ICANS is a neuropsychiatric syndrome with heterogeneous clinical manifestations; however, akinetic mutism is a recurrent and specific feature that might help discriminate it from other encephalopathies.[2,3] Interestingly, we observed 3 COVID-19 patients presenting with a similar phenotype to Pilotto et al's case, including transitory akinetic mutism, where other likely causes were reasonably excluded and SARS-CoV-2 real-time polymerase chain reaction in CSF tested negative (unpublished data).

Diffuse slowing on electroencephalogram, unremarkable brain magnetic resonance imaging, and mildly elevated white blood cell count (WBC) and protein levels in CSF are common findings in ICANS,[2,3] and were also observed in Pilotto et al's case.[1]

The authors described elevated CSF interleukin (IL)-8 and tumor necrosis factor (TNF)-α levels that decreased with clinical improvement, whereas WBC remained stable.[1] Neurotoxicity grade in ICANS correlates with CSF cytokine levels, including IL-8, TNF-α, and IL-6, and not with CAR-Ts or WBC in CSF, suggesting a causative role of the former.[3] Specifically, IL-8 was found significantly increased in the CSF relative to blood, consistent with local CNS production in ICANS.[3] Pilotto et al's patient had mild systemic inflammation; thus, although matched serum and CSF cytokines were not reported, it is feasible to suspect that the IL-8 CSF/serum ratio would have been elevated.

Their patient had a dramatic response to corticosteroids,[1] although spontaneous clinical recovery has been observed in other patients with COVID-19–associated encephalopathy.[5] ICANS usually resolves on its own; however, corticosteroids are the first-line therapy for severe cases.[2,3]

The overlapping features of this case report and neurotoxicity related to CAR-T therapy bring into question the possibility of a shared, cytokine-mediated pathophysiology, which can further inform treatments.

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Potential Conflicts of Interest

Nothing to report.

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Reply to the Letter "COVID-19-Associated Encephalopathy and Cytokine-Mediated Neuroinflammation"

Andrea Pilotto, MD,[1,2] Alessandro Padovani, MD, PhD,[1] and ENCOVID-BIO Network[1]

Muccioli et al proposed an interesting comparison between the case of encephalitis related to severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection we described and immune effector cell-associated neurotoxicity syndrome (ICANS). Indeed, the clinical phenotype characterized by akinetic mutism, normal brain magnetic resonance imaging (MRI), frontal slowness on electroencephalogram (EEG), hyperproteinorrachia with mild pleocytosis, and response to steroid treatment fit well with ICANS, and, more in general, with a central nervous system (CNS) cytokine-induced event.

In this case, SARS-CoV-2 infection triggered neuroinflammation but the underlying mechanisms are unknown. In order to clarify the role of inflammation in pathogenesis, we measured the values of cytokines in serial serum samples obtained the same day of cerebrospinal fluid (CSF) analysis before and after steroid therapy. Interleukin (IL)-8 and IL-6 exhibited higher levels in CSF compared with serum with a reduction in both compartments after steroid therapy (Table1), in line with what is typically observed in ICANS.[1] In addition to that, we here report the serial results of glial and astrocytic markers (triggering receptor expressed on myeloid cells 2 [TREM-2], chitinase-3-like protein 1 [YKL-40], and glial fibrillary acidic protein [GFAP]). The patient exhibited increased CSF levels of TREM-2, a microglia activation marker able to modulate neuroinflammation in acute and chronic CNS disorders. Furthermore, GFAP, a CNS-specific astrocyte marker recently pointed out as main driver of ICANS[2] appeared to be elevated, despite neuronal damage markers at the upper limit of normal distribution. These results fit well with the recent observation of increased plasma levels of GFAP and NfL detected in patients with moderate to severe coronavirus disease 2019 (COVID-19).[3] The patient also presented elevation of YKL-40, a glial glycoprotein known to be released in cytokine-stress syndromes by activation of TNF-alpha and IL-6. These additional findings further support cytokine-

TABLE 1: Cytokine Analyses in Cerebrospinal Fluid and Serum

	Day 4			Day 8		
	CSF	SERUM	RATIO	CSF	SERUM	RATIO
Cytokines						
IL-6, pg/ml	2.36	4.48	0.53	2.59	0.97	2.75
IL-8, pg/ml	>1100	98.3	11.2	97	8.19	11.8
TNF-α, pg/ml	1.31	2.21	0.59	0.28	1.36	0.20
Glial CSF markers						
GFAP, pg/ml	244			271		
TREM2, pg/ml	4610			4260		
YKL-40, ng/ml	201			381		

GFAP = Glial fibrillary acidic protein; IL-6 = interleukin 6; IL-8 = interleukin 8; TNF-α = tumor necrosis factor alpha; TREM-2 = triggering receptor expressed on myeloid cells 2; YKL-40 = Chitinase-3-like protein 1.

mediated neuroinflammation as the main driver of encephalitis in this patient. The high levels of interleukins in CSF compared with serum, as well as the increase of CNS-specific GFAP, speak against passive leakage across the blood–brain barrier, and instead suggest an intrathecally active inflammatory process. Several works reported similar cases during the last months,[4-6] showing that many patients with SARS-CoV-2 encephalitis exhibited clinical and imaging findings highly consistent with previously reported inflammatory-mediated neurotoxicity,[1,2] whereas direct invasion and autoimmune responses appeared to be a rare condition. Despite the interesting insights given by this case report, larger studies are urgently needed to confirm cytokine-induced neuroinflammation as a main driver of SARS-CoV-2 related encephalitis, as this issue has deep consequences for the management and treatment of this growing condition worldwide.

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Author Contribution

Andrea Pilotto and Alessandro Padovani: study concept and design, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript for content.

Potential Conflicts of Interest

Nothing to disclose.

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