


A case of successive development of possible acute necrotizing encephalopathy after COVID-19 pneumonia

SAGE Open Medical Case Reports
Volume 10: 1–4
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DOI: 10.1177/2050313X221083653
journals.sagepub.com/home/sco



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Abstract

COVID-19 infection often results in an excessive inflammatory response with a spectrum of neurological manifestations. Here, we describe an 81-year-old female with severe COVID-19 pneumonia and subsequent alteration of consciousness after high-dose intravenous dexamethasone and remdesivir. A non-contrast head computed tomography (CT) demonstrated bilateral hypodensities involving bilateral cerebellar hemispheres, thalami, cerebral peduncles and medial parieto-occipital areas. There was no improvement and repeat CT showed progression with findings suggestive of acute necrotizing encephalopathy. Interleukin-6 levels were initially normal; however, subsequent levels were found to be markedly elevated. Acute necrotizing encephalopathy associated with COVID-19 may occur in the setting of severe pneumonia and may represent an immune-mediated process involving inflammatory cytokines such as interleukin-6.

Keywords

COVID-19, acute necrotizing encephalopathy, interleukin-6

Date received: 6 October 2021; accepted: 9 February 2022

Background

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is recognized to cause multisystem inflammatory syndrome associated with immune dysregulation, affecting both adults and children. Neurological manifestations such as acute cerebrovascular disease, seizure, meningitis, encephalitis and Guillain–Barré syndrome (GBS) have been frequently reported.^{1–3} We report a case of possible COVID-19-associated acute necrotizing encephalopathy (ANE) with alteration of consciousness.

Case presentation

An 81-year-old female with a medical history of hypertension and hypercholesterolaemia developed high-grade fever and non-productive cough 8 days prior to admission. Her initial vital signs showed a body temperature of 38.6°C, blood pressure 143/87, heart rate 99, respiratory rate 18 and oxygen saturation was 90% on room air. Physical examination showed bilateral fine crepitation

corresponding with bilateral patchy opacities on the chest radiograph. Neurological examination revealed no abnormality. Polymerase chain reaction (PCR) for SARS-CoV-2

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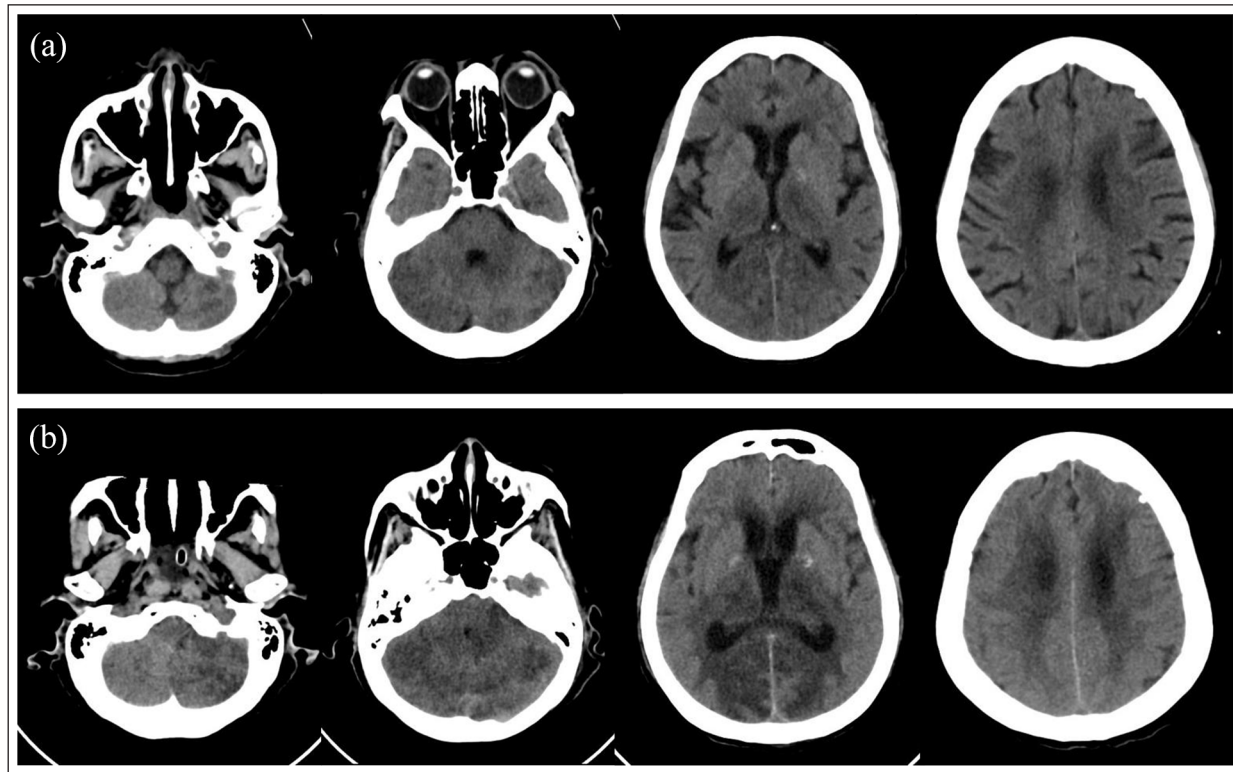


Figure 1. (a) CT non-contrast on admission Day 5 showing hypodense lesions involving bilateral cerebellar hemisphere, both thalami, cerebral peduncles and medial parieto-occipital lobes. Bilateral basal ganglia hyperdensity present due to age-related calcification. (b) CT non-contrast on admission Day 9 showed increased area of symmetrical hypodense lesions involving bilateral cerebellar hemisphere, both thalami, internal capsules, pons, cerebral peduncles and medial parieto-occipital lobes with pressure effect causing crowded foramen magnum.

from nasopharyngeal and throat swabs was positive and she was admitted to COVID-19 care.

The initial blood test results showed elevated D-dimer, 1907 ng/mL; high-sensitivity C-reactive protein (hs-CRP), 47.6 mg/L; mildly elevated interleukin (IL)-6, 13.3 pg/mL; procalcitonin, 0.22 ng/mL; and lymphopenia, $1.59 \times 10^9/L$. Treatment with oral favipiravir and intravenous dexamethasone 5 mg every 8 h were administered. Chest radiograph showed progressing pneumonia resulting in worsening hypoxemia; thus, the patient required high-flow nasal cannula (HFNC). Oral favipiravir was switched to intravenous remdesivir 1 day after admission. Repeat inflammatory markers tests showed markedly elevated D-dimer, 9800 ng/mL; hs-CRP, 16.4 mg/L; mildly elevated IL-6, 14.2 pg/mL; and procalcitonin, 0.10 ng/mL. CT pulmonary artery showed bilateral peripheral predominant ground-glass opacities, and no embolism. The patient's overall condition was stable after switching to remdesivir. Tocilizumab was not administered as the IL-6 and hs-CRP levels remained relatively low.

The patient became unresponsive on the fifth day of admission with no significant change in her vital signs. On examination, the patient was unresponsive to deep pain stimulation. Both pupils were 2 mL but sluggish to light. Brainstem reflexes were intact. Further examination was

unremarkable, with flaccid tone, depressed tendon reflexes and flexor plantar response bilaterally. She was intubated for airway protection. Non-contrast head CT revealed symmetrical ill-defined hypodense lesions involving bilateral parieto-occipital lobes, medial temporal lobes, thalami and cerebellar hemispheres (Figure 1(a)). Subsequent inflammatory marker tests showed markedly elevated D-dimer, 4924 ng/mL; hs-CRP, 169 mg/L; elevated IL-6, 134.5 pg/mL; and procalcitonin 0.09 ng/mL despite improvement in pneumonia. She remained comatose. A non-contrast head CT was repeated 4 days later (on Day 9 of admission), which showed progression of hypodensity lesions and marked cerebral edema (Figure 1(b)). CT angiography of the brain and neck showed no occlusion or significant stenosis, and delayed phase showed no venous sinus occlusion. The final diagnosis of possible ANE was made from the patient's radiological findings. The additional immunomodulatory agents were not given as the process was likely irreversible due to significant progression of intracranial involvement, and family decided to opt for palliative care due to poor prognosis. Magnetic resonance imaging (MRI) was not done as there was no dedicated MRI machine for COVID-19 patients. Lumbar puncture was not performed as viral encephalitis was unlikely and radiological findings were consistent with the symptoms.

Comprehensive 48 cytokines panel found markedly elevated RANTES, 10,831 pg/mL (Appendix Table 1). RAN Binding Protein 2 gene (*RANBP2*) analysis found no mutation at Thr585Met. The patient was provided with palliative care and passed away on Day 15 of admission.

Discussion

ANE is a rare encephalopathy, commonly preceded by acute viral infection in children.⁴ Its clinicopathological feature includes multiple symmetrical necrotic brain lesions involving thalami with supra and infra-tentorial lesions corresponding to parenchymal changes from edema to petechial hemorrhage and necrosis.⁵ It notably develops secondary to influenza A or B, human herpesvirus 6 and more recently cases predominantly in adults associated with COVID-19.^{3,6}

COVID-19 is known to cause immune dysregulation toward innate immunity elicited by neutrophil response, followed by increases in proinflammatory cytokines such as IL-1 beta, IL-6, IL-8 and tumor necrosis factor alpha (TNF- α) with bias toward Th1 response resulting in cytokine storm.⁷ High level of IL-6 is currently used as a prognostic indicator.⁸ Levels of proinflammatory cytokines have been considered an important role in the pathogenesis of ANE, and many case reports emphasized an increase in IL-6 ranging from a small increase to a very high level of IL-6.⁹ Possible contribution to the development of ANE in this patient includes underlying endothelial dysfunction given the patient's advanced age and mediation from other inflammatory cytokines.¹⁰ *RANBP2* encodes the protein involved in signaling with the nuclear membrane and interacts with the nuclear pore protein complex. Mutation of *RANBP2* results in increased susceptibility to mitochondrial dysfunction and blood-brain barrier maintenance, and has been implicated in familial ANE following viral illness.³ Analysis in our patient found no mutation, suggesting that excessive inflammation caused ANE in this case.

The patient developed neurological symptoms despite high dose of dexamethasone and improvement of her pneumonia. Further immunotherapy was not provided as the process was unlikely irreversible due to extensive necrosis, and there is no sufficient evidence of benefit from immunotherapy in late stage of ANE. One study reported satisfactory recovery, in three pediatric-related ANE, with early administration of intravenous methylprednisolone and tocilizumab.¹⁰ A review of current case reports of patients present with COVID-19 pneumonia and subsequent development of ANE has shown that none of the patients received tocilizumab.^{6,11–14}

Exaggerated immune responses to infection with elevated proinflammatory cytokines leading to proteolytic breakdown of the blood-brain barrier are central to the pathogenesis of ANE.⁵ Additional neuropathogenesis may involve mitochondrial dysfunction, metabolic and neuronal disruption either as a consequence of direct viral invasion or

via excessive cytokines.¹⁵ Early cytokines may not necessarily include IL-6, and the data have shown elevated level of IL-1, TNF- α and several other cytokines.¹⁶ Individuals may later develop IL-6 predominant cytokine with downstream phosphorylation via tyrosine kinase leading to increased risk of ANE.³ Therefore, we believed that early aggressive immunosuppression given concomitantly with immunomodulation maybe beneficial and should be given.

Recently, World Health Organization (WHO) initiated a randomized controlled trial with three treatment arms with the aim to reduce unhealthy levels of cytokines. Artesunate, an anti-malarial medication could inhibit nuclear factor kappa B (NF- κ B) signaling pathway with subsequent reduction in downstream IL-1, IL-6 and TNF- α production.¹⁷ Infliximab, a monoclonal against TNF- α that directly binds to soluble and transmembrane TNF- α . Imatinib, a tyrosine kinase inhibitor, reduces downstream inflammatory signaling from IL-6, and also protects against capillary leakage and alveolar edema.¹⁸ Trials involving modulation of aberrant cytokines will lead to further understanding of inflammation in COVID-19 and improved care for patients.

Lumbar puncture was not performed in this patient as other encephalitides were unlikely, but a non-contrast head CT finding of bilateral thalamic and parieto-temporal hypodensities could be secondary to viral encephalitides.¹⁹ This represents a limitation in this case report.

Conclusion

This case report suggests that IL-6 and other inflammatory cytokines in COVID-19 are the main components in the development of ANE, especially when *RANBP2* mutation, a known genetic susceptibility for the development of ANE, was absent. The benefit of tocilizumab and other immunomodulators to reduce the risk of ANE by inhibiting upstream IL-6-mediated proinflammatory cascade and its counterparts remains possible and should be investigated.

Acknowledgements

The authors thank the emerging infectious disease team, internal medicine and nursing colleagues of King Chulalongkorn Memorial Hospital for their exceptional care for these critically ill patients.

Author contributions

P.H. acquired the data; coordinated imaging; designed and conceptualized case; and drafted the manuscript for intellectual content. T.P. designed and conceptualized case; and revised the manuscript for intellectual content. W.R. and P.T. performed data acquisition; and designed and conceptualized case. Y.J., S.B. and C.R. coordinated laboratory test. T.H. designed and conceptualized case; and revised the manuscript for intellectual content.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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Appendix

Table 1. Human cytokines and chemokines panel, 48-plex (all units in pg/mL).

FGF basic = 68	IL-2 = 48	IL-10 = 193	MIP-1 α = 165
Eotaxin = 1123	IL-4 = 148	IL-12 (p70) = 21	MIP-1 β = 1573
G-CSF = 169	IL-5 = 39	IL-13 = 17	PDGF-BB = 652
GM-CSF = 25	IL-6 = 222	IL-15 = 24	RANTES = 10,831
IFN- γ = 69	IL-7 = 25	IL-17A = 45	TNF- α = 70
IL-1 β = 84	IL-8 = 622	IP-10 = 3110	VEGF = 74
IL-1 α = 178	IL-9 = 183	MCP-1 (MCAF) = 43	CTACK = 166
IL-1 α = 55	GRO- α = 116	MIG = 2287	MIF = 1537
IL-2R α = 178	HGF = 2406	β -NGF = 36	TRAIL = 88
IL-3 = 39	IFN- α 2 = 50	SCF = 741	IL-18 = 1337
IL-12 (p40) = 36	LIF = 56	SCGF- β = 2486	M-CSF = 567
IL-16 = 1171	MCP-3 = 137	SDF-1 α = 472	TNF- β = 467