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.

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.

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

References:
1. Yun J, Kim J, Lee JH, Park JS, Lee JS, Kim JS, Kim JH, Lee JH. A case report of varicella zoster meningitis as co-infection with breakthrough COVID-19 in an immunocompetent patient. J Korean Med Sci. 2022 May 16;37(19):e161.
2. Finsterer J. Immunodeficiency Should Be Excluded in Patients With Recurrent Viral Meningitis and Breakthrough COVID-19. J Korean Med Sci. 2022 May 16;37(19):e161.
3. https://doi.org/10.3346/jkms.2022.37.e161
4. eISSN 1598-6357·pISSN 1011-8934
5. © 2022 The Korean Academy of Medical Sciences.
6. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
7. ORCID ID
Josef Finsterer ©
https://orcid.org/0000-0003-9339-7305
8. Disclosure
The author has no potential conflicts of interest to disclose.

See the article “A case report of varicella zoster meningitis as co-infection with breakthrough COVID-19 in an immunocompetent patient” in volume 37, number 8, e61.
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.

REFERENCES

1. Yun S, Kim J, Shin HR. A case report of varicella zoster meningitis as co-infection with breakthrough COVID-19 in an immunocompetent patient. J Korean Med Sci 2022;37(8):e61. [PubMed] [CrossRef]
2. Salinas AF, Mortari EP, Terreri S, Quintarelli C, Pulvirenti F, Di Cecca S, et al. SARS-CoV-2 vaccine induced atypical immune responses in antibody defects: everybody does their best. J Clin Immunol 2021;41(8):1709-22. [PubMed] [CrossRef]
3. Domingues RB, Leite FBVMF, Senne C. Cerebrospinal fluid analysis in patients with COVID-19-associated central nervous system manifestations: a systematic review. Arq Neuropsiquiatr 2022;80(3):296-305. [PubMed] [CrossRef]
4. Wang RJ, Wang DX, Wang JW, Feng ZJ. Analysis of 62 adult patients with viral meningitis. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 2009;23(3):218-20. [PubMed]
5. Jafri L, Farooq Khan A, Arshad T, Kanwar D. A case series on enteroviral meningitis in Pakistan. Cureus 2021;13(10):e19048. [PubMed] [CrossRef]
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. 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 leaded to hyper-inflammatory status and immune dysregulation (especially T cell dysfunction), which could promote VZV infection.

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. 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, which affects VZV co-infection. 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. 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. 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.

REFERENCES

1. Yun S, Kim J, Shin HR. A case report of varicella zoster meningitis as co-infection with breakthrough COVID-19 in an immunocompetent patient. J Korean Med Sci 2022;37(8):e61.
   PUBMED | CROSSREF

2. Diez-Domingo J, Parikh R, Bhavsar AB, Cisneros E, McCormick N, Lecrenier N. Can COVID-19 increase the risk of herpes zoster? A narrative review. Dermatol Ther (Heidelb) 2021;11(4):1119-26.
   PUBMED | CROSSREF

3. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20(6):355-62.
   PUBMED | CROSSREF

4. Zheng HY, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. Cell Mol Immunol 2020;17(5):541-3.
   PUBMED | CROSSREF

5. Yi S, Kim JM, Choe YJ, Hong S, Choi S, Ahn SB, et al. SARS-CoV-2 Delta variant breakthrough infection and onward secondary transmission in household. J Korean Med Sci 2022;37(1):e12.
   PUBMED | CROSSREF

6. Domingues RB, Leite FBVM, Senne C. Cerebrospinal fluid analysis in patients with COVID-19-associated central nervous system manifestations: a systematic review. Arq Neuropsiquiatr 2022;80(3):296-305.
   PUBMED | CROSSREF

7. Normandin E, Holroyd KB, Collens SI, Shaw BM, Siddle KJ, Adams G, et al. Intrathecal inflammatory responses in the absence of SARS-CoV-2 nucleic acid in the CSF of COVID-19 hospitalized patients. J Neurol Sci 2021;430:120023.
   PUBMED | CROSSREF

8. Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HH. Taiwan COVID-19 outbreak investigation team. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med 2020;180(9):1156-63.
   PUBMED | CROSSREF

9. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020;26(5):672-5.
   PUBMED | CROSSREF