Aseptic Meningitis Following the Second Dose of Comirnaty Vaccination in an Adolescent Patient

A Case Report

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Abstract: Vaccination is currently the best strategy to control the coronavirus disease 2019 epidemic. This report describes a case of aseptic meningitis 3 weeks after administration of the second dose of Comirnaty. The patient recovered with conservative and symptomatic care after 5 days of admission. Surveillance of rare adverse events, including aseptic meningitis, and their management should be prompt and appropriate.

Key Words: adverse drug reaction, aseptic meningitis, COVID-19, COVID-19 vaccines

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Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is deemed to be the most practical and promising strategy to control the ongoing coronavirus disease 2019 (COVID-19) epidemic. Multiple vaccines have been, and are still being, developed based on several different platforms. RNA vaccines were the first vaccines developed for SARS-CoV-2, which traditionally have never been used in the vaccine industry.[1] Therefore, concerns regarding safety and side effects are as high as concerns for vaccine efficacy. Until recently, despite uncommon issues with myocarditis and pericarditis mainly in male adolescents and young adults, the overall benefits of vaccination seem to outweigh the rare risks.[2]

In Korea, Comirnaty (previously, BNT162b2, Pfizer-BioNTech COVID-19 vaccine) was introduced in February 2021. Studies reporting the side effects of Comirnaty were similar to studies outside of Korea, which mostly reported local and systemic adverse effects as common. Headache was reported as one of the most frequent systemic adverse effects.[3] With severe headaches, indications for cerebrospinal fluid (CSF) examination are considered; therefore, it is plausible that thorough CSF examinations are conducted globally. Nevertheless, only one case of aseptic meningitis following the first dose of Comirnaty has been reported in a 42-year-old female.[4] This report describes a case of aseptic meningitis in an adolescent documented following the second dose of Comirnaty and could not be explained by any other possible causes.

CASE

A previously healthy 18-year-old man presented with a chief complaint of headache that started 2 days before his visit. Accompanying symptoms included nausea, febrile sense, and chills. The patient's headache was generalized and recurring. The headache was relived on sitting and aggravated on lying down. On discussing medical history, the patient reported receiving the second dose of Comirnaty vaccine 3 weeks before the initial symptom but denied recent travel or contact with another person with respiratory symptom(s). Vital signs were as follows: blood pressure 157/67 mm Hg; pulse rate 62 bpm; respiratory rate 20 breaths/min; and body temperature 37.9°C. The patient was generally ill-looking. No neurologic deficit nor signs of meningeal irritation was noticed on physical examination. However, meningitis of either bacterial or viral origin was suspected, and CSF analysis was performed alongside other evaluations (Table 1). Complete blood cell counts were as follows: white blood cell (WBC) 10,020/μL (segmented neutrophil 82.1%); hemoglobin 15.5 g/dL; and platelet count 209,000/μL. CSF analysis revealed the possibility of meningitis favoring viral over bacterial origin: WBC 115/μL (normal < 5); monomorphorous leukocyte 99.1% (normal ≥ 75); red blood cell 180/μL; glucose 65 mg/dL (normal > 50 or 75% serum glucose); and protein 67.2 mg/dL (normal 20–45). The CSF opening pressure could not be measured owing to technical issues. The nasopharyngeal swab results for SARS-CoV-2 (Xpert Xpress SARS-CoV-2, Cepheid, Sunnyvale, CA) were negative.

Based on results of the CSF analysis, treatment with vancomycin (1 g per dose, every 8 hours) and cefotaxime (2 g per dose, every 8 hours) was initiated along with blood and CSF cultures. Intravenous mannitol was also administered and maintained with an initial loading dose based on the risk of increased intracranial pressure. His headache persisted on hospital day (HD) 2, but peak body temperature was attenuated to 37.6°C. On HD 3, despite a normalized body temperature, the patient reported a slight improvement but had persistent nausea and headache. Brain magnetic resonance imaging with diffusion was then performed as the patient vomited for the first time that morning, which revealed evidence of subtle leptomeningeal enhancement along both cerebral convexity on the fluid attenuated inversion recovery sequence. This is consistent with meningitis. As blood and CSF culture results showed no organism growth, antibiotics targeting bacterial meningitis were discontinued. On HD 4, the patient showed substantial improvement in general appearance with no remnant headache. The patient was able to walk actively around the ward corridors without assistance. On HD 5, mannitol administration was discontinued at midnight, and the patient was well through noon. The patient was discharged with full recovery.

Tests for SARS-CoV-2 antibody (Ab) were performed during admission. The SARS-CoV-2 Ab test (Seegene, Seoul, Korea) detects antibodies against nucleocapsid (N) and spike (S1) proteins separately through an electrochemiluminescence immunoassay analyzer and enzyme-linked immunosorbent assay, respectively. The presence of both SARS-CoV-2 Ab (N) and SARS-CoV-2 Ab (S1) usually implicates prior infection with SARS-CoV-2. On the contrary, as all vaccines, including mRNA vaccines, target-spike proteins, the presence of SARS-CoV-2 Ab (S1) along with the absence of SARS-CoV-2 Ab (N) generally results when antibodies

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TABLE 1. Laboratory Findings in a Patient Suspected for Aseptic Meningitis Following Second Dose of Comirnaty

Complete Blood Cell Count	
White blood cell (/μL)	10,020
Neutrophil (%)	82.1
Lymphocyte (%)	10.7
Hemoglobin (g/dL)	15.5
Platelet (/μL)	209,000
Erythrocyte sedimentation rate (mm/h)	2
Chemical	
Aspartate aminotransferase (IU/L)	15
Alanine aminotransferase (IU/L)	8
BUN (mg/dL)	8.4
Creatinine (mg/dL)	0.97
Albumin (g/dL)	4.4
Glucose (mg/dL)	110
hs-C-reactive protein (mg/dL)	0.74
Cerebrospinal fluid	
White blood cell (/μL)	115
Monomorphorous (%)	99.1
Red blood cell (/μL)	180
Glucose (mg/dL)	65
Protein (mg/dL)	67.2
Lactate dehydrogenase (IU/L)	24
Urinalysis	
Protein	Negative
White blood cell (/HPF)	0–1
Red blood cell (/HPF)	0–1
Complement	
C3 (mg/dL)	123
C4 (mg/dL)	37
Antibodies	
Epstein-Barr virus viral-capsid antigen IgM Ab	Negative
Cytomegalovirus IgG/M Ab	Negative
Fluorescent antinuclear Ab	Negative
Anti-double stranded DNA Ab	Negative
Myelin oligodendrocyte glycoprotein Ab	Negative
Aquaporin-4 Ab	Negative
PCR	
Respiratory panel (virus*/bacteria†)	Negative/ Negative
Cerebrospinal fluid panel (virus‡/bacteria§)	Negative/ Negative

*Adenovirus, Influenza A/B virus, Parainfluenza virus 1/2/3/4, Human rhinovirus, Bocavirus 1/2/3/4, Coronavirus 229E/NL63/OC43, Enterovirus, Metapneumovirus, and Respiratory syncytial virus A/B.

†*Bordetella pertussis, Chlamydophila pneumoniae, Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae,* and *Streptococcus pneumoniae*

‡Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus type 1/2, Human herpes virus 6, and Varicella-zoster virus.

§Group B Streptococcus, *Haemophilus influenzae* type b, *Listeria monocytogenes, Neisseria meningitidis,* and *Streptococcus pneumonia*.

HPF indicates high power field.

originate from vaccination.[5] The test results for the patient were as follows: SARS-CoV-2 Ab (S1) Positive 5.12 (cutoff 1.00 S/Co); SARS-CoV-2 Ab (N) Negative 0.10 (cutoff 1.00 COI).

Other test results that were negative are as follows (detailed pathogens are listed in Table 1): multiple respiratory PCR tests for common respiratory viruses (Anyplex II RV16 Detection, Seegene) and bacterium (Allplex PneumoBacter Assay, Seegene); CSF multiple PCR tests for common neurotropic viruses (Seeplex Meningitis-V1 ACE Detection, Seegene) and bacterium (Seeplex Meningitis-B ACE Detection, Seegene); myelin oligodendrocyte glycoprotein Ab; Aquaporin-4 Ab; fluorescent antinuclear Ab; anti-double stranded DNA Ab; c-antineutrophil cytoplasmic Ab (ANCA); p-ANCA; Epstein-Barr virus viral-capsid antigen IgM Ab; and cytomegalovirus IgG/M Ab. Complement 3 and 4 levels were within normal limits.

This study was approved by the Institutional Review Board (IRB) of Chungbuk National University Hospital (IRB No. 2021-09-006). Informed written consent for the publication of this report was obtained from the both the patient and the legitimate guardian.

DISCUSSION

This report describes a case of aseptic meningitis following the second dose of Comirnaty in an adolescent patient. Specific portions of the current vaccines are novel to the industry, and therefore, attention should be paid to all possible side effects. Furthermore, consideration of several case reports of viral meningitis and meningoencephalitis in COVID-19 augments a rare, but possible, association between vaccine administration and aseptic meningitis.[6]

Theoretically, the chances of meningitis following vaccination are considerably low and other direct causes are more likely.[7] However, the present case has been extensively scrutinized for other possible explanations and only negative test results were obtained for those avenues. The possibility of the patient experiencing asymptomatic COVID-19 still remains. To note, the patient was a high school student studying at a boarding school and recalled to have undergone 3 to 4 SARS-CoV-2 PCR tests in 2021 and more tests in 2020 for surveillance. All of whose results were negative. Additionally, the patient was an only child with no known exposure to COVID-19. Furthermore, despite the ongoing COVID-19 epidemic in Korea, the prevalence of COVID-19 in Korea is lower than that in other developed countries owing to strict and rigid public regulations. Therefore, it is reasonable to assume that the patient's Ab result was triggered by vaccination.

As SARS-CoV-2 is a novel virus, various serology tests have been, and are being, developed. Some tests rely on IgG and IgM, while others use total antibodies that target specific proteins as used in this study. The test used in this study meets the basic requisites for evaluation by measuring total antibodies, which is also supported by the Centers for Disease Control and Prevention for its higher sensitivity.[8] In addition, the 3- to 4-week interval between the second dose of Comirnaty and the serology test was appropriate for obtaining optimal results.

Aseptic meningitis following vaccination has been reported after measles, mumps, and rubella (MMR) vaccination in the 1990s and early 2000s, when a mumps strain from Urabe was used.[9] Even then, the possibilities of becoming ill from wild viruses were much higher than those from attenuated live vaccines. Additionally, reports of aseptic meningitis following vaccines other than MMR vaccines are even scarce. In general, vaccination has decreased the prevalence of viral meningitis with negligible risk of vaccine-induced meningitis. As mRNA vaccines are relatively new to vaccine history, surveillance is needed. There are considerable differences between the first report by Saito et al and the case presented herein.[4] First, in the present case, the patient was an adolescent, while in the previous case, the patient was a 42-year-old woman. Second, in the case from Saito et al, the patient showed clinical symptoms after the first dose of Comirnaty. Third, the clinical course of the patient was more favorable in the current case. Considering the prevalence of autoimmune disease, there could have been augmented immunologic processes as their patient was an older woman. However, clear mechanisms of drug-induced meningitis (including vaccines) are not yet fully understood, and further surveillance and investigations are expected.[10] Furthermore, it remains unclear why reports of aseptic meningitis are scarce when CSF evaluations are more frequent. For now, it may be reasonable to consider the possibility of aseptic meningitis in vaccinated individuals to rule out other causes and to anticipate self-limited illness with recovery. Nevertheless, as there are few similar reports, optimal management should be explored and investigated.

Extensive investigations of other potential causes have been ruled out in the current study. The possibility of aseptic meningitis

following Comirnaty or other mRNA vaccines should be considered when a patient presents with severe headache regardless of age or dose counts.

REFERENCES

1. Krammer F. SARS-CoV-2 vaccines in development. *Nature.* 2020;586:516–527.
2. Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the advisory Committee on Immunization Practices—United States, June 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:977–982.
3. Chapin-Bardales J, Gee J, Myers T. Reactogenicity following receipt of mRNA-based COVID-19 vaccines. *JAMA.* 2021;325:2201–2202.
4. Saito K, Shimizu T, Suzuki-Inoue K, et al. Aseptic meningitis after vaccination of the BNT162b2 mRNA COVID-19 vaccine. *Neurol Sci.* 2021;42:4433-4435..
5. Jones JM, Stone M, Sulaeman H, et al. Estimated US infection- and vaccine-induced SARS-CoV-2 seroprevalence based on blood donations, July 2020-May 2021. *JAMA.* 2021;326:1400–1409.
6. Lv P, Peng F, Zhang Y, et al. COVID-19-associated meningoencephalitis: a care report and literature review. *Exp Ther Med.* 2021;21:362.
7. Jolles S, Sewell WA, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. *Drug Saf.* 2000;22:215–226.
8. Centers for Disease Control and Prevention. *Interim Guidelines for COVID-19 Antibody Testing*. Centers for Disease Control and Prevention. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html. Accessed September 6, 2021.
9. Di Pietrantonj C, Rivetti A, Marchione P, et al. Vaccines for measles, mumps, rubella, and varicella in children. *Cochrane Database Syst Rev.* 2020;4:CD004407.
10. Marinac JS. Drug- and chemical-induced aseptic meningitis: a review of the literature. *Ann Pharmacother.* 1992;26:813–822.