Comorbidity of purulent meningitis with COVID-19: A case report

Ping Zhang¹, Chao Pan¹, Jiahui Wang¹, Yang Ma¹, Huaqiu Zhang², Zhouping Tang¹(✉)

¹ Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China
² Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China

ABSTRACT

To date, only a few cases of intracranial infection related to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) were reported. Here we describe a case of coronavirus disease 2019 (COVID-19) that was comorbid with purulent meningitis. A 62-year-old male patient was diagnosed with moderate COVID-19 and had no fever or cough after treatment. However, he suffered from a head injury and experienced headache and fever immediately after the accident. Computed tomography (CT) of the brain showed bilateral frontal lobe contusion, subdural hematoma, and subarachnoid hemorrhage. In the following days, the patient suffered from recurrent fever, although chest CT did not show evidence of worsening of infection. Several lumbar punctures were made, confirming increased cerebrospinal fluid (CSF) pressure and karyocyte count. SARS-CoV-2 nucleic acid was not detected in CSF but revealed the presence of Escherichia coli. Thus, the patient was diagnosed with purulent meningitis, presumably caused by brain trauma or the immunologic dysfunction caused by COVID-19, which was supported by the significant reduction of all kinds of immune cells. Since immunologic dysfunction is commonly presented in COVID-19 patients, comorbidity with meningitis should be considered when a COVID-19 patient presents with headache and fever. Lumbar punctures and CSF cultures may help in the diagnosis.

1 Introduction

Since December 2019, the coronavirus disease 2019 (COVID-19) has affected more than 100 million people worldwide and caused more than half a million deaths. Increasing evidence warns that severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) could have neuro-
invasive potential and induce neurological diseases [1]. To date, only a few cases of intracranial infection related to SARS-CoV-2 were reported. Here, we describe a case of comorbidity of COVID-19 with purulent meningitis in a patient presenting with headache and recurrent fever after brain trauma.

2 Case report

A 62-year-old man presented with COVID-19 at the specialized ward of Tongji Hospital (Wuhan, China) after experiencing brain trauma 5 h before the visit. Since February 8, 2020, the patient had a fever and dry cough. Blood routine analysis found a decreased lymphocyte count of $0.61 \times 10^9/L$ (normal range: 1.1–3.2 $\times 10^9/L$). A computed tomography (CT) of the chest showed bilateral pulmonary multiple patchy shadows and interstitial changes, suggesting viral pneumonia. Though SARS-CoV-2 nucleic acid analysis from two throat swabs was negative, SARS-CoV-2-specific IgM and IgG were detectable in the serum. Thus, the patient was diagnosed with moderate COVID-19 and admitted to another designated hospital. After receiving antiviral and supportive treatments, the patient had no fever or cough. However, on March 10, he accidentally fell and hit his occiput against a hard floor. Soon after, he suffered from headache and vomiting, with no observable symptoms of unconsciousness, seizure, or paralysis. The patient also had a medical history of hypertension. At admission, the examination revealed an elevated body temperature of 38.2 °C and a blood pressure of 155/89 mmHg. When the patient was submitted to oxygen inhalation through a nasal catheter (3 L/min), the peripheral oxygen saturation was 97%. The patient was conscious but had dysphoria. Through careful physical examination, nuchal rigidity was observed. Emergent brain CT showed bilateral frontal lobe contusion, subdural hematoma, and subarachnoid hemorrhage.

After admission, the patient persistently complained of headache and fever and immediately underwent blood examinations. Arterial blood gas analysis indicated a PaO$_2$ of 75.0 mmHg (normal range: 80.0–100.0 mmHg) and a PaCO$_2$ of 33.2 mmHg (normal range: 35.0–45.0 mmHg). A peripheral blood routine test indicated a white blood cell count of $7.13 \times 10^9/L$ (normal range: 3.5–9.5 $\times 10^9/L$), a neutrophil count of $6.08 \times 10^9/L$ (normal range: 1.8–6.3 $\times 10^9/L$), a lymphocyte count of 0.49 $\times 10^9/L$ and a normal platelet count. The coagulation function test showed normal prothrombin and activated partial thromboplastin times but an elevated D-dimer of 16.39 μg/mL fibrinogen-equivalent units (FEU; normal range: < 0.5 μg/mL FEU). Blood biochemical testing revealed normal liver and kidney functions. The blood electrolytes and cardiac troponin were in normal ranges. The inflammatory indicators were elevated, with a hypersensitive C-reactive protein level of 10.8 mg/L (normal range: < 1 mg/L) and a procalcitonin level of 0.43 ng/mL (normal range: < 0.05 ng/mL). Blood immunoglobulins and complements were normal. The analysis of peripheral blood lymphocyte subsets revealed significant reductions in immune cells, including T lymphocytes, B lymphocytes, and natural killer (NK) cells (Table 1). The patient was tested again for COVID-19 and was tested positive with serum SARS-CoV-2-specific IgM and IgG. However, the throat swab test for SARS-CoV-2 nucleic acid, blood and sputum cultures, and G and GM tests were negative. Abdominal CT and ultrasound examinations reported no sign of infection. A CT of the brain was performed again in 24 h and showed bilateral frontal subdural hematoma, bilateral frontal lobe hemorrhage and edema, and...
subarachnoid hemorrhage [Figs. 1 (A) and (B)]. The pulmonary CT showed bilateral multiple ground-glass opacities and patchy shadows [Figs. 1 (C) and (D)]. In the following 72 h, the brain CT was repeated daily and did not show any worsening of hemorrhage.

| Item                                                   | Value  | Reference range |
|--------------------------------------------------------|--------|-----------------|
| Total T lymphocytes (CD3+CD19−) (%)                    | 78.16  | 50.00–84.00     |
| Total T lymphocytes (CD3+CD19−) (μL)                   | 384    | 955–2860        |
| Total B lymphocytes (CD3−CD19+) (%)                    | 8.16   | 5.00–18.00      |
| Total B lymphocytes (CD3−CD19+) (μL)                   | 40     | 90–560          |
| Helper/induced T lymphocytes (CD3+CD4+) (%)            | 35.10  | 27.00–51.00     |
| Helper/induced T lymphocytes (CD3+CD4+) (μL)          | 173    | 550–1440        |
| Suppressor/cytotoxic T lymphocytes (CD3+CD8+) (%)      | 29.51  | 15.00–44.00     |
| Suppressor/cytotoxic T lymphocytes (CD3+CD8+) (μL)     | 145    | 320–1250        |
| NK cells (CD3−CD16−CD56+) (%)                         | 12.65  | 7.00–40.00      |
| NK cells (CD3−CD16−CD56+) (μL)                        | 62     | 150–1100        |
| T lymphocytes + B lymphocytes + NK cells (%)           | 98.97  | 95.00–105.00    |
| T lymphocytes + B lymphocytes + NK cells (μL)          | 486    |                 |
| Th/Ts                                                  | 1.19   | 0.71–2.78       |

**Table 1** Peripheral blood lymphocyte subsets of the patient.

![CT images](image-url)  
**Fig. 1** CTs of the brain and chest. On March 11, brain CT (A and B) showed bilateral frontal lobe hemorrhage and edema, bilateral frontal subdural hematoma, and subarachnoid hemorrhage; chest CT (C and D) showed bilateral multiple ground-glass opacities and patchy shadows. On March 15, brain CT (E and F) showed bilateral frontal lobe hemorrhage and edema, as well as bilateral frontal subdural hematoma, which was similar to the former imaging; chest CT showed (G and H) partial absorption of the pulmonary infection. On April 2, repeated brain CT (I and J) showed edema in the bilateral frontal lobe without hemorrhage; chest CT (K and L) showed obvious absorption of the pulmonary infection.
The patient received mannitol, piperacillin-tazobactam, and supportive treatments. However, the patient’s headache and fever persisted. On March 15, his body temperature reached 39.3 °C. CTs of the brain and chest were performed again. The brain hemorrhage and edema did not progress [Figs. 1 (E) and (F)], and the pulmonary infection was partially absorbed [Figs. 1 (G) and (H)]. Subsequently, a lumbar puncture was made on March 16. The cerebrospinal fluid (CSF) was turbid and bloody, with a pressure of 300 mmH₂O. The CSF red blood cell count was 6400 × 10⁶/L (normal range: 0 × 10⁶/L), while the karyocyte count was 400 × 10⁶/L (normal range: 0–8 × 10⁶/L), consisting of 80% neutrophil granulocytes, 15% lymphocytes, and 5% monocytes. Total protein in CSF was 1202 mg/L (normal range: 150–450 mg/L), and 724 mg/L (normal range: 100–300 mg/L) for albumin. The CSF glucose was 2.03 mmol/L (normal range: 2.22–3.89 mmol/L), and the chlorine was 113.2 mmol/L (normal range: 120–132 mmol/L). The India ink and acid-fast staining were negative. CSF SARS-CoV-2 nucleic acid was tested by a reverse transcription-polymerase chain reaction and showed a negative result. According to the CSF presentation, purulent meningitis was diagnosed. A combination of meropenem and vancomycin was chosen for empiric antibiotic therapy. After 3 days of updated antibiotic treatment, the patient’s body temperature decreased to the normal range. The lumbar puncture was repeated on March 19, showing a CSF pressure of 320 mmH₂O, a red blood cell count of 570 × 10⁶/L, and a karyocyte count of 10 × 10⁶/L. The CSF total protein and albumin were 585 mg/L and 335 mg/L, respectively. The CSF glucose and chlorine were in normal ranges. As CSF karyocytes were clearly decreased, the antibiotic therapy was changed into a combination of ceftriaxone and vancomycin. However, on March 22, the patient had a fever again, with a body temperature of 38.6 °C. The white blood cell count increased to 20.08 × 10⁹/L, with a neutrophil count of 18.11 × 10⁹/L and a lymphocyte count of 1.17 × 10⁹/L.

To investigate the cause of the recurrent fever, another lumbar puncture was performed on March 23, 2020. The CSF was yellow and slightly turbid, with a pressure of 150 mmH₂O. The CSF karyocyte count was 100 × 10⁶/L. The CSF total protein and albumin were 800 mg/L and 525 mg/L, respectively. The CSF glucose and chlorine were 3.02 mmol/L and 113.2 mmol/L, respectively. The CSF bacterial culture indicated the presence of *Escherichia coli* resistant to ampicillin, piperacillin, cefotaxime, and cotrimoxazole. The patient was diagnosed with purulent meningitis that was most likely caused by an extended-spectrum beta-lactamase-producing *E. coli*. Therefore, antibiotic therapy was changed into meropenem, which gradually improved the fever and headache. The lumbar puncture was repeated on March 31, showing a normal CSF pressure of 120 mmH₂O and a CSF karyocyte decrease to 44 × 10⁶/L. The CSF protein and glucose were normal. Brain and chest CTs were repeated on April 2, showing the persistence of bilateral frontal lobe edema and hemorrhage absorption [Figs. 1 (I) and (J)]. The pulmonary infection was also clearly absorbed [Figs. 1 (K) and (L)].

3 Discussion

We present a case of COVID-19 and purulent meningitis comorbidity. In this COVID-19 patient, the significantly increased CSF karyocytes and *E. coli* in CSF culture indicated purulent meningitis. There was no direct evidence of SARS-CoV-2 infection in the central
nervous system (CNS), as demonstrated by the absence of SARS-CoV-2 nucleic acid in the CSF. The purulent meningitis was not directly caused by SARS-CoV-2, although COVID-19 might be one of the precipitating factors of bacterial infection.

The angiotensin-converting enzyme 2 (ACE2) receptor is the target of SARS-CoV-2 [2]. Endothelial and neuronal expression of the ACE2 receptor has been confirmed in the human CNS [3], which renders the brain a potential SARS-CoV-2 target. At present, only a few cases of SARS-CoV-2 intracranial infection were reported. In China, Beijing Ditan Hospital claimed a case of symptomatic encephalitis with SARS-CoV-2 in the CSF [4]. A report from Moriguchi et al. from Japan also described CNS involvement in a COVID-19 patient, who was diagnosed with meningitis/encephalitis and confirmed by virus detection in CSF [5]. In addition, two other case reports of COVID-19 indicated meningoencephalitis or encephalitis in the absence of SARS-CoV-2 in CSF [6, 7]. These cases provide evidence that SARS-CoV-2 can directly invade the CNS.

Here we present a case of COVID-19 comorbidity with purulent meningitis. The patient’s brain trauma may have caused meningitis. Though no obvious fracture was observed on the brain CT, tiny cracks in the skull base might have existed, which facilitated communications between intracranial and extracranial environments. Another important inducement should be the immunologic dysfunction caused by COVID-19. SARS-CoV-2 mainly acts on lymphocytes, inducing dysregulation of the immune response [8]. A decreased lymphocyte count is a characteristic of COVID-19. The analysis of the patient’s lymphocyte subsets revealed significant reductions in T lymphocytes, B lymphocytes, and NK cells, which confirmed the state of immunosuppression. Since immunologic dysfunction is commonly presented in COVID-19 patients, comorbidity with meningitis should be one of the considerations when a COVID-19 patient presents with headache and fever. Lumbar punctures and CSF cultures, as well as metagenomic next-generation sequencing of CSF, could help in the diagnosis.

Ethic approval

This study was approved by the ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China. Written informed consent to publish was obtained from the patient’s relatives.

Conflict of interests

The authors declare that they have no competing interests.

Financial support

This study was supported by HUST COVID-19 Rapid Response Call, Huazhong University of Science and Technology, China (No. 2020kfy XGYJ084).

Authors’ contributions

PZ interpreted the patient data and drafted the manuscript. CP, JW and YM analyzed the data and reviewed the literatures. HZ and ZT interpreted the data and revised the manuscript. ZT acquired the funding and supervised the study. All authors read and approved the final manuscript.

References

[1] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the
respiratory failure of COVID-19 patients. J Med Virol 2020, 92(6): 552–555.

[2] Yan RH, Zhang YY, Li YN, et al. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020, 367(6485): 1444–1448.

[3] Baig A, Khaleeq A, Ali U, et al. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020, 11(7): 995–998.

[4] Zhou LY, Zhang M, Wang J, et al. Sars-Cov-2: Underestimated damage to nervous system. Travel Med Infect Dis 2020, 36: 101642.

[5] Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020, 94: 55–58.

[6] Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. Brain Behav Immun 2020, 87: 33.

[7] Ye MX, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. Brain Behav Immun 2020, 88: 945–946.

[8] Qin C, Zhou LQ, Hu ZW, et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020, 71(15): 762–768.

Ping Zhang received her M.D. degree from Huazhong University of Science and Technology, China (2018) and Heidelberg University, Germany (2016). She is now an attending doctor in Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Her current research interests focus on the clinical and basic studies of cerebrovascular diseases and neurointensive care. E-mail: ppkitty0609@163.com

Chao Pan received his Ph.D. degree from Huazhong University of Science and Technology, China (2017). He is now an attending doctor in Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. His research focuses on the clinical and basic studies of hemorrhagic stroke. E-mail: punctualpc@163.com

Jiahui Wang received her B.S. degree from the Second Clinical College of Huazhong University of Science and Technology in June 2018. Now she is a M.S. candidate in the Department of Neurology in Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology. Her research focuses on the prevention and treatment of transient ischemic attack. E-mail: jiahuiwanghust@qq.com
Yang Ma received her M.S. degree from the Department of Neurology in Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology in June 2020. Now she works in the Department of Neurology in Changzhou No.2 People's Hospital affiliated to Nanjing Medical University. Her research focuses on assessing damage of blood-brain barrier after bilateral common carotid artery occlusion. E-mail: 2390873531@qq.com

Huaqiu Zhang received his Ph.D. degree from Huazhong University of Science and Technology, China. He is now a professor and associate head of Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. His current research interests focus on the clinical and basic studies of brain tumor, as well as the surgical treatment of cerebral vascular diseases. E-mail: zanghq_04@yahoo.com

Zhouping Tang received his Ph.D. degree from Huazhong University of Science and Technology, China (2004). He is the associate director of Opticals Valley Branch of Tongji Hospital. He is a professor and associate head of Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. He has published many high-quality papers on journals including Neurology, Stroke, Molecular Neurobiology. His current research interests focus on the clinical and basic studies of hemorrhagic stroke, minimal invasive intracerebral hemorrhage evacuation and other cerebral vascular diseases. E-mail: ddjtzp@163.com