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Immunodeficiency Should Be Excluded in Patients With Recurrent Viral Meningitis and Breakthrough COVID-19

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Disclosure

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To the Editor:

We read with interest the article by Yun et al.¹ about an 18 years old male with a previous history of meningitis of unknown etiology at age 6 years, who developed fever and throbbing headache five days prior to the diagnosis viral meningitis due an infection with the varicella zoster virus (VZV). Though the patient had received the second dose of the Biontech Pfizer vaccine (BPV) 7 weeks prior to admission he tested recurrently positive for SARS-CoV-2 until discharge.¹ The patient profited from administration of acyclovir and made a complete recovery.¹ The study is appealing but raises concerns that require discussion.

A shortcoming is that no explanation was provided why the patient had experienced a meningitis at age 6 years, a second meningitis at age 18 years, a VZV infection despite having been vaccinated against VZV, why the polymerase chain reaction (PCR) for SARS-CoV-2 remained positive throughout hospitalisation, and why the anti-SARS-CoV-2 vaccination was ineffective. Was the history positive for other infections than those mentioned in the case description? Was the patient investigated for an immunodeficiency syndrome? How was a chronic infection with SARS-CoV-2, HIV or tuberculosis excluded? Was the patient truly immune competent as indicated in the introduction? An explanation for the breakthrough COVID-19 could be that SARS-CoV-2 vaccinations itself can cause immunodeficiency.²

A further shortcoming of the study is that the cerebrospinal fluid (CSF) was not tested for cytokines, chemokines, neurofilament light chain (NfL), and for tau. In a systematic review about the CSF findings in COVID-19 patients, 85% had elevated cytokines and chemokines, 71% had elevated NfL, and 36% had elevated tau.³ We should know if the CSF was investigated for mycobacterium tuberculosis and if the CSF was cultivated for bacteria.

Another shortcoming is that it is not mentioned if the patient received any treatment for the SARS-CoV-2 infection. Additionally, it is quite unusual that meningitis symptoms had improved already after one day under acyclovir. We should be told if the patient received any other medication in addition to acyclovir.

Though it is mentioned that cerebral MRI was normal on admission, we should be told if contrast medium was applied. Occasionally meninges enhance upon contrast medium in patients with meningitis.⁴

Though the neurological examination was normal, we should be told if the patient complained about photophobia, previously reported as a manifestation of viral meningitis.⁵

Which was the cause of meningitis at age 6y? Did the patient undergo CSF investigations at that time?

Surprisingly, the patient was discharged although he tested positive for SARS-CoV-2 in the upper and lower respiratory tract.¹ Which was the proof that the patient was not infectious at the time of discharge? How was the PCR test in the lower respiratory tract carried out? Did the patient undergo bronchoscopy?

Overall, the interesting study has limitations which challenge the results and their interpretation. Patients experiencing recurrent meningitis should undergo extensive work-up for immunodeficiency. Patients with a SARS-CoV-2 associated meningitis require comprehensive work-up of the CSF.

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The Author's Response: Response to the Comment: Immunodeficiency Should Be Excluded in Patients With Recurrent Viral Meningitis and Breakthrough COVID-19

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Disclosure

The authors have no potential conflicts of interest.

Dear Editor:

We are grateful for the interest to our case reports, and valuable comments by Finsterer J. We reported a rare case of varicella zoster virus (VZV) meningitis co-infection with breakthrough coronavirus disease 2019 (COVID-19) in a young, immunocompetent patient.¹ The letter to the editor presented some questions and concerns about the case report, so we would like to clarify some issues raised by the author.

First, the author suggested whether the patient was real immunocompetent. We appreciate the thoughtful advice and agree that we should have excluded the possibility of immunodeficiency. However, the patient had no infection or hospitalization history other than meningitis history at 6 years old. He didn't have past medical history of tuberculosis (TB), and the chest X-ray revealed no evidence of active or old TB infection. The serum human immunodeficiency virus (HIV) antibody test was negative. Besides we couldn't review the medical data of past hospitalization because it was long time ago, and the patient and his family remembered that the patient got spinal tapping on the past hospitalization but etiology of meningitis was unknown. We suggested that the breakthrough infection of VZV may be related to COVID-19. As we described in discussion of the case report, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection led to hyper-inflammatory status and immune dysregulation (especially T cell dysfunction), which could promote VZV infection.²⁻⁴ The breakthrough infection of SARS-CoV-2 has been reported in immunocompetent patients, and one of the report in Korea presented breakthrough infection rate even high as 43.1% in patients who received second dose of BNT162b2 mRNA SARS-CoV-2 vaccine.⁵

About the inquiries of the case, we had bacterial culture, fungal culture, TB polymerase chain reaction (PCR), acid-fast bacilli smear and culture of cerebrospinal fluid (CSF) and the result was all negative. However, we didn't measure cytokines, chemokines, neurofilament light chain (NFL), and tau in CSF. This is limitation of our study, because elevated cytokines, chemokines, and NFL in COVID-19 patients reveals hyper-inflammatory status,^{6,7} which affects VZV co-infection.^{2,3} In addition, we performed brain magnetic resonance imaging (MRI) with contrast on first day of hospitalization, and there was no abnormal enhancement. We should have mentioned about MRI enhancement findings in our case reports, and thank you for your thorough advice.

On clinical course, the patient admitted to hospital on 5 days after symptom developed, and took painkiller (non-steroidal anti-inflammatory drugs and acetaminophen) for symptom relief. And the headache and fever improved soon after the admission. The patient did not have photophobia during the admission.

The PCR test for SARS-CoV-2 test was done in upper (nasopharyngeal) and lower (sputum) respiratory tract, and the result was consistently positive. Some recent studies suggested that risk of transmission in COVID-19 patients are low 5 days after symptom onset, especially in patients with mild respiratory symptoms.^{8,9} Considering low risk of transmission, Korea Centers for Disease Control and Prevention recommended to release isolation after 7 days of SARS-CoV-2 infection in patients with asymptomatic or mild respiratory symptoms, even if PCR test for SARS-CoV-2 is consistently positive.

Overall, we agree with the comment about some limitations of our case reports. However, our study showed we should be aware of other viral infections including VZV in COVID-19

patients. The further study with comprehensive work up for immunodeficiency should be done in SARS-CoV-2 associated meningitis.

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