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Remdesivir for the Treatment of Human Coronavirus OC43 Encephalitis

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ABSTRACT

Human coronavirus OC43 (HCoV-OC43) is predominantly associated with mild respiratory infections. HCoV-OC43 also has neuroinvasive properties, and severe encephalitis has been described in immunocompromised patients, with fatal outcomes due to the lack of specific antiviral treatment. We report a case of severe febrile encephalitis attributed to HCoV-OC43 that progressively worsened over 3 months in a 65-year-old immunocompromised man. Clinical symptoms improved remarkably after treatment with remdesivir, with an increase of the Glasgow Coma Score from 8 to 14 within 7 days.

1 | Introduction

Human coronavirus OC43 (HCoV-OC43) is predominantly associated with mild respiratory infections. HCoV-OC43 has also neuroinvasive properties [1]. Although the prevalence of neurological complications associated with HCoV-OC43 is unknown in immunocompetent subjects [2, 3], severe encephalitis has been described in immunocompromised patients, with fatal outcomes due to the lack of specific antiviral treatment [4–6]. Encephalitis in immunocompromised patients is particularly difficult to diagnose, as the clinical presentation may be atypical, and the differential diagnosis may include rare opportunistic pathogens or a noninfectious cause [4, 7]. Here, we describe a case of severe encephalitis attributed to HCoV-OC43 in a stem cell transplant recipient, whose symptoms improved rapidly after remdesivir treatment.

2 | Case Report

A 65-year-old male patient, with no history of neurological or psychiatric disease, underwent allogeneic stem cell transplantation in 2020 for myelodysplastic syndrome. He was classified as intermediate risk with a Hematopoietic Cell Transplantation-specific comorbidity Index of 1 (due to mild hepatic comorbidity) [8]. In August 2022, a relapse of the myelodysplastic syndrome was treated with azacitidine-venetoclax until complete remission. In February 2023, the subject was hospitalized in a context of progressive febrile encephalitis, including fever, altered vigilance, progressive lethargy, personality changes, and swallowing disorders. The patient's neurological condition progressively deteriorated over the following months, reaching a Glasgow Coma Score (GCS) of 8 (E2V2M4) in June. Lumbar punctures performed showed pleocytosis (32 and 19 leukocytes/mm^3) and normal protein levels in March. Magnetic resonance imaging (MRI) showed multiple nonspecific hyperintensities distributed around the lateral ventricles and in subcortical areas (Figure 1). Extensive microbiological investigations, including metagenomic next-generation sequencing (mNGS) in plasma and cerebrospinal fluid (CSF), yielded no neurotropic pathogen (see Supporting Information S1: Table 1), except the detection of HCoV-OC43 in nasopharyngeal swab (NPS) and broncho-alveolar fluid in March

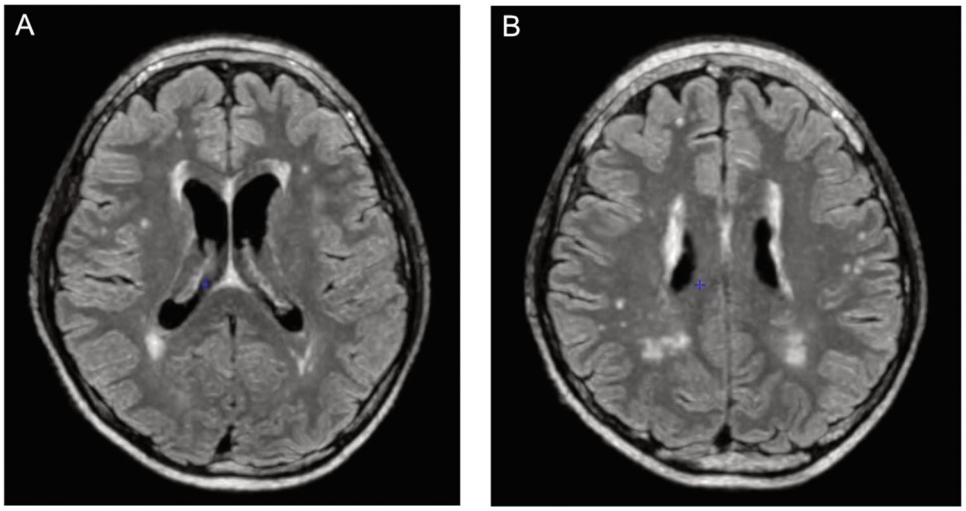

FIGURE 1 | Brain magnetic resonance imaging. Fluid attenuated inversion recovery axial sequences showing multiple nonspecific hyperintensities distributed around the lateral ventricles (A) and in subcortical areas (B).

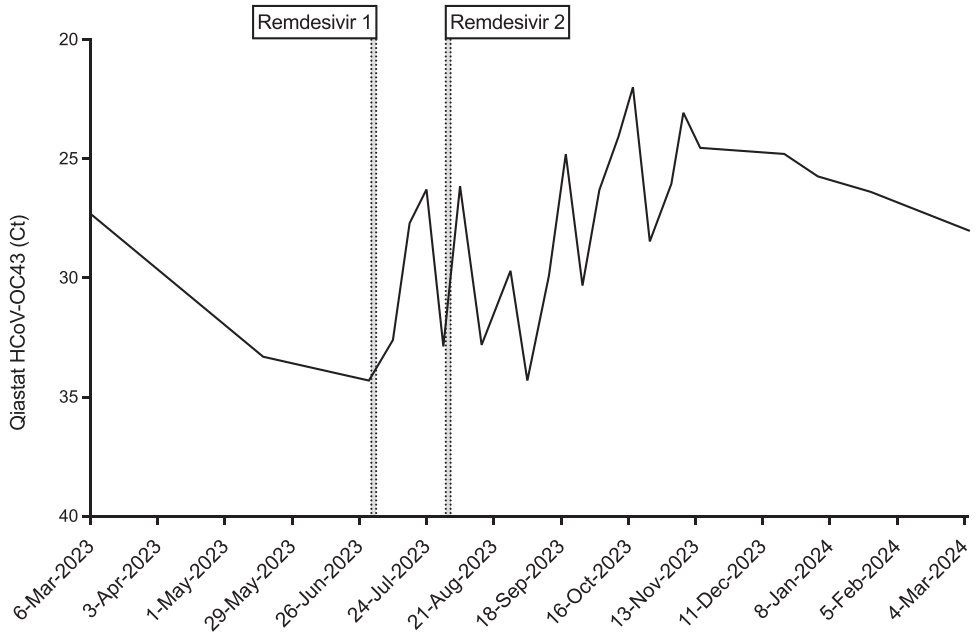

FIGURE 2 | Monitoring of human coronavirus OC43 RNA load detected in the patient's nasopharyngeal swab from March 2023 to March 2024. HCoV-OC43, human coronavirus OC43; Ct, cycle threshold.

(Cycle threshold (Ct): 27.3 and 29.4, respectively). HCoV-OC43 was also detected with a low viral load in one out of the two CSF samples retested after nucleic acid pre-amplification to increase sensitivity (see Supporting Information S1: Table 3), and, with high RNA load in all subsequent NPS tested throughout the 1-year follow-up period (see Supporting Information S1: Table 2 and Figure 2). The complete genome of HCoV-OC43 was sequenced from two NPS collected in March and July 2023, and phylogenetic analysis identified HCoV-OC43 strain as genotype H (see Supporting Information S1: Figure 1). Because of the absence of focal abnormalities on the MRI and the patient's serious condition, no brain biopsy was performed for diagnostic purposes. Because of the severity of symptoms and evidence of its potent antiviral in vitro activity against HCoV-OC43 [9, 10], remdesivir was administered intravenously (200 mg on Day 1, 100 mg on Days 2 and 3) in June. The patient showed remarkable clinical and neurological improvement within 7 days, reaching a GCS of 14 (E4V5M5), apyrexia, recovery of speech, correct responses to simple commands and oral food intake, enabling him to be transferred to a rehabilitation unit within 14 days. No immunomodulatory therapy was administered during, before or after the days of treatment with remdesivir, which was well tolerated with no drug-related clinical or biological side effect. A second course of remdesivir did not achieve a full clinical recovery, and some neurological sequelae persisted, especially motor disability, partly explained by the wasting of muscular mass during the acute phase of encephalitis. Unfortunately, the patient died from intercurrent sepsis 13 months after the initial hospitalization. Informed consent from the patient was obtained for the use of the data for this study.

3 | Methods

3.1 | HCoV-OC43 RT-PCR in NPS and BAL

A multiplex, real-time PCR assay (QIAstat-Dx Respiratory SARS-CoV-2 Panel, Qiagen, Courtaboeuf, France) was performed in NPS and BAL to detect and monitor HCoV-OC43 RNA. In accordance with the manufacturer's instructions, 300 μL of NPS medium or BAL were loaded into the test cartridge. QIAstat-Dx Respiratory SARS-CoV-2 Panel assay also allow the detection of 21 viral and bacterial respiratory targets for common pathogens causing respiratory infections, including Influenza A/B, Human coronavirus 229E/HKU1/NL63, SARS-CoV-2, Human parainfluenza virus 1-4, RSV A/B, Human metapneumovirus A/B, Human adenoviruses, Rhinovirus/Enterovirus, Mycoplasma pneumoniae, Bordetella pertussis and Chlamydophila pneumoniae.

3.2 | HCoV-OC43 RT-PCR in Plasma and CSF

Total nucleic acid extraction was performed from 200 μL of plasma and CSF samples with an EMAG platform (Biomérieux, Marcy l'Etoile, France). Real-time RT-PCR assay (HCoV/HPIV R-GENE, Biomérieux, Marcy l'Etoile, France) was performed on plasma and CSF samples. Before the HCoV/HPIV R-GENE RT-PCR, a random nucleic acid amplification using the MALBAC Single Cell WGA assay (Yikon Genomics, Shanghai, China) was performed to increase the sensitivity of the technique and enable the detection of very low HCoV-OC43 RNA loads. HCoV/HPIV R-GENE assay allows the detection of Human coronavirus OC43/229E/HKU1/NL63 and Human parainfluenzae virus 1/2/3/4. HCoV/HPIV R-GENE assay cannot detect SARS-CoV-2. The tests were performed in accordance with the manufacturer's instructions.

3.3 | Metagenomic Next-Generation Sequencing (mNGS)

Plasma and CSFs samples were transported on dry ice and kept frozen at −80°C before testing. Nucleic extraction protocols, quality controls, kit used for library preparation and sequencing, bioinformatic analysis pipeline were previously described [7]. Library sequencing was performed on a NextSeq. 500 instrument (Illumina; Evry, France). A total of 98, 47 and 88 million reads were sequenced (1 × 150 bp) for plasma and CSFs samples, respectively.

3.4 | HCoV-OC43 Genome Acquisition and Genotyping

Two NPS collected in March and July 2023 were retrospectively sequenced by mNGS to obtain the HCoV-OC43 whole genome. The two consensus genomes have been deposited in GenBank (PQ510827 and PQ510828). The HCoV-OC43 genotype was determined using a whole-genome phylogenic analysis with 11 reference genomes from GenBank (see Supporting Information S1: Supplementary Methods).

4 | Discussion

We report a case of febrile encephalitis attributed to HCoV-OC43, which progressively worsened over 3 months in an immunocompromised adult patient whose symptoms improved rapidly and remarkably after treatment with remdesivir.

Identifying the etiology of encephalitis is challenging, especially in immunocompromised patients in whom a large proportion of encephalitis cases remain unexplained, also due to the presence of rare opportunistic pathogens. In addition, the pathogen may not be present in the CSF, but only in the brain biopsy, which has a higher positivity rate in cases of unexplained neurological symptoms [7]. Here, conventional HCoV-OC43 RT-PCR and mNGS were unable to detect the virus in CSF, and random nucleic acid amplification combined with HCoV RT-PCR was required to detect a low HCoV-OC43 RNA load in the CSF. These results are similar to the three cases of fatal HCoV-OC43 encephalitis reported, where HCoV-OC43 was not detected in the CSF in two [5, 6], and CSF could not be tested in the third case [4]. Although brain biopsy is associated with better results than CSF in identifying a pathogen for viral encephalitis, it could not be performed in our case. Among the fatal HCoV-OC43 encephalitis cases previously reported, brain biopsy was performed before the patient's death in two cases [4, 5], but the mNGS results were available before death in only one case [5]. To conclude, in addition to the fact that the diagnosis of HCoV-OC43 infection is probably too rarely suspected (and thus rarely investigated) in immunocompromised patients with unexplained encephalitis, the prevalence of HCoV-OC43 encephalitis in this population may be underestimated because of the difficulty of rapidly identifying the virus in CSF and brain samples. In cases similar to ours where no analysis of brain samples is available, the detection of high viral loads in NPS samples over a long period and the acquisition of the complete HCoV-OC43 genome sequences suggest productive viral replication and could motivate the initiation of antiviral treatment.

No specific antiviral treatment has been approved for cases of severe infections due to HCoV-OC43. In the case reported by Nilsson et al. [5], where the virus was found in the brain biopsy, an experimental treatment with lopinavir boosted by ritonavir was initiated, but the patient died after 10 days of treatment. In our subject, we proposed to use remdesivir because of its in vitro activity against HCoV-OC43 [9, 10], its availability, and its good tolerance observed in large cohorts of patients with COVID-19 [11, 12]. The rapid improvement of neurological symptoms, within 7 days after remdesivir treatment, suggests evaluating prospectively the efficacy of this drug in the treatment of severe HCoV-OC43-related infections in immunocompromised subjects. Moreover, because of its broad-spectrum antiviral activity and its good safety profile, remdesivir may also be considered as a probabilistic therapeutic option in immunocompromised subjects presenting with severe encephalitis of suspected viral origin, in which the pathogen can be difficult to identify.

Without a brain biopsy, we cannot confirm the role of HCoV-OC43 in the patient's neurological symptoms. However, this hypothesis seems probable given the absence of other neurological pathogens, the detection of HCoV-OC43 in a CSF

sample, and symptom similarity to known cases of HCoV-OC43 encephalitis. We also cannot demonstrate the remdesivir's causality in the patient's improvement. However, this seems plausible given the rapid clinical improvement observed 7 days after the initial remdesivir treatment in a patient with progressive neurological deterioration over 3 months. Even if HCoV-OC43 seems to us to be the most likely etiology of the patient's encephalitis, we cannot exclude formerly the role of another undetected neurotropic agent, which could also be sensitive to remdesivir, because of its broad-spectrum antiviral activity.

Our observation suggests that remdesivir may be an interesting option for the treatment of severe HCoV-OC43 encephalitis in immunocompromised individuals. Prospective studies are needed to evaluate its efficacy and safety in these life-threatening diseases without an approved antiviral regimen to date.

Author Contributions

All authors were involved in patient care, data analysis, and interpretation. Jacques Fourgeaud and Pierre Frange drafted the first version of the manuscript, and all authors participated in the revision of the manuscript and approved the manuscript as submitted. All authors agree to be responsible for all aspects of the work.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The complete consensus is that human coronavirus OC43 genome data are available in the GenBank database under access numbers PQ510827 and PQ510828. The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. M. Dubé, A. Le Coupanec, A. H. M. Wong, J. M. Rini, M. Desforges, and P. J. Talbot, "Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43," *Journal of Virology* 92 (2018): e00404-18, https://doi.org/10.1128/jvi.00404-18.

2. H. Park, K.-R. Kim, H. J. Huh, et al., "Complications of the Central Nervous System in Pediatric Patients With Common Cold Coronavirus Infection During 2014–2019," *Journal of Korean Medical Science* 38 (2023): e358, https://doi.org/10.3346/jkms.2023.38.e358.

3. M. Jevšnik, A. Steyer, M. Pokorn, et al., "The Role of Human Coronaviruses in Children Hospitalized for Acute Bronchiolitis, Acute Gastroenteritis, and Febrile Seizures: A 2-Year Prospective Study," *PLoS One* 11 (2016): e0155555.

4. S. Morfopoulou, J. R. Brown, E. G. Davies, et al., "Human Coronavirus OC43 Associated With Fatal Encephalitis," *New England Journal of Medicine* 375 (2016): 497–498.

5. A. Nilsson, N. Edner, J. Albert, and A. Ternhag, "Fatal Encephalitis Associated With Coronavirus OC43 in an Immunocompromised Child," *Infectious Diseases* 52 (2020): 419–422.

6. M. C. Kasereka and M. T. Hawkes, "Neuroinvasive Potential of Human Coronavirus OC43: Case Report of Fatal Encephalitis in an Immunocompromised Host," *Journal of Neurovirology* 27 (2021): 340–344.

7. J. Fourgeaud, B. Regnault, V. Ok, et al., "Performance of Clinical Metagenomics in France: A Prospective Observational Study," *Lancet Microbe* 5 (2024): e52–e61.

8. M. L. Sorror, M. B. Maris, R. Storb, et al., "Hematopoietic Cell Transplantation (HCT)-Specific Comorbidity Index: A New Tool for Risk Assessment Before Allogeneic HCT," *Blood* 106 (2005): 2912–2919.

9. A. J. Brown, J. J. Won, R. L. Graham, et al., "Broad Spectrum Antiviral Remdesivir Inhibits Human Endemic and Zoonotic Deltacoronaviruses With a Highly Divergent RNA Dependent RNA Polymerase," *Antiviral Research* 169 (2019): 104541.

10. P. Li, Y. Wang, M. M. Lamers, et al., "Recapitulating Infection, Thermal Sensitivity and Antiviral Treatment of Seasonal Coronaviruses in Human Airway Organoids," *EBioMedicine* 81 (2022): 104132.

11. R. L. Gottlieb, C. E. Vaca, R. Paredes, et al., "Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients," *New England Journal of Medicine* 386 (2022): 305–315.

12. F. Ader, M. Bouscambert-Duchamp, M. Hites, et al., "Remdesivir Plus Standard of Care Versus Standard of Care Alone for the Treatment of Patients Admitted to Hospital With COVID-19 (DisCoVeRy): A Phase 3, Randomised, Controlled, Open-Label Trial," *Lancet Infectious Diseases* 22 (2022): 209–221.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.