Posterior reversible encephalopathy syndrome associated with SARS-CoV-2 infection

INTRODUCTION
The symptoms of COVID-19 include fever, fatigue and respiratory illness ranging from cough to acute respiratory distress syndrome (ARDS).\(^1\) Neurological complications, such as encephalopathy, are more and more reported. They can result from direct viral invasion, hypoxic, toxic or immune-mediated injury. In this report, we describe a patient with posterior reversible encephalopathy syndrome (PRES) associated with SARS-CoV-2 infection.

CASE DESCRIPTION
The patient is a 69-year-old woman, with history of coronary artery disease, an endometrial cancer, in remission since 2018, and no history of hypertension. She presented to the stroke unit, in the end of March 2020, few days before the epidemic peak in France, for three generalised seizures, mutism and delirium, and 7 days’ history of unusual asthenia. Temperature was 37°C, blood pressure at 200/116 mmHg and oxygen saturation was 95% while she was breathing ambient air. The pulmonary examination was normal. Neurological examination found no focal motor or sensor deficit. Brain MRI, performed 5 hours after the onset of seizures, showed bilateral and symmetric T2 and fluid-attenuated inversion recovery imaging hyperintensities located mainly in the temporal and occipital lobes with increased apparent diffusion coefficient values and leptomeningeal enhancement in the same areas in 3D T1 gadolinium sequence (figure 1). There were no signs of intracranial haemorrhage in susceptibility weighted imaging (images not shown). The vessel’s imaging was normal. The electroencephalogram showed intermittent focal slow delta waves in posterior regions particularly in the left temporo-occipital region. Laboratory tests showed a lymphopenia at 0.3 per mm\(^2\), elevated C reactive protein (CRP) with average of 88 per litre of over 7 days, slight hyponatremia at 132 mmol/L only the first day. Creatinine was 65 μmol/L and remains normal. Phosphoremia, magnesemia, calcium, Prothrombin time and activated partial thromboplastin time and fibrinogen were normal. There was no transaminis. Cerebrospinal fluid (CSF) analysis showed normal protein level (0.25 g/L) and white cell count (0.001 x 10\(^3\)/L). No oligoclonal bands and no onconeural antibodies were found. PCR assay of the CSF was negative for Herpes simplex virus, Human Herpesvirus-6, Varicella-zoster virus, Cytomegalovirus, Epstein Barr virus and John Cunningham virus. Real-time reverse transcription PCR (RT-PCR) of SARS-CoV-2 was positive in nasopharyngeal swab and negative in CSF. Chest CT done, in admission, sixth day after asthenia, did not show COVID-19 pneumonia or neoplasm. Treatment included antiepileptic drugs and intravenous nicardipine to <140/90 mm Hg. On the third day, the patient has evolved well neurologically. The speech was fluent and informative. She had discrete attention difficulties, recall disorder and simultagnosia. The 5-Word Test was 10/10 and 18/20 on a weighted basis. There was no need to treat specifically SARS-CoV-2 infection. MRI at day 8 showed resolution of the oedema, confirming the diagnosis of PRES (figure 1).

DISCUSSION
The clinical manifestations of COVID-19 are typically fatigue, fever, respiratory involvement ranging from cough to ARDS, septic shock and coagulation dysfunction leading to thrombotic events. Neurological complications were reported in 36.4% of 214 patients with COVID-19; impaired consciousness was more common in severe COVID-19 than those with non-severe disease (14.8% vs 2.4%). However, in this study, only clinical symptoms were reported without MRI or CSF study. Our patient did not have fever or suggestive pneumonia in chest CT on admission. The RT-PCR of SARS-CoV-2 does not appear to be a false positive because of its excellent specificity and the presence of symptoms that could be associated with SARS-CoV-2 infection like asthenia, encephalopathy, lymphopenia and positive CRP.

PRES is a clinicoradiological syndrome characterised by acute cerebral endotheliopathy with consecutive disruption of the blood–brain barrier (BBB) and vasogenic oedema. The diagnosis is based on (1) at least one acute neurological symptoms (seizure, altered mental state, headache, visual disturbances); (2) more or equal than one risk factor; (3) brain imaging with bilateral vasogenic oedema, cytotoxic oedema with patterns of PRES or normal brain imaging; and (4) no other alternative diagnosis.\(^3\)

The link between PRES and SARS-CoV-2 infection is not clear. Following SARS-CoV-2 infection, the expression and function of ACE 2 (ACE2) proteins are reduced, resulting in hypertension that may induce PRES.\(^2\) Furthermore, vascular endothelial dysfunction has been recently proposed as complication of SARS-CoV-2 infection. SARS-CoV-2 infects the host using the ACE2 receptor, which is expressed in several organs and endothelial cells, resulting in diffuse endothelial inflammation. The SARS-CoV-2-infection-related endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds. In the brain, this endotheliitis seems to induce increased permeability of the BBB, leading to a brain oedema.\(^2\) Few cases of PRES associated with COVID-19 have been published recently but are most often in severe forms requiring mechanical ventilation. Furthermore, there were other classical causes of PRES in these patients such as ARDS, tocilizumab, sepsis and acute kidney injury requiring haemodialysis,\(^4\) severe hypoxic pneumonia and treatment targeting SARS-CoV-2 that the authors could not determine the exact aetiology of PRES.\(^5\)

Our case is characterised by the occurrence of PRES, early in the course of the disease, in a non-severe form of SARS-CoV-2 infection without the need for
respiratory assistance and no confounding factors related to severity such as ARDS, cytokine storm syndrome, immunotherapy, critical illness-related encephalopathy, multidrug regimens or metabolic disorders. The cancer was in remission for 2 years. In the absence of all these factors, it is conceivable that PRES could be considered as a complication of SARS-CoV-2 infection by means of this endotheliopathy.

**CONCLUSION**

This is an exceptionally well-documented case of PRES associated with a non-severe SARS-CoV-2 infection. Our observation adds further evidence that endotheliopathy related to SARS-CoV-2 infection may play a major role to cause PRES. We advocate that timely MRI is mandatory in suspected cases of PRES especially in the context of confirmed SARS-CoV-2 infection to better characterise and manage the PRES.

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