A parturient with COVID-19 pneumonia, complicated with posterior reversible encephalopathy syndrome in puerperium

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SUMMARY

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may give rise to vascular complications and endothelial dysfunction, leading to the posterior reversible encephalopathy syndrome (PRES). Of note, steroids and immunomodulatory agents are known to precipitate PRES. Here we report a case of a 25-year-old postpartum woman with PRES, presumably caused by laboratory-confirmed COVID-19 during the recovery phase. At the gestational age of 34 weeks, she was initially hospitalised for mild COVID-19 infection. However, she developed COVID-19-related hyperinflammation on day five of the illness and was treated with remdesivir (antiviral agent), high-dose steroids, and tocilizumab (TCZ, an interleukin-6 inhibitor). In anticipation of ongoing respiratory compromise, she underwent an elective caesarean section, with a healthy 2.6 kg baby girl born. Her condition was stabilised post-operatively, but by day ten of the illness, she developed severe headaches, confusion, and seizures that were aborted pharmacologically. Throughout the hospitalisation, she was normotensive. The findings of brain magnetic resonance imaging (MRI) were consistent with the diagnosis of PRES. Her condition steadily improved with symptomatic treatment, consisting of adequate hydration, close monitoring, and antiepileptic agents. On day fourteen of the illness, she achieved a complete recovery. In this case, we highlight that PRES is a potential neurological complication of COVID-19 infection in the context of pregnancy without pre-eclampsia or eclampsia and should be considered as one of the differential diagnoses in the presence of abrupt neurologic manifestations. Additionally, the use of steroids and immunomodulatory agents in treating the COVID-19 infection should be judicious.

INTRODUCTION

Since the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as a novel culprit of pneumonia in 2019, approximately five hundred million people across the globe have been diagnosed with COVID-19, with more than seven million deaths at present.[1] As of July 11, 2022 in the United States, 222372 pregnant women had COVID-19, with 304 (0.14%) deaths being reported.[2] Recent studies have shown that pregnant women are at higher risk of developing severe COVID-19 pneumonia, especially those with obesity, pre-existing medical conditions, and obstetric complications.[2] Though the clinical course of COVID-19 among pregnant women is often insidious, this cohort deserves timely treatment for COVID-19, including steroids, antiviral agents, and immunomodulatory agents.

Neurological manifestations are not uncommon among pregnant women with COVID-19. The spectrum of symptoms can range from fatigue, myalgia, headaches to seizures, delirium and stroke-like manifestations. Interestingly, any type of neurologic complaint can be a warning sign of severe COVID-19 infection and debilitating neurological complications. The neurological complications are, for instance, stroke, encephalopathy and Guillain-Barré syndrome (GBS), which can potentially have an adverse impact on maternal and neonatal outcomes. Additionally, antenatal changes in physiology and immunomodulation can trigger an exacerbation of COVID-19 disease, as well as the neuroinvasive propensity of the SARS-CoV-2 virus.[3]

A scoping review conducted by João et al. summarised 18 case reports of COVID-19 pneumonia in pregnancy that were published from inception until November 25, 2021.[4] Of 18 cases with COVID-19-related neurological involvement in pregnancy, only four (22.2%) had PRES with hypertension. Of note, PRES is seemingly a rare but severe complication of COVID-19 in pregnancy. In this article, we described a puerperal case with COVID-19 and PRES without hypertension, pre-eclampsia, or eclampsia, that was diagnosed on clinical, laboratory, and radiological grounds.

CASE PRESENTATION

A 25-year-old primigravida at 34-week gestation, presented to our centre with fevers for one day. The antenatal period was uneventful, and she had received two doses of the COVID-19 vaccine to date. The blood pressure (BP) readings during antenatal care were normotensive. She was in close contact with her husband, who had COVID-19. As the COVID-19 saliva test was positive and the home quarantine was unfeasible, she was hospitalised for a mild COVID-19 illness. On arrival, she was not in respiratory distress, with an

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unremarkable respiratory examination and stable hemodynamic parameters. Notably, she was normotensive. The nasopharyngeal swab of rtPCR for SARS-CoV-2 performed in the ward was positive for COVID-19 infection, with the RdRp CT value of 15 and E gene of 15.36. The baseline laboratory investigations were normal (Table I).

On day four of the illness, she became dyspnoeic, requiring high-flow oxygen therapy. Further laboratory evaluation is described in Table I. At that juncture, a 3-day course of intravenous remdesivir (a loading dose of 200 mg/day, followed by 100 mg/day) was administered for viral pneumonitis. On day 5 of illness, her condition declined further with pulmonary involvement (Figure IA and 1B) and an uptrend in inflammatory parameters (Table I). Due to the development of COVID-19-related hyperinflammation, she was treated with a 10-day course of intravenous methylprednisolone, 2 mg/kg/day for the first 3 days, followed by 1 mg/kg/day for another 3 days, then oral prednisolone with an equivalent dose of dexamethasone, 6 mg/day for the remaining 4 days. Additionally, a dose of intravenous TCZ, 8 mg/kg was administered. In anticipation of further clinical deterioration, she underwent an elective caesarean section under general anaesthesia on day 6 of the illness, and a live baby girl weighing 2.6 kg was delivered with a good Apgar score. No intraoperative complications were encountered. Postoperatively, she was extubated and transferred to the general ward. At the hospital, her condition had stabilised, and the oxygen requirement was gradually weaned off by day eight of the illness.

On day 10 of the illness, as well as the fifth postoperative day, she developed thunderclap headaches and vomiting, followed by multiple episodes of seizures on the same day. Seizures were later aborted by phenytoin. Apart from having a fluctuating Glasgow Coma Scale (GCS) ranging from 13 to 14 (eye opening scaled by three points, verbal response scored four to five, and motor response scaled by six), she was found hemodynamically stable and normotensive with the BP ranging 100-120/70-80. Throughout the entire hospitalisation, there was no fluctuation or uptrend in blood pressure readings. Apart from having an abnormal GCS score, other neurological findings were grossly normal, with absent meningism. She did not exhibit any visual disturbances. The laboratory assessment immediately performed at that point did not specifically pinpoint any organ impairment or electrolyte imbalances. The autoimmune screen was negative. The inflammatory biomarkers described in Table I, were normal. The brain MRI with gadolinium contrast (Figure IC-F) depicts T1-weighted hypointense and T2-weighted/(fluid-attenuated inversion recovery) FLAIR/apparent diffusion coefficient (ADC) hyperintense lesions in bilateral fronto-parieto-occipital areas, in favour of vasogenic oedema in PRES. Additionally, diffused-weighted imaging (DWI) does not demonstrate the feature of restricted diffusion, and there is no intracranial haemorrhage on the brain MRI. The electroencephalogram (EEG) did not detect any epileptiform discharges. A lumbar puncture was not performed as her husband had not consented.

She was managed conservatively and successfully evolved, with a complete GCS recovery by day 14 of her illness before she was discharged home with her newborn. One year later, she remained well and did not report any significant complications caused by previous insults. The antiepileptic agent was successfully ceased. No head MRI was repeated in the interim.

DISCUSSION

We report the case of a pregnant woman with COVID-19 who developed PRES. First described by Hinchey et al. in 1996,[5] PRES was often described in the presence of malignant hypertension, along with other special conditions including renal disease, auto-immune diseases, pre-eclampsia or eclampsia. The incidence of PRES is increasing among non-pregnant individuals with severe COVID-19 infection. Most reported cases required mechanical ventilation and immunomodulatory therapy.[6,7] The diagnosis of PRES in our case was confirmed clinically and radiologically. Thus far, none of these patients were found to have strong evidence of the SARS-CoV2 genome in the cerebrospinal fluid.

Historically, it was believed that PRES was characterised by dysregulation of cerebral circulatory flow caused by malignant hypertension, severe infection, inflammation or vasotoxicity. Of note, eclampsia preceded by chronic hypertension and pre-eclampsia is a common aetiology for developing PRES. It can be implicitly explained by a rapid alteration in blood pressure that has disrupted cerebral perfusion, leading to an eventual breakdown of the blood brain barrier and causing cerebral oedema. Interestingly, dysregulation of placental ACE2 caused by COVID-19 infection can significantly lead to preeclampsia or eclampsia, which later explains the development of PRES.[8] As opposed to the previous idea, our case did not exhibit signs of preeclampsia or eclampsia, and the patient remained normotensive throughout the pregnancy. To date, data are limited to correlating the relationship between the normal physiological changes in pregnancy and COVID-19-related PRES. Further scrutiny is required.

On the other hand, recent studies suggested that the disturbance of cerebral microcirculation and vascular endothelial glycocalyx caused by the direct binding of SARS-CoV-2 with ACE2 receptors on capillary endothelium was the leading cause of PRES in normotensive individuals affected by COVID-19 infection.[7,9] In addition, an immune dysregulation caused by the SARS-CoV-2 virus may potentially facilitate the production of cytokines, notably IL-6 and TNF-α, thereby giving rise to a detrimental effect on endothelial layers in the CNS, increasing the permeability of the blood brain barrier and causing the formation of vasogenic oedema.[6,7] Another potential leading theory of the pathogenesis of PRES suggests that SARS-CoV-2 virions directly gain entry into the CNS and bind with ACE2 receptors on neurons and glial cells, conspicuously culminating in direct neurological damage and hence cytotoxic oedema of brain tissues.[7]

Owing to the anti-inflammatory effects, steroids and TCZ are strongly advised as one of the mainstay treatments for COVID-19-related cytokine release syndrome. Following

evidence-based reviews of the benefits of low-dose dexamethasone in treating COVID-19-related hyperinflammation, TCZ was later advocated by the COVID-19 treatment guidelines panels.[10] Notwithstanding, data on the efficacy and safety net of high-dose steroids used in COVID-19 treatment, for instance, pulse steroid therapy, is limited, and its use may exhibit detrimental effects on clinical outcomes.[11] In fact, the administration of TCZ and high-dose steroids may potentially contribute to PRES. Although its mechanism has not been well studied, the possible harmful effects of TCZ and high-dose steroids on the neurological system are essentially based on previous case reports.[6,12-14]

Interestingly, Sofía Lallana et al. reported eight cases of PRES associated with COVID-19, and half of those patients were given TCZ.6 The inhibitory effect of TCZ on IL-6 receptor blockade resulted in an abrupt accumulation of IL-6 levels in cerebral microvascular endothelial cells, leading to direct injury to endothelial walls.[12] Similarly, there is a time-related association between PRES and steroid exposure, as demonstrated in previous studies.[13,14] In our case, the brief duration of steroid administration raises the possibility that the development of PRES is presumably caused by high-dose steroids, even though our patient did not have hypertension or reversible cerebral vasoconstriction syndrome (RCVS). Though the mechanism by which steroids cause PRES is unknown, a plausible explanation for steroid-induced PRES includes hypertension caused by the effect of mineralocorticoids or RCVS.[13] Given the possibility of neurological complications from TCZ and high-dose steroids, their use should be cautious.

In the acute or subacute setting, the spectrum of PRES-related clinical characteristics is heterogeneous, ranging from headaches or visual disturbances to encephalopathy, for instance, seizures, focal neurological deficits and altered sensorium. Among the adult population with COVID-19 and PRES, not involving pregnant women, hypertensive crisis and altered mental status were the most common presentations, and the rates of invasive mechanical ventilation and intensive care unit (ICU) admission were high, up to 80%.15 Interestingly, João et al. reported nine COVID-19 cases in pregnancy with hypertensive presentation and CNS involvement, of which four had PRES with acute cognitive impairment and seizures.[4] These manifestations are strongly associated with well-recognised risk factors, including blood pressure fluctuation, renal impairment, malignancy, immunosuppressive or cytotoxic agents, autoimmune disorders, pre-eclampsia and eclampsia.

Besides clinical signs and symptoms, radiological findings are mandatory to help diagnose PRES. Classically, the brain imaging demonstrates symmetrical vasogenic oedema involving bilateral parietal and occipital lobes, characterised by hypodense lesions on CT and hyperintense areas on T2-weighted and FLAIR MRI. Interestingly, sites of atypical PRES may include the frontal lobes, brainstem, cerebellum and basal ganglia. Provided with MRI imaging availability, MRI should be considered to exclude other differential diagnoses, for instance, stroke, hypoxic encephalopathy, viral encephalitis/meningitis, vasculitis, demyelination disorders, venous thrombosis and metabolic diseases. Additionally, Rubaya Yeahia et al. reported that most patients (15/30, 50%) exhibited haemorrhagic foci on brain MRI imaging.[15]

Notably, PRES is often self-limiting if the precipitating cause is treated or removed, and the target BP remains within a normal range. Indeed, optimal blood pressure control and stabilisation of COVID-19-associated hyperinflammation are of paramount importance for treating PRES. Additionally, a prompt cessation of offending drugs, for instance, cytotoxic and immunomodulatory agents should be executed. The outcome of COVID-19-related PRES is overall favourable, provided with appropriate medical management. Even though it is rare, a small portion of patients with COVID-19-associated PRES may experience continuous disease progression, leading to cerebral haemorrhage, necrotising cystic cavitations, and even death.[15] Noteworthy to mention is that the obstetric and neonatal outcomes vary among the non-COVID-19 pregnant cases with PRES, determined by prompt treatment of the underlying diseases. To date, the national maternity dataset on COVID-19 complicated with PRES is not widely available.

CONCLUSION

PRES is recognised as one of the neurological complications of severe COVID-19 among pregnant women. Notwithstanding the fact that the association of COVID-19 infection with PRES is known, there are cases in normotensive puerperal individuals without pre-eclampsia or eclampsia, and the outcomes are less commonly described. Coupled with the impairment of vasoreactivity and potential adverse effects of tocilizumab (TCZ), these risk factors may place pregnant women with COVID-19 at a higher risk of PRES. Given that neurological manifestation is one of the key features of COVID-19 infection, clinicians should consider PRES as a potential cause of encephalopathy in pregnancy. Physicians should judiciously utilise steroids and TCZ in treating the COVID-19 infection. Little information is known about the association between pregnancy-related PRES and COVID-19. Future studies on further exploration of their relationship should be considered.

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