SARS-CoV-2 infection of the CNS in a patient with meningeosis carcinomatosa

Author(s): Philipp A. Steininger, MD; Frank Seifert, MD, Professor; Stefanie Balk, MD; Joji Kuramatsu, MD; Andreas E. Kremer, MD, PhD; Roland Coras, MD; Tobias Engelhorn, MD, Professor; Clara Maier; Matthias Tenbusch, Professor; Klaus Korn, MD; Armin Ensser, MD, Professor

Corresponding Author: Philipp A. Steininger, philipp.steininger@uk-erlangen.de

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Affiliation Information for All Authors: Philipp A. Steininger, Institute of Clinical and Molecular Virology, University Hospital of Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany; Frank Seifert, Department of Neurology, University Hospital of Erlangen, Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; Stefanie Balk, Department of Neurology, University Hospital of Erlangen, Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; Joji Kuramatsu, Department of Neurology, University Hospital of Erlangen, Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; Andreas E. Kremer, Department of Medicine 1, University Hospital of Erlangen, Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; Roland Coras, Department of Neuropathology, University Hospital of Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; Tobias Engelhorn, Department of Neuroradiology, University Hospital of Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; Clara Maier, Institute of Clinical and Molecular Virology, University Hospital of Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany; Matthias Tenbusch, Institute of Clinical and Molecular Virology, University Hospital of Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany; Klaus Korn, Institute of Clinical and Molecular Virology, University Hospital of Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany; Armin Ensser, Institute of Clinical and Molecular Virology, University Hospital of Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany

Number of characters in title: 75

Abstract Word count: 0

Word count of main text: 1282

References: 7

Figures: 1
Tables: 0


**Study Funding:** The authors report no targeted funding

**Disclosures:** P.A. Steininger reports no disclosures relevant to the manuscript; F. Seifert reports no disclosures relevant to the manuscript; S. Balk reports no disclosures relevant to the manuscript; J. Kuramatsu reports no disclosures relevant to the manuscript; A.E. Kremer reports no disclosures relevant to the manuscript; R. Coras reports no disclosures relevant to the manuscript; T. Engelhorn reports no disclosures relevant to the manuscript; C. Maier reports no disclosures relevant to the manuscript; M. Tenbusch reports no disclosures relevant to the manuscript; K. Korn reports no disclosures relevant to the manuscript; A. Ensser reports no disclosures relevant to the manuscript.
**Pearls**

- Neurological SARS-CoV-2 disease can present with fever, headache and meningism.
- For diagnosis of SARS-CoV-2 infection of the CNS, a SARS-CoV-2 RT-PCR from CSF samples should be performed, since viral RNA may be detected in CSF for longer periods than in respiratory samples.
- Determination of the SARS-CoV-2 specific IgG antibody index (AI) in CSF and serum is feasible for the detection of a SARS-CoV-2 specific intrathecal IgG antibody synthesis.

**Oy-sters**

- Neurological SARS-CoV-2 disease can present without accessory respiratory symptoms and signs.
- A negative SARS-CoV-2 RT-PCR in respiratory specimens does not exclude SARS-CoV-2 infection of the CNS.
- In patients with meningosis neoplastica, presenting with acute neurological symptoms, the possibility of concomitant CNS infection should always be considered.
The disease caused by pandemic SARS-Coronavirus-2 (SARS-CoV-2), COVID-19, primarily manifests as respiratory illness. Disease severity ranges from asymptomatic infections to acute respiratory distress syndrome (ARDS). Recent observations demonstrated that SARS-CoV-2 can also cause neurological symptoms, which is known for many coronaviruses, including SARS-CoV-1 and MERS-CoV. (1) However, risk factors for neurological complications of COVID-19, clinical presentation and the appropriate virological diagnostic approach need to be further analyzed. Here, we report a case of SARS-CoV-2 infection of the CNS in a patient with meningeosis carcinomatosa.

Case presentation
A 53-year-old male patient was transferred to our hospital (day 1) with fever and increasing headache since one day. The day before admission, a nasopharyngeal swab of the patient was positive for SARS-CoV-2 RNA, while the patient reported no respiratory symptoms. Due to suspected meningitis, an empirical anti-infective treatment consisting of ceftriaxone, ampicillin and acyclovir was immediately initiated. Adenocarcinoma of the esophagus (ypT1bpN2M0R0) had been diagnosed four months earlier, which was resected after four cycles of neoadjuvant chemotherapy with the FLOT regimen (folinic acid, 5-fluoruracil, oxaliplatin, docetaxel). At neurological examination, he presented with meningism and decreased vigilance. The patient did not show any signs of a respiratory infection. The respiratory rate was 12 breaths per minute and the oxygen saturation was 96% without additional oxygen supply. Differential blood count showed leukocytopenia (2.88/nL), a normal neutrophile granulocyte count (2.46/nL) and absolute lymphocytopenia (0.34/nL). Together with normal CRP (2.8 mg/L), these laboratory findings were suggestive for a viral infection. Cerebrospinal fluid (CSF) analysis on day 1 revealed lymphoto-monocytic pleocytosis (57 leukocytes/µL, 96.5% mononuclear cells; 3 RBCs/µL), with elevated lactate.
(5.84 mmol/L) and protein levels (1363 mg/L) while glucose level was highly decreased (12 mg/dL). The neuropathological cytological analysis of the CSF demonstrated malignant epithelial cells (expressing the epithelial membrane antigen EMA) in terms of a meningeosis neoplastica. MRI of the brain on day 4 revealed several infra- and supratentorial lesions (Figure, A). This was suggestive for cerebral metastasis of the esophageal carcinoma. CT scan of the chest and abdomen on day 6 showed partial atelectasis of the pulmonary right lower lobe and typical postoperative changes with reactively enlarged mediastinal lymph nodes. There was neither evidence for COVID-19 pneumonia nor for local recurrence of the adenocarcinoma or further organ metastases.

Microbiological culture and a universal bacterial 16S-rDNA PCR were negative in the CSF sample from day 2. Since a nasopharyngeal swab of the patient was positive for SARS-CoV-2 RNA one day before admission to our hospital, further diagnostics for SARS-CoV-2 was initiated. Real-time RT-PCR analyses, using an in-house method targeting the SARS-CoV-2 E gene (screening assay) and the RdRp gene (confirmatory assay), were performed according to a previously published protocol. (2) On day 2, both screening and confirmatory assay were positive for SARS-CoV-2 RNA in the CSF (cycle threshold [ct] 19.5 and 21.6, respectively) and in the serum sample (ct 28.8 and 32.9, respectively), while PCR analysis of a nasopharyngeal swab was negative on day 5. Seroconversion was detected by an in-house FACS antibody assay, using the SARS-CoV-2 full-length S protein, for IgM antibodies on day 2 and for IgG antibodies on day 6, verifying an acute SARS-CoV-2 infection. (3) Furthermore, IgM (not shown) and IgG antibodies to SARS-CoV-2 were also detected in CSF from day 23 and 26 (Figure, B). Clinically, there was a significant reduction of the headache on day 3. In follow-up PCR analyses, SARS-CoV-2 RNA was detected in low concentration in a CSF sample on day 20 (ct value 33.9), whereas the last two CSF and serum samples obtained on day 23 and day 26 were PCR-negative.
Determination of the SARS-CoV-2 specific IgG antibody indices (AIs) for these two CSF/serum pairs was performed by using the FACS antibody assay for quantitation of SARS-CoV-2 IgG antibodies and kinetic nephelometry for measurement of total IgG concentrations in CSF and serum. The SARS-CoV-2 IgG CSF/serum ratios were $140 \times 10^{-3}$ and $90 \times 10^{-3}$ on day 23 and day 26, respectively. In comparison, the total IgG quotients were only $27.7 \times 10^{-3}$ and $17.6 \times 10^{-3}$ for the two CSF/serum pairs. The SARS-CoV-2 IgG specific AI, calculated by dividing the pathogen-specific IgG quotient by the total IgG quotient (4), was 5.1 for both pairs. In cases without pathogen-specific intrathecal antibody synthesis, the AI is expected to be 1.0 (range 0.5-1.5). Thus, the elevated antibody index of 5.1 in two CSF/serum pairs of this patient, five times higher than expected from IgG diffusion across the blood-brain barrier, demonstrated intrathecal antibody synthesis. This is an additional indicator for an active or past SARS-CoV-2 replication in the CNS compartment.

Later in the course of disease, after elimination of the virus, intrathecal chemotherapy and radiotherapy were initiated due to progression of the cerebral metastases.

**Discussion**

Our report describes the first case of a SARS-Coronavirus-2 meningitis in a patient with meningeosis carcinomatosa. SARS-CoV-2 infection of the CNS was confirmed by detection of viral RNA in two independent CSF samples and SARS-CoV-2 specific intrathecal IgG antibody synthesis.

There is increasing awareness for the neurotropic potential of SARS-CoV-2, yet the exact mechanism for entry in the CNS is unknown. Infection via the olfactory epithelium and nerve or haematogenous infection by viremia are currently discussed routes for neuroinvasion. (5) Meningeosis carcinomatosa might enhance the neuroinvasiveness of SARS-CoV-2 by increasing the permeability of the blood-brain-barrier, or might allow spread of virus from the brain into haematogenous circulation. From a pathophysiological
perspective, the latter mechanism might be more likely in our patient. First, on day 2 the viral RNA concentration in CSF was more than 100-fold higher than in serum, verifying autochthonous virus replication within the CNS compartment. Second, detection of SARS-CoV-2 RNA in the blood is usually considered as a virological marker for severe pulmonary or systemic disease (6), but our patient did neither present with severe respiratory nor other extra-neurological symptoms.

SARS-CoV-2 infection of the CNS was also reported in an apparently immunocompetent patient. (7) Therefore, it remains unclear, whether neoplastic meningitis and immunosuppression are relevant risk factors for a neuroinvasive SARS-CoV-2 infection, or if both conditions appeared coincidentally in our patient without a pathophysiological link. A limitation in the attribution of the patient’s headache as a neurological manifestation of COVID-19 is that this symptom could be also caused by the meningeosis carcinomatosa or cerebral metastasis. However, there was a significant improvement of the headache on day 3, which correlated with the beginning of the adaptive immune response of the patient, since IgM antibody seroconversion was detected on day 2. Additionally, neither an antiedematous nor antineoplastic therapy were administered at this time.

Our case demonstrates that in patients with neurological symptoms, PCR diagnosis for SARS-CoV-2 RNA from both respiratory and CSF specimen is required. In the course of neurological SARS-CoV-2 disease, viral RNA might be undetectable in respiratory samples, while SARS-CoV-2 RNA can be detected in CSF for longer periods, in our case for 18 days. Additionally, the detection of seroconversion and quantitation of SARS-CoV-2 specific antibodies in CSF and serum can contribute to the diagnosis COVID-19 associated neurological involvement.
## Appendix 1. Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philipp Steininger, MD</td>
<td>University Hospital of Erlangen</td>
<td>conceptualized case, wrote the manuscript, performed the molecular diagnostics, interpreted data</td>
</tr>
<tr>
<td>Frank Seifert, MD, Professor</td>
<td>University Hospital of Erlangen</td>
<td>treated the patient, collection of patient samples, reviewed the final manuscript</td>
</tr>
<tr>
<td>Stefanie Balk, MD</td>
<td>University Hospital of Erlangen</td>
<td>treated the patient, data acquisition, reviewed the final manuscript</td>
</tr>
<tr>
<td>Joji Kuramatsu, MD</td>
<td>University Hospital of Erlangen</td>
<td>treated the patient, reviewed the final manuscript</td>
</tr>
<tr>
<td>Andreas E. Kremer, MD, PhD</td>
<td>University Hospital of Erlangen</td>
<td>treated the patient, revised the manuscript, reviewed the final manuscript</td>
</tr>
<tr>
<td>Roland Coras, MD</td>
<td>University Hospital of Erlangen</td>
<td>performed the neuropathology, reviewed the final manuscript</td>
</tr>
<tr>
<td>Tobias Engelhorn, MD, Professor</td>
<td>University Hospital of Erlangen</td>
<td>interpreted the CT and MRI images, reviewed the final manuscript</td>
</tr>
<tr>
<td>Clara Maier</td>
<td>University Hospital of Erlangen</td>
<td>performed the antibody tests, created the figure, reviewed the final manuscript</td>
</tr>
<tr>
<td>Matthias Tenbusch, Professor</td>
<td>University Hospital of Erlangen</td>
<td>performed the antibody tests, created the figure, reviewed the final manuscript</td>
</tr>
<tr>
<td>Klaus Korn, MD</td>
<td>University Hospital of Erlangen</td>
<td>co-wrote the manuscript, assisted with expertise, data interpretation and discussion, reviewed the final manuscript</td>
</tr>
<tr>
<td>Armin Ensser, MD, Professor</td>
<td>University Hospital of Erlangen</td>
<td>conceptualized case, wrote the manuscript, interpreted data</td>
</tr>
</tbody>
</table>
Figure

A MR image of the brain on day 4

Upper row: axial T1w MR imaging after intravenous contrast media application revealed two supra- and two infratentorial parenchymal lesions with slight perifocal edema (red circles). With regard to the adenocarcinoma of the esophagus, these lesions were suggestive for cerebral metastasis of the esophageal carcinoma.

Lower row (left and middle): axial T1w MR imaging after intravenous contrast media application demonstrating slight generalized atrophy of the brain with subsequent slightly enlarged sulci and ventricles without clear signs of a hydrocephalus referring in particular to the temporal horns.

Lower row (right): sagittal T1w MR imaging after intravenous contrast media application demonstrating infratentorial leptomeningeal thickening and increased contrast enhancement (yellow circles).

B FACS-based quantitative measurement of SARS-CoV-2 specific IgG antibodies in serum and CSF

Seroconversion for SARS-CoV-2 IgG was detected on day 6. The SARS-CoV-2 IgG CSF/serum ratio for paired CSF/serum samples on day 23 and day 26 was $140 \times 10^{-3}$ and $90 \times 10^{-3}$, respectively. Based on total IgG and albumin values for CSF and serum, the SARS-CoV-2 IgG specific antibody index (AI) was 5.1 for both pairs. This verified a SARS-CoV-2 specific intrathecal IgG antibody synthesis.

< = under detection limit; n.d. = not determined
References


SARS-CoV-2 infection of the CNS in a patient with meningeosis carcinomatosa
Philipp A. Steininger, Frank Seifert, Stefanie Balk, et al.
Neurology published online December 8, 2020
DOI 10.1212/WNL.0000000000011357

This information is current as of December 8, 2020

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2020/12/08/WNL.0000000000011357.citation.full

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
COVID-19
http://n.neurology.org/cgi/collection/covid_19
Meningitis
http://n.neurology.org/cgi/collection/meningitis
Metastatic tumor
http://n.neurology.org/cgi/collection/metastatic_tumor
MRI
http://n.neurology.org/cgi/collection/mri

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2020 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.