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CASE STUDY

Clinical and radiological features of severe acute respiratory syndrome coronavirus 2 meningo-encephalitis

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Abstract

Background and purpose: This case illustrates for the first time the clinical and radiological evolution of SARS-CoV-2 meningo-encephalitis.

Methods: A case of a SARS-CoV-2 meningo-encephalitis is reported.

Results: A 65-year-old man with COVID-19 presenting with meningo-encephalitis without respiratory involvement is described. He had fever, diarrhea and vomiting, followed by diplopia, urinary retention and sleepiness. Examination disclosed a convergence strabismus and ataxia. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis, oligoclonal bands and increased interleukin 6 level. SARS-CoV-2 was detected in the CSF through reverse transcriptase polymerase chain reaction, but not in nasopharyngeal, tracheal secretion and rectal samples. Brain magnetic resonance imaging showed lesions on white matter hemispheres, the body and splenium of the corpus callosum and resembling the projection of corticospinal tract, remarkably on cerebellar peduncles.

Conclusions: This demonstrates the challenges in diagnosing COVID-19 in patients with neurological presentations.

KEYWORDS
COVID-19, diagnosis, meningo-encephalitis, polymerase chain reaction, SARS-CoV-2

INTRODUCTION

Acute respiratory syndrome is the typical presentation of COVID-19, but other organs and systems may also be affected [1]. A patient with COVID-19 presenting with meningo-encephalitis without respiratory involvement is reported.

CASE REPORT

A 65-year-old man with a history of diabetes, coronary artery disease and hypothyroidism presented with fever, diarrhea and vomiting on the first day (D1). On D4 acute diplopia, urinary retention and excessive sleepiness were noticed. He denied headache or respiratory symptoms. Examination disclosed a somnolent but oriented patient with convergence strabismus, mild ataxia in both arms and brisk deep tendon reflexes. Brain and chest computed tomography and brain magnetic resonance imaging (MRI) were normal. Cerebrospinal fluid (CSF) showed lymphocytic pleocytosis, oligoclonal bands with the same pattern observed in serum and a remarkably increased interleukin 6 level (Table 1). SARS-CoV-2 was detected in the CSF through reverse transcriptase polymerase chain reaction (RT-PCR), but it was not detected in nasopharyngeal (D4 and D6), tracheal secretion (D13) and rectal (D19) samples. Investigation was negative for other pathogens in the CSF (Table 1). The patient received ceftriaxone and acyclovir for 3 days. On D6, he presented impairment of consciousness and bilateral Babinski sign. Orotracheal intubation was performed to protect the airway and mechanical ventilation was initiated.

Electroencephalography showed no epileptic features. High D-dimer blood levels (6373 ng/ml) and bilateral deep venous

TABLE 1 Longitudinal cerebral spinal fluid characteristics. The CSF reverse-transcriptase–polymerase-chain-reaction (RT-PCR) for Herpes simplex virus 1 and 2, Herpes simplex virus, Varicella-Zoster and other viral and bacterial pathogens were negative. (FilmArray® Meningitis/Encephalitis (ME) Panel-BioMeriuex UK Limited, London, UK, and XGen Multi Neuro 9, Mobius Life Science, Pinhais, Brasil)

	Day 4	Day 6	Day 18
Cells (mm^3, NR 0–5)	212	176	65
Proteins (mg/L, NR <40)	86	66	67
Lymphocyte (%)	46	72	74
Glucose (mg/dl, NR 40–80)	57	54	63
Lactate (mg/dl, NR 11–19)	32	24	17
Viral and bacterial pathogens	Negative	Negative	Negative
Oligoclonal bands with the same pattern in the serum	Not tested	Positive	Positive
Interleukin-6 (pg/ml, NR < 7)	4506	Not tested	8.45
RT-PCR for SARS-CoV-2	Positive	Negative	Not tested
Metagenomic Next-generation Sequencing	Negative	Negative	Not tested
IgM for SARS-CoV-2	Negative	Negative	Negative
IgG for SARS-CoV-2	Negative	Negative	Negative

Abbreviations: NR, normal range; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

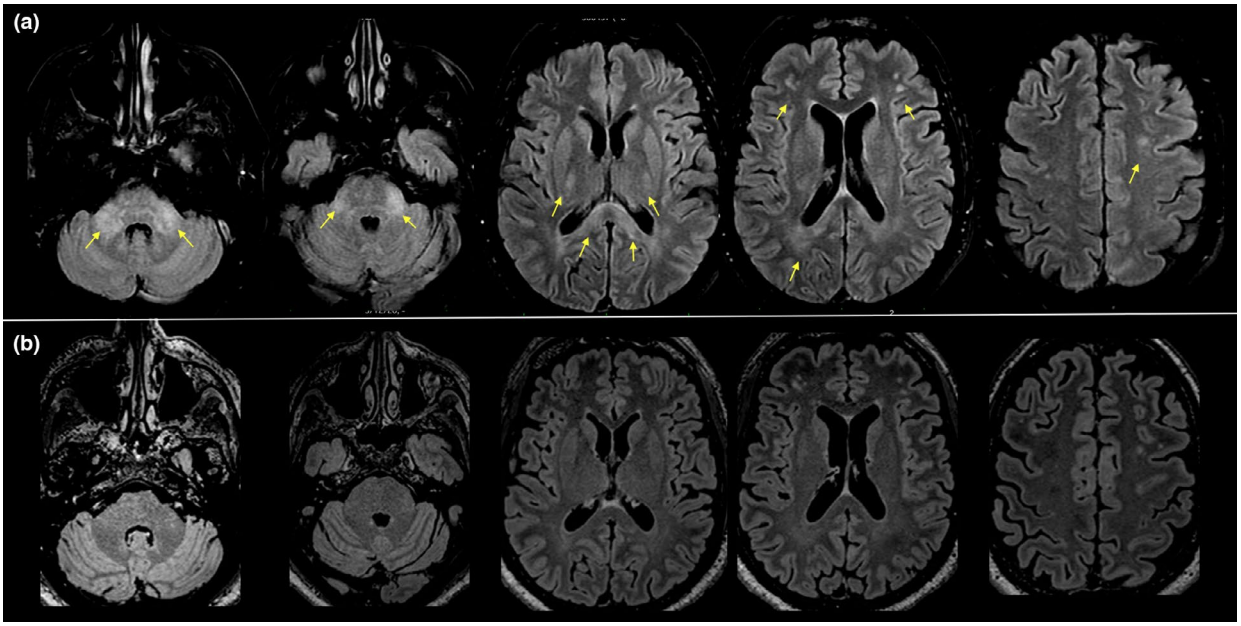

FIGURE 1 (a) Brain magnetic resonance images performed on D16 showing multiple patchy areas of hyperintensity on axial fluid-attenuated inversion recovery (FLAIR) sequence in both hemispheres, affecting deep and subcortical regions, and remarkably on the body and splenium of the corpus callosum, on both cerebellar peduncles and resembling the projection of corticospinal tract. (b) Brain magnetic resonance FLAIR images on D73 showing improvement of the white-matter abnormalities. No diffusion restriction or abnormal gadolinium enhancement was noted on both MRI exams [Colour figure can be viewed at wileyonlinelibrary.com]

thrombosis (ultrasonography) were present. Brain MRI performed on D16 showed multiple patchy areas of hyperintensity on the fluid-attenuated inversion recovery (FLAIR) images on white matter hemispheres, the body and splenium of the corpus callosum and on both cerebellar peduncles (Figure 1).

The patient improved progressively and was discharged 21 days after admission with diplopia and urinary retention. CSF samples collected in the recovery phase (D18) showed mild pleocytosis. SARS-CoV-2 immunoglobulin M antibodies were detected in serum on D30. Brain MRI performed on D73 disclosed marked improvement of the lesions. Neurological examination disclosed only mild cerebellar dysarthria and memory deficit (25 out of 30 in the Montreal Cognitive Assessment).

Written informed consent was obtained from the patient. The local ethics committee of the Instituto D'Or de Pesquisa e Ensino (IDOR) approved the study.

DISCUSSION

Meningo-encephalitis in the context of COVID-19 may occur through direct invasion of the brain by the virus [2–4], intracranial cytokine storm with blood–brain barrier breakdown [5] or autoimmune disorders secondary to viral illness [6,7]. There are few other reports of patients with confirmed RT-PCR for SARS-CoV-2 in CSF [3, 8]. In one report, the authors discussed that the observed temporal lobe and hippocampal lesions could be secondary to multiple epileptic seizures rather than by direct viral invasion [3]. In the other report, brain MRI was not performed. Our patient did not have seizures and electroencephalography showed no epileptic discharges. In addition, the lesions described here are analogous to those of zika virus encephalomyelitis described by our group [9]. In this carefully studied case, the clinical and radiological evolution of the SARS-CoV-2 meningo-encephalitis is shown through serial examinations of brain MRI and inflammatory markers in the CSF.

Most previous reports of SARS-CoV-2-associated meningitis-encephalitis had pulmonary involvement and/or a detectable RT-PCR of the nasopharynx [3, 5–7]. In this case, no clinical, radiological or laboratory evidence of respiratory involvement was present. Diagnosis was challenging since only one out of the two RT-PCRs for SARS-CoV-2 in CSF was positive and four other RT-PCRs collected in other samples (nasopharynx, rectal and tracheal secretion) were negative. Indeed, even in cases of suspected viral invasion of the central nervous system, the SARS-CoV-2 RNA is rarely detected in vivo. This can be explained by the very early viral central nervous system invasion and its clearance before neurological symptoms occur [10]. Other possible explanations include low levels of viral RNA, a sequence mismatch between viral template and primers or probes [11] or absence of virus in the subarachnoid space despite its presence in selected parenchymal areas [12]. Similarly, in the context of enterovirus D68 (EV-D68) associated acute flaccid myelitis (AFM), the presence of enterovirus RNA by RT-PCR was demonstrated in the CSF only in one of 55 children. Detection of intrathecal antibody synthesis was significantly more sensitive than RT-PCR for the diagnosis EV-D68-associated AFM [11]. In our patient, evaluation for SARS-CoV-2 antibodies in the CSF was negative at three different time points.

CONCLUSION

This case illustrates the clinical and radiological evolution of SARS-CoV-2 meningo-encephalitis. It also demonstrates the challenges in diagnosing COVID-19 in patients with predominantly neurological presentations.

CONFLICT OF INTEREST

None.

CONSENT

Consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. https://doi.org/10.1001/jama.2020.1585.
2. De Felice FG, Tovar-Moll F, Moll J, Munoz DP, Ferreira ST. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the central nervous system. *Trends Neurosci*. 2020;43(6):355-357. https://doi.org/10.1016/j.tins.2020.04.004.
3. 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. https://doi.org/10.1016/j.ijid.2020.03.062.
4. 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. https://doi.org/10.1016/j.bbi.2020.04.024.
5. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology*. 2020;296:E119-E120. https://doi.org/10.1148/radiol.2020201187.
6. Dogan L, Kaya D, Sarikaya T, et al. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: case series. *Brain Behav Immun*. 2020;1591(20):155-158. https://doi.org/10.1016/j.bbi.2020.05.022.
7. Pilotto A, Odolini S, Stefano Masciocchi S, et al. Steroid-responsive encephalitis in COVID-19 disease. *Ann Neurol*. 2020;88(2):423-427. https://doi.org/10.1002/ana.25783.
8. Huang YH, Jiang D, Huang JT. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav Immun*. 2020;87:149. https://doi.org/10.1016/j.bbi.2020.05.012.
9. Galliez RM, Spitz M, Rafful PP, et al. Zika virus causing encephalomyelitis associated with immunoactivation. *Open Forum Infect Dis*. 2016;3(4):ofw203. https://doi.org/10.1093/ofid/ofw203.
10. Panciani PP, Saraceno G, Zanin L, et al. SARS-CoV-2: "Three-steps" infection model and CSF diagnostic implication. *Brain Behav Immun*. 2020;1591(20):128-129. https://doi.org/10.1016/j.bbi.2020.05.002.
11. Mishra N, Ng TFF, Marine RL, et al. Antibodies to enteroviruses in cerebrospinal fluid of patients with acute flaccid myelitis. *MBio*. 2019;10(4):e01903–19. https://doi.org/10.1128/mBio.01903-19.
12. Hixon AM, Frost J, Rudy MJ, et al. Understanding enterovirus D68-induced neurologic disease: a basic science review. *Viruses*. 2019;11(9):821. https://doi.org/10.3390/v11090821.

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