceptance could be a decisive thrust. Vaccine efficacy followed by chances of serious adverse reactions have significant effect in vaccine acceptance.⁶ Anticipating adverse reactions in vulnerable populations, minimising adverse reactions and educating the vaccinees will certainly improve the vaccine acceptance.

Learning points

- ▶ mRNA-1273 SARS-CoV-2 vaccine could potentially lead to febrile illness with altered mental status requiring hospitalisation.
- ▶ It is unclear if patients with previous SARS-CoV-2 infection are more prone for adverse reactions after vaccination.
- ▶ Potential risks and benefits of a second dose of mRNA COVID-19 vaccine in individuals with prior infection merits continued surveillance and robust clinical research.

Contributors PSH, ET and NM wrote the case report. MS was involved in planning and supervision.

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.

Patient consent for publication Obtained.

Provenance and peer review Not 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.

REFERENCES

- 1 Gee J, Marquez P, Su J. *MMWR, first month of COVID-19 vaccine safety monitoring — United States, December 14, 2020–January 13, 2021*. 2020.
- 2 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.
- 3 Krammer F, Srivastava K, Alshammary H, *et al*. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. *N Engl J Med* 2021;384:1372–4.
- 4 Salmerón Ríos S, Mas Romero M, Cortés Zamora EB, *et al*. Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A study. *J Am Geriatr Soc* 2021;69:1441–7.
- 5 Callegaro A, Borleri D, Farina C, *et al*. Antibody response to SARS-CoV-2 vaccination is extremely vivacious in subjects with previous SARS-CoV-2 infection. *J Med Virol* 2021;93:4612–5.
- 6 Kaplan RM, Milstein A. Influence of a COVID-19 vaccine's effectiveness and safety profile on vaccination acceptance. *Proc Natl Acad Sci U S A* 2021;118:e2021726118.

Copyright 2021 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow