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CASE REPORT

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A fatal case of COVID-19-associated meningoencephalitis in a patient coinfected with influenza A

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ABSTRACT

We report a case of COVID-19-associated meningoencephalitis with a fatal outcome in a male patient with concomitant influenza A, who had been hospitalized at the beginning of 2022, in the Northeastern region of Brazil. He died due to cardiopulmonary arrest after developing *status epilepticus* on the third day of hospitalization. The SARS-CoV-2 RNA was detected in cerebrospinal fluid and Influenza A was detected in the nasopharyngeal swab. Meningoencephalitis due to COVID-19 is a rare manifestation and physicians must be aware of this complication, mainly during the pandemic. In viral co-circulation situations, the possibility of respiratory coinfections should be remembered.

KEYWORDS: COVID-19. Meningoencephalitis. Influenza A. Coinfection.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by a betacoronavirus SARS-CoV-2 was discovered in Wuhan, China, in December 2019[1]. COVID-19 usually manifests as a respiratory illness and can lead to acute respiratory failure and death. Millions of cases have been reported worldwide. The World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic and it continues to have a major impact on health care and social systems worldwide. In Brazil, despite the vaccination efforts, severe cases are registered in each new wave[2]. The emergence of more contagious variants, such as delta (B.1.617) and omicron (B.1.1.529), played a big part in the spread of the virus, which made it harder to beat the pandemic[1,3].

Furthermore, several extrapulmonary symptoms of COVID-19 have caught the attention of clinicians around the world. A variety of neurological symptoms and syndromes, caused by SARS-CoV-2, have been reported such as meningoencephalitis, myelitis, and acute encephalomyelitis (ADEM)[3]. Though knowledge about SARS-CoV-2 infection in the central nervous system (CNS) is developing rapidly, the pathogenesis of CNS involvement still needs to be understood. Two main theories are currently accepted: direct viral involvement during the viremic phase, and indirect mechanisms mediated by cytokine storms[3,4].

During the first month of 2022, Brazil experienced a high number of influenza cases simultaneously with the third wave of COVID-19. During this period, 63,981 cases of COVID-19 were identified as being from variants of concern (VOC), split between 33,266 (52.0%) cases of VOC Delta, 25,164 (39.3%) cases of VOC Gamma, 5,093 (8.0%) cases of VOC Omicron, and 458 (0.7%) cases of VOC Alfa or VOC Beta[5]. The cases of influenza were primarily influenza A (H3N2). Other respiratory viruses were

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also reported, such as influenza B and respiratory syncytial virus (RSV), but in much lower numbers[5].

Here, we document a case of COVID-19-associated meningoencephalitis with a fatal outcome in a male patient with concomitant influenza A who had been hospitalized during the beginning of 2022, in Northeastern Brazil. Medical records were reviewed during the patient's hospitalization at the Hospital Sao Jose de Doencas Infecciosas (HSJ), an infectious disease center in Fortaleza city, Ceara State, Brazil. This case report is part of a cohort study approved by the Research Ethics Committee of the Hospital Sao Jose de Doencas Infecciosas (HSJ) (CAAE Nº 55499022.8.0000.5044).

CASE REPORT

A 31-year-old male patient, with no previous comorbidities, presented to the emergency department with a headache, a stiff neck, behavioral changes and aggressiveness, two days after getting over flu-like symptoms. He had a five-day history of runny nose, fever, and cough. The patient had previously received two inactivated vaccine doses for SARS-CoV-2. During physical examination, the patient was disoriented and had a seizure which was reversed with anticonvulsant drugs. He was sent to the intensive care unit (ICU) because of sensory deficits and drowsiness. Cranial tomography findings were normal. Cerebrospinal fluid (CSF) analysis revealed white blood cell count of 553 cells/mm^3 (91% lymphocytes and 8% monocytes), glucose of 60 mg/dL, protein of 61.6 mg/dL, lactate dehydrogenase of 32 mg/dL, and negative CSF Gram stain. SARS-CoV-2 RNA was identified in the CSF through qPCR using the Allplex™ SARS-CoV-2/FluA/FluB/RSV Assay (Allplex; Seegene). Chest radiography findings were unremarkable. Influenza A was detected by qPCR in the nasopharyngeal and oropharyngeal swabs by using the same assay.

The patient only had neurological symptoms and no respiratory manifestations. After three days in the ICU, despite the antiepileptic drugs, he presented with *status epilepticus* requiring sedation, analgesia and invasive mechanical ventilation. Immediately thereafter, he suddenly went into cardiopulmonary arrest and death, despite prompt cardiopulmonary resuscitation. Figure 1 shows the chronology of the case, including the clinical aspects and outcomes.

DISCUSSION

The maintenance of circulating respiratory viruses, such as COVID-19 and influenza, raises the possibility of coinfection. Studies in animal models have shown that simultaneous or sequential infection by H1N1 and SARS-CoV-2 may increase lung damage despite the lowered SARS-CoV-2 viral loads caused by prior H1N1 infection[6]. Aloisame *et al.*[7] investigated 48 COVID-19 patients and found viral coinfection in 27 of them, with influenza A H1N1 (n = 17) and human adenovirus (n = 10) being the most common. The same study also identified viral coinfections as a factor that increased ICU admission and mortality in these patients. The clinical impact of influenza virus and SARS-CoV-2 coinfection on each corresponding disease is still unknown. In the reported case studies, the use of influenza antivirals in these patients makes it difficult to assess the true impact of coinfection without any therapeutic intervention[7,8].

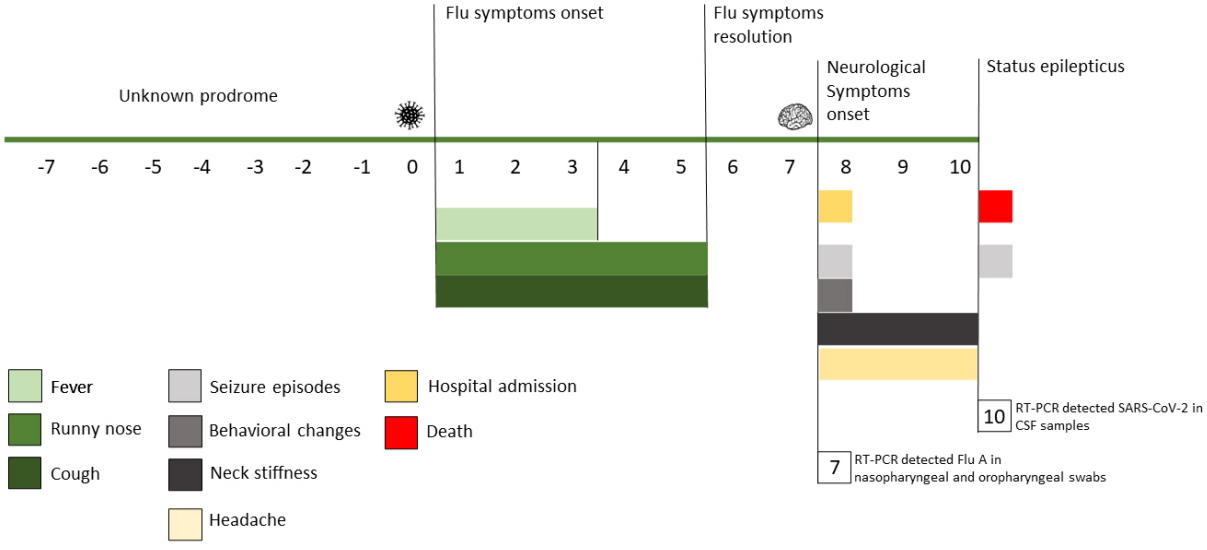

Figure 1 - Case chronology, including clinical aspects and outcome.

In our case, it is possible that the first flu-like symptoms were related to influenza A, followed by the neurological symptoms related to COVID-19. However, it is worth noting that influenza A may also manifest itself with neurotropism. Influenza A may manifest as meningitis, encephalitis, acute flaccid paralysis, or acute necrotizing encephalopathy. In this case, influenza A in the CSF was ruled out by qPCR[9]. There are few cases of meningoencephalitis due to COVID-19 confirmed by PCR in CSF[3,10-14]. The first death attributed to COVID-19-related meningitis occurred in India, in a 58-year-old male patient with positive RT-PCR for SARS-CoV-2 in the nasopharyngeal swabs. In the Indian case, RT-PCR was not performed in CSF[10]. Moreover, SARS-CoV-2 detected by RT-PCR in CSF is a rare finding in meningoencephalitis cases registered in the scientific literature[3,9,10]. To the best of our knowledge, few cases were reported of meningoencephalitis by COVID-19 confirmed by RT-PCR with fatal outcomes and associated with other viral infections, as in this case.

SARS-CoV-2, influenza virus (Flu), and RSV are major pathogens that primarily target the human respiratory system. Both viruses present non-specific symptoms, and their circulation periods may coincide as described by our case which occurred during influenza A season[4,8]. The Allplex™ SARS-CoV-2/FluA/FluB/RSV Assay (Allplex; Seegene) was the assay performed in our case. The Allplex™ SARS-CoV-2/FluA/FluB/RSV Assay is a multiplex real-time PCR assay intended for the detection of the N, RdRP, and S genes of SARS-CoV-2, Flu A and B viruses, and RSV A/B in a single tube[9]. The Allplex kit was developed to perform a rapid and suitable diagnosis of respiratory infection of the most common agents[9]. A Korean study analyzing the three commercially available tests (PowerChek™ SARS-CoV-2, Influenza A&B Multiplex Real-time PCR Kit, STANDARD™ M Flu/SARS-CoV-2 Real-time Detection Kit; and Allplex™ SARS-CoV-2/FluA/FluB/RSV Assay) found that all three kits had positive and negative predictive values greater than 92% and ≥ 0.95 kappa value in the detection of SARS-CoV-2 and flu A/B; all three kits did not cross-react with common respiratory viruses[15].

Most deaths related to SARS-CoV-2 neurological syndromes were attributed to brain complications such as hemorrhage and brain herniation with subsequent cerebral death[10-14]. Five fatal cases of COVID-19-associated neurological complications have been reported – two meningoencephalitis cases, two acute necrotizing encephalitis (ANE) cases, and one case with both hypothesized meningoencephalitis and ANE simultaneously[10-14]. Two cases occurred in children; the first was a 5-year-old girl with COVID-19 meningoencephalitis and simultaneous CNS tuberculosis, which quickly evolved to severe cerebral hypertension and encephalopathy, turning into brain herniation a few days later. This last case had CDC protocol confirmed SARS-CoV-2 in CSF with a brain biopsy[11]. The second case was a 2-month-old child with signs of both meningoencephalitis and ANE confirmed by magnetic resonance imaging (MRI); the child had multiple hemorrhagic foci and needed orotracheal intubation, but died[11,14]. Complications related to COVID-19 meningoencephalitis were described as recurrent seizures, cerebral hypertension, multiple hemorrhagic foci, encephalopathy, sepsis, cardiac arrest, and death[10-14]. In our case, we hypothesized the possibility of cerebral hypertension complicated with *status epilepticus*.

Status epilepticus (SE) and epileptic seizures have been reported during COVID-19[16,17]. A recent systematic review with 39 patients presenting COVID-19-related SE concluded that this could be an underreported manifestation related to COVID-19 infection, although the exact mechanisms are still not fully understood[16]. Many mechanisms have been hypothesized, such as (1) neural damage due to systemic inflammatory syndrome during cytokine release[3,4,16]; (2) the increase of blood viscosity due to COVID-19, in which hyperviscosity is a known trigger factor for SE[16,17]; and (3) direct action of the virus inducing encephalitis or meningitis[10-14,16,17]. In general, these mechanisms may be divided as direct (direct action by the virus) or indirect (related to cytokine storm and blood viscosity)[3,4,16,17]. Intriguingly, COVID-19-related SE is not observed only in adults during viremic and immune phases but also in children, and even during post-COVID-19 phase[16,17]. Rarely, some reports bring up the role of vaccination and *status epilepticus* but the results come down to anecdotal evidence[16].

In this case, no antiviral treatment was performed. Remdesivir was only approved in Brazil in March 2021 for cases of pneumonia requiring supplemental oxygen. Currently, new drugs such as nirmatrelvir plus ritonavir, for the treatment of COVID-19 in adults who do not require supplemental oxygen, and baricitinib, which reduced mortality in hospitalized adults with COVID-19 in need of oxygen, are also already part of the therapeutic arsenal against this disease[18,19]. However, none of these drugs had their impact assessed in relation to CNS infections. In addition, no antiviral drugs were available in the period of the hospitalization.

Our case report presentation has some limitations. First, it is a single case report which may have many unknown and undetected variables involved in the outcome. Second, RT-PCR targeting other respiratory viruses were not available at our center to rule out other respiratory

coinfections. Third, the Allplex™ SARS-CoV-2/FluA/FluB/RSV Assay is well established for respiratory samples, but there is a lack of evidence regarding the CSF. Finally, interleukin-6 levels and MRI that could aid the diagnosis were not available at our center at the time of diagnosis. To the best of our knowledge, this is the first report of COVID-19-related meningitis diagnosed by this method, and not the RT-PCR following the CDC protocol.

CONCLUSION

COVID-19 involvement of the CNS has shown many neurological manifestations that have been evident during the pandemic. Our case is rare due to the clinical presentation, the simultaneous Flu A infection, and the diagnostic tool used to achieve the COVID-19-related meningitis. Another important learning point to be mentioned is that it is essential to ensure that we are well prepared to deal with future influenza seasons, with the expectation that additional COVID-19 waves may coincide during the seasonal influenza in years to come. Currently, Brazil is facing the emergence of new, more contagious Omicron subvariants (BQ.1), which raises the possibility of new waves, even during the Influenza circulation period[20].

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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