Title: Coronavirus disease 2019 (COVID-19) during pregnancy: a case series

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Condensation From this most comprehensive virological assessment to date, there was no evidence to support vertical transmission of SARS-CoV-2.

Short Title COVID-19 during pregnancy

AJOG at a Glance

A. Why was this study conducted?

The reports regarding the clinical characteristics of COVID-19 in pregnancy are limited. Only two studies reporting 18 mothers and 19 infants have been published. Similar to SARS-CoV, vertical transmission of SARS-CoV-2 has not yet been observed.

B. Key findings

We have performed the most comprehensive virological assessment to date. We also find no evidence to support vertical transmission of SARS-CoV-2.

C. What does this add to what is known?

It is possible to provide care for SARS-CoV-2 infected mothers during late pregnancy and both caesarean and vaginal birth without adverse outcomes for the mother, infant and healthcare staff. Our findings reinforce the need for the prospective study of overall impact and long-term prognosis of SARS-CoV-2 on pregnancy and neonate outcomes.

Abstract

Background: Coronavirus disease 2019 (COVID-19) is a new viral respiratory disease and whether pregnant women are at increased risk of infection is unknown. Viral pneumonia is an important indirect cause of maternal death. Little is known about the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy.

Objective: To describe the clinical characteristics of COVID-19 in pregnancy and their newborn infant, and we sought to explored whether the SARS-CoV-2 can be intrauterine vertically transmitted.

Study Design: The study was a case series study conducted in the obstetric ward of Tongji Hospital affiliated to Huazhong University of science and technology, Wuhan, China. Demographic, clinical, laboratory and radiological profiles of the SARS-CoV-2 infection case series. A systematic testing procedure for SARS-CoV-2 infection using oropharyngeal swab, placenta tissue, vaginal mucus, and breast milk of mothers. and oropharyngeal swab, umbilical cord blood, and serum of newborns was conducted.

Results: We have conducted the most thorough virological assessment to date, and we include a longer clinical observation in mother-infant dyads during hospitalization. The clinical course and outcomes of three pregnant women who acquired SARS-CoV-2 infection late pregnancy are described in mother-infant dyads. Two had caesarean delivery in their third trimester. All patients showed an uneventful perinatal course, and a successful outcome. No infants became

infected by vertical transmission or during delivery.

Conclusion: No evidence to suggest the potential risk of intrauterine vertical transmission in the case series and further in-depth study is needed. Both the pregnancy woman and infant showed fewer adverse maternal and neonatal outcomes.

Key words pregnancy, neonate, COVID-19, SARS-CoV-2, vertical transmission

Introduction

An outbreak of respiratory illness, named coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in late 2019, resulting in tens of thousands of confirmed cases in China, with additional cases identified in a growing number of other countries[1-3].

The whole population is thought susceptible to SARS-CoV-2 and it is suspected that pregnant women are likely to be at increased risk of severe infections, with the potential for adverse maternal and perinatal outcomes.[4] This concern is based on experience of the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), caused by related coronaviruses, which were found to be associated with worse outcome during pregnancy. [5-8] There are no previous reports suggesting mother to child transmission of infections caused by the coronavirus family, but at present this is still unknown for SARS-CoV-2. The reports regarding the clinical characteristics of COVID-19 in pregnancy are limited. Two recent publications by Chen et al. and Zhu et al. describing COVID-19 in pregnancy observed few adverse outcomes, with no evidence for vertical transmission currently.[9 10] Herein, we report three pregnant patients who acquired the infection during the last trimester in Wuhan, with a longer period of clinical observation and outcomes described in the mothers and their newborn infants.

Materials and Methods

Study Design and Sources of Cases

Between February 2, 2020 and February 5, 2020, three women in late pregnancy diagnosed with COVID-19 according to New Coronavirus Pneumonia Prevention and Control Program (Trail 5th edition) published by the National Health Commission of China[11] enrolled in the obstetric ward of Tongji Hospital, a tertiary hospital in Wuhan. No cases were missed during this period. Informed consent was obtained from each pregnant woman. For the newborn infant, proxy oral informed consent was provided by a parent or legal guardian. The case series study was approved by the institutional ethics board of Tongji Hospital affiliated to Huazhong University of science and technology (Approval Number TJ-C2030).

Procedures and data collection

We reviewed the perinatal demographic, clinical, laboratory and radiological data from the participants electronic medical records. Data available included detailed information of clinical presentation, obstetric management and complications, investigations, treatments and maternal and neonatal outcomes. Additional epidemiological data were obtained through telephone interviews with participants and their families. If data were missing or unclear from the medical records, we obtained data by direct communication with attending doctors. The clinical outcomes were followed up to Feb 13, 2020. The data were reviewed by a trained team of obstetricians and clinical laboratory doctors. The

disease onset date was defined as the day when the symptom related to COVID-19 was noticed.

Diagnostic testing for SARS-CoV-2

Oropharyngeal swab specimens were collected from mothers and their neonates. After collection, swabs were placed in viral transport medium. Specimens were stored between 2°C and 8°C until testing. Total RNA was extracted using automated Nucleic Acid Extraction System 9600E (Xi'an TianLong Science and Technology Co., Ltd., Xi'an, China). Real-time reverse transcription polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 was performed using a SARS-CoV-2 ORF1ab/N gene detection kit (Shanghai Huirui Biotechnology Co.,Ltd, Shanghai, China), a product based on the recommendation of the National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention (http://ivdc.chinacdc.cn/kyjz/202001/t20200121_211337.html). Open reading frame 1ab gene (ORF1ab) and nucleocapsid gene (N) were amplified and tested using the following primers and probes: ORF1ab forward primer 5'-CCCTGTGGGTTTTACACTTAA-3', ORF1ab reverse primer 5'-ACGATTGTGCATCAGCTGA-3', ORF1ab probe 5'-FAM-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3', N forward primer 5'-GGGGAACTTCTCCTGCTAGAAT-3', N reverse primer 5'-CAGACATTTTGCTCTCAAGCTG-3', N probe 5'-ROX-TTGCTGCTGCTTGACAGATT-TAMRA-3'. Five μL of RNA solution was added into the 20 μL reaction mixture.

Real-time RT-PCR was performed using the following cycling parameters: reverse transcription at 50 °C for 15 minutes, denaturation at 95 °C for 5 minutes, 45 cycles of denaturation at 94 °C for 10 seconds and extension at 55 °C for 45 seconds, fluorescence was measured in each cycle. A negative real-time RT-PCR result was defined as undetectable or a cycle threshold value (Ct-value) of >= 39.2, a positive result was defined as a Ct-value <35. Results were reported positive when both ORF1ab gene and N gene tested to be positive. Specimens tested as Ct-value of >=35 and <39.2 were retested for confirmation, a retest Ct-value of <39.2 was treated as positive, otherwise negative.

Results

Between the 2nd and 5th February 2020, the obstetrics ward admitted a total of 17 pregnant women, of which three (17.6%) were diagnosed with COVID-19. All the three patients were from Wuhan city. The patient's ages ranged from 30 to 34 years. All three pregnancies were infected in the third trimester and delivered at term. The newborn infants survived and were uninfected. The three patients had previously been cared for in different obstetric wards during the same period. All the Healthcare Personnel (HCP) in the obstetric and newborn infant wards used appropriate personal protective equipment (PPE) according to current guidance[12].

Patient 1 and Newborn infant 1

Patient 1 was a 34-year-old woman (gravida 2, para 0) with a history of

hypothyroidism for 4 years and epiglottic cysts. The potential exposure to SARS-CoV-2 reported was a visit to Wuhan Children's hospital for a routine examination on Jan. 27, 2020. She reported the initial onset of fever (37.8℃) on 1st February 2020 (40 weeks gestational age), eight hours before presentation to the obstetric ward in Tongji hospital on 2nd February 2020.

A systematic testing procedure for SARS-CoV-2 infection was used, including computed tomography (CT) of the chest and serial RT-PCR assays. On admission chest auscultation was normal, however chest CT revealed bilateral infiltrates, worse on the left, including involvement of the upper lobe of left lung, localized emphysema in the right lower lobe and a few linear fibrotic changes in the middle lobe of the right lung (figure 1). Repeat CT scans of the chest, performed on 8th February (eight days after onset) and 13th February (13 days after onset), showed progression of the changes compared with the previous study (Figure 1). A positive result for SARS-CoV-2 PCR performed on an oropharyngeal swab was obtained on 2nd February. Subsequent RT-PCR assays on oropharyngeal swab specimens were positive on 5th February, and turned negative on the 7th and 9th February. SARS-CoV-2 RT-PCR tests were performed on breast milk, placenta, and vaginal mucus from the 2nd February 2 to 12th February and all results were negative. A positive result for SARS-CoV-2 PCR performed on faeces was obtained on 7th February and was negative on 12th February (on an anal swab). A respiratory sputum specimen was obtained from her husband tested negative for SARS-CoV-2 by RT-PCR on 2nd February.

A 3,250 g male newborn was delivered by cesarean delivery on 2nd February (gestational age 40 weeks). There was evidence of meconium staining of the embryonic membranes. Apgar scores at 1 and 5 minutes were 8 and 9, respectively. After delivery, the infant was immediately moved to a sealed incubator with a separate air exchange system in the neonatal ward and received initial care from HCP completely protected according to the current PPE guidelines[12]. Efforts were made during delivery to minimize and exposure to maternal blood and neonate washing was conducted in neonate ward. The infant was not breast fed. The neonate presented chronic fetal distress in utero, chorioamnionitis and Meconium Stained Amniotic Fluid (MSAF). All of the following samples of newborn tested negative for SARS-CoV-2 PCR: umbilical cord blood, plasma serum and whole blood collected at 34min after birth, oropharyngeal swab collected on one day after delivery. The clinical details of mother and infant 1 are summarised in Table 1 and Figure 2.

The patient was transferred back to the maternity ward after delivery. Oxygen therapy, antiviral, antibiotics and anti-inflammatory treatment were administered. The antiviral therapy including: atomized inhalation of interferon (40μg, bid) and ganciclovir (0.25g, IV). She did not require ventilatory support.

Patient 2 and Newborn infant 2

Patient 2 was a 34-year-old woman (gravida 3, para 1) with no history of underlying medical conditions. The potential exposure to SARS-CoV-2 reported was a stay in BAIJIA maternity hospital in Wuhan for a routine obstetric

examination from 25th to 26th January 2020. No other exposure to SARS-CoV-2 was identified and she had consistently worn a mask for protection. Her family members reported no respiratory symptoms. She reported the initial onset of fever on 30th January 2020 (37 weeks gestational age). She visited the outpatient department of Tongji Hospital on 30th January and was admitted to the obstetric ward on 5th February 2020.

A systematic assessment for SARS-CoV-2 infection was conducted similar to patient 1. CT of the chest was performed on 30th January and showed bilateral ground glass opacity (GGO), consolidation, nodules in the left lower lobe and patchy consolidation in the right middle lobe. A repeat chest CT scan, performed on 13th February (15 days after onset), showed progression of the changes compared with the previous study (Figure 1). An oropharyngeal specimen collected on admission (5th February 2020, seven days after illness onset, one day before delivery) tested positive for SARS-CoV-2 by RT-PCR with a CT value of 28, and was negative on 13th February.

The patient returned to the maternity ward after delivery. Oxygen therapy, antibiotic and anti-inflammatory treatment were used. Oral Arbidol hydrochloride (a broad-spectrum antiviral compound that blocks viral fusion) was administered (3g, qd). She did not require ventilator support.

A 3,250g female newborn was delivered by cesarean delivery on 6th February (gestational age 38+4 weeks). Apgar scores at 1 and 5 minutes were 8 and 9, respectively. After delivery, the biosafety protection and medical care was the

same as Infant 1 and neonate washing was conducted in neonatal ward. The newborn showed slightly decreased responsiveness and muscle tone, which recovered by 7th February. SARS-CoV-2 RT-PCR tests were performed on oropharyngeal swabs, serum, whole blood, urine and faeces collected 27 minutes after birth and all results were negative. Subsequent RT-PCR assays on oropharyngeal swab, urine and faeces were again negative from 7th through 13th February. The clinical details of mother and infant 2 are shown in Table 1 and Figure 2.

Patient 3 and Newborn infant 3

Patient 3 was a 30-year-old woman (gravida 3, para 1) with a history of gestational hypertension during her first pregnancy. The potential exposure to SARS-CoV-2 was she reported a visit to Tongji hospital for a routine obstetric examination on 20th Jauary 2020. No other exposure to SARS-CoV-2 was identified and she consistently wore a mask for protection. Her family members reported no respiratory symptoms. She reported the initial onset of cough on 25th January 2020 (37 weeks gestational age). She was admitted to the obstetric ward on 5th February 2020.

The assessment for SARS-CoV-2 infection (similar to patient 1 and 2) showed GGO, subsolid patchy and linear fibrosis in the left lung, increased mediastinal small lymph nodes on a chest CT scan performed on admission. A further chest CT scan was performed on 10th February (16 days after onset) showed improvement compared with the previous imaging (Figure 1). The SARS-CoV-2

RT-PCR performed on an oropharyngeal swab specimen gave a positive result on 6th February. Follow up oropharyngeal swab specimens were collected and tested positive on 10th February but turned negative on 11th February. SARS-CoV-2 RT-PCR was performed on breast milk, anal swab, and vaginal mucus on 11th February, and all results were negative.

A 3,670g female newborn was delivered by vaginal delivery based on maternal request on 9th February. Apgar scores at 1 and 5 minutes were 8 and 9, respectively. After delivery, the biosafety protection and medical care was the same as Infant 1 and 2, and neonate was washed in the neonatal ward. SARS-CoV-2 RT-PCR tests were performed on oropharyngeal swabs, plasma, whole blood, urine and faeces from 10th and 11th February and all results were negative. Detailed information of mother and infant 3 is shown in Table 1 and Figure 2.

The patient was transferred back to the maternity ward after delivery. Oxygen and antiviral therapy (Arbidol hydrochloride 3g, qid orally) were administered. She did not require ventilator support.

Comment

Principal findings

We report three patients with confirmed SARS-CoV-2 infection during the 3rd trimester of pregnancy living in Wuhan. The patients showed an uneventful perinatal course, and successful outcomes. No infants became infected by vertical transmission or during delivery. Serial specimens collected from the newborn

infants at different time points after birth were all negative for SARS-CoV-2 by RT-PCR.

Our patients initially presented with mild symptoms, only fever or cough, and all showed chest CT abnormalities during infection. There was progression of CT abnormalities in two patients (patient 1 and 2), and improvement in the CT appearance of patient 3 on the 16th day of illness.

Results in context

There are limited data concerning the clinical features and impact of SARS-CoV-2 infection during pregnancy and the perinatal outcome of patients diagnosed with COVID-19.

One of the infants in our study showed Meconium Stained Amniotic Fluid (MSAF), but all outcomes were good. However, Zhu and colleagues[10], reported 6 out of 10 neonates born pre-term, and Chen et al[9], who reported 6 out of 9 neonates born preterm. In the study of Zhu et al a number of whom experienced significant complications, and one died. Therefore evidence is building that COVID-19 pregnancy is not without risk, albeit less serious than SARS, in which adverse outcomes were reported for 10 of 12 pregnancies, including 4 first trimester miscarriages.[5] To date, all affected mothers with COVID-19 have recovered.[9 10]

Research implications

The overall impact and long-term prognosis of SARS-CoV-2 on pregnancy and neonatal outcomes needs further evaluation. The possibility of intrauterine

vertical transmission of SARS-CoV-2 requires in-depth investigation including placental histopathology and PCR to look for SARS-CoV-2. Moreover, a prospective study of COVID-19 in pregnant women in from early pregnancy, to evaluate the potential for vertical transmission is urgently needed.

Strengths and limitations of the study

In this case series, which we believe has performed the most comprehensive testing for SARS-CoV-2 in pregnancy and in newborns, we find no evidence to support the vertical transmission of SARS-CoV-2. The conclusions of this study are consistent with the finding the two previous studies on COVID-19 infection in pregnancy women [9 10] and with observations in SARS. Two neonates with COVID-19 have been reported, but in each case infection after birth cannot be excluded.[13]

Importantly, we and others have now shown that it is possible to provide care for SARS-CoV-2 infected mothers during late pregnancy and both caesarean and vaginal birth without adverse outcomes for the mother, infant and healthcare staff. This information will benefit those planning care for non-infection related medical interventions in patients who may be infected with SARS-CoV-2. It should be noted, however, that we only report three mother-infant dyads, all of whom were not severely affected and did not have any evidence of virus detectable in blood.

This study has several limitations. First, due to the limited sample size of study subjects, only a limited number of intrauterine specimens were obtained

during labor. Second, we retrospectively evaluated the clinical data collected from both patients and newborns.

Conclusion

Despite the lack of evidence of intrauterine vertical transmission, infections that can occur during vaginal delivery are worthy of concern. Therefore, clinicians should remain vigilant for potential vertical transmission events of SARS-CoV-2 during late pregnancy or delivery. The approach of medical protection of newborns after birth is successful and needs further strengthening, including use of personal protection precautions to reduce the risk of transmission.

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Weiyong Liu, Mr. Bo Zhang and Dr. Yanjun Lu did the laboratory tests.

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Table 1 Demographics, Clinical characteristics, Treatment and Laboratory Findings of Three Pregnant Women and Newborn Infant

Subject No.	1	2	3
Pregnant Women			
Demographics, obstetric characteristics, and clinical outcomes			
Age (Years)	34	34	30
Occupation	Employee	Self-employed	Self-employed
Underlying comorbidities	Hypothyroidism for 4 years / Epiglottic cysts	None	Gestational diabetes
Other medical histories during pregnancy	None	Scarred uterus / Accreta placenta	None
Gravidity	2	3	3
Parity	0	1	1
History of abortion	Yes	Yes	Yes
Start of pregnancy	Apr.29, 2019	May.11, 2019	May.7, 2019
Date of delivery	Feb. 2, 2020	Feb. 6, 2020	Feb. 5, 2020
End of pregnancy, gestational age, Week/trimester	40/third	38+4/third	39+5/third
Delivery details	Cesarean delivery at term	Cesarean delivery at term	Vaginal delivery at term
Indication of cesarean delivery	COVID-19	COVID-19	
Intrauterine fetal distress	Yes	No	No
Embryonic membrane	Thickening / Stained yellow	Normal	Normal
Maternal outcome	Remained in hospital	Remained in hospital	Remained in hospital
Fetal outcome	Survived / Chronic fetal distress in utero/ Chorioamnionitis	Survived	Survived
Clinical characteristics and treatment			

Signs and symptoms at admission			
Fever	Yes	Yes	No
Cough	No	Yes	Yes
Temperature (℃)	37.8	38.0	37.0
Onset to hospitalization (Day)	1	6	10
Gestational age at illness onset (Week)	40	37	37
Chest CT findings			
CT evidence of pneumonia	Yes	Yes	Yes
Unilateral pneumonia	No	No	Yes
Bilateral pneumonia	Yes	Yes	No
Treatment			
Oxygen therapy	Yes	Yes	Yes
Antiviral treatment	Yes	Yes	Yes
Ganciclovir	Yes	No	No
Abedore hydrochloride	No	Yes	Yes
Interferon	Yes	No	No
Antibiotic treatment	Yes	Yes	No
Glucocorticoids	Yes	Yes	No
Laboratory results			
Blood routine			
Leucocytes (× 10^9 per L; normal range 3.5–9.5)	**11.96**	**10.17**	7.63
Neutrophils (× 10^9 per L; normal range 1.8–6.3)	**9.97**	**8.25**	5.54
Lymphocytes (× 10^9 per L; normal range 1.1–3.2)	**11.50**	1.41	1.7
Eosinophils (× 10^9 per L; normal range 0.02–0.5)	0.00	**0.01**	0.04
Basophil (× 10^9 per L; normal range 0.00–0.1)	0.01	0.01	0.1
Platelets (× 10^9 per L; normal range 125.0–350.0)	**81.00**	152	
Haemoglobin (g/L; normal range 115.0–150.0)	129.00	145	114
Blood biochemistry			

Albumin (g/L; normal range 40.0–55.0)	**32.2**	**36**	**32.5**
Alanine aminotransferase (U/L; normal range 0.0–33.0)	6.5	14	9
Aspartate aminotransferase (U/L; normal range 0.0–32.0)	25.7	22.1	14
Infection-related biomarkers			
Procalcitonin (ng/mL; normal range 0.02–0.05)	0.03	**0.07**	NA
C-reactive protein (mg/L; normal range 0.0–1.0)	NA	**11.5**	**14.7**
Interleukin-6 (pg/mL; normal range 0.0–7.0)	**44.18**	**43.72**	NA
Erythrocyte sedimentation rate (mm/h; normal range 0.0–20.0)	26	NA	NA
Serum ferritin (ng/mL; normal range 15.0–150.0)	151.9	NA	21.1
Newborn Infant			
Demographics			
Gender	Male	Female	Male
Gestational age (Weeks)	40	38+4	39+5
No. of embryo	Singleton	Singleton	Singleton
Birthweight (g)	3250	3250	3670
1 min Apagr score	8	8	8
5 min Apagr score	9	9	9
Clinical characteristics	Meconium Stained Amniotic Fluid (MSAF)	Slight decreased responsiveness and muscle tension	None
Laboratory results			
Leucocytes (× 10^9 per L; normal range 5–20)	13.24	**22.19**	18
Neutrophils (× 10^9 per L; normal range 2–10)	**9.52**	**16.4**	**11.7**
Lymphocytes (× 10^9 per L; normal range 3–8)	2.43	3.31	3.8
Eosinophils (× 10^9 per L; normal range 0.2–2)	0.11	0.35	0.88
Basophil (× 10^9 per L; normal range 0.0–0.2)	0.01	**0.2**	0.1
Platelets (× 10^9 per L; normal range 150.0–300.0)	218	137	208
Haemoglobin (g/L; normal range 148.0–190.0)	**160**	**158**	195

Blood biochemistry			
Albumin (g/L; normal range 38.0–54.0)	38.3	32.6	32.1
Alanine aminotransferase (U/L; normal range 0.0–41.0)	11	18	24
Aspartate aminotransferase (U/L; normal range 0.0–40.0)	143	28	**150**
Infection-related biomarkers			
Procalcitonin (ng/mL; normal range 0.0–5.0)	NA	0.23	0.33
C-reactive protein (mg/L; normal range 0.0–5.0)	< 0.5	< 0.1	NA

Abbreviations: NA, not available; COVID-19, 2019 novel coronavirus disease; Abnormal value are of laboratory results are highlighted in bold.

Figure legend

Figure 1. Chest CT images of three patients who diagnosed with SARS-CoV-2 infection.

A: Patient 1 at two days after illness onset (A1) and eight days after onset (A2). CT images show infiltrates and linear fibrosis. A2 showed progressive abnormality compared to A1.

B: Patient 2 on the illness onset (B1) and 15 days after onset (B2). CT images shows GGO, patchy consolidation, pleural effusion. B2 showed progressive abnormality compared to B1.

C: Patient 3 at 11 days after illness onset (C1) and 16 days after illness onset (C2). CT images show GGO, subsolid patch and linear fibrosis. C2 showed absorption and improvement compared to C1.

Figure 2. Timeline of symptoms, clinical events, CT scan and laboratory test according to day of illness.

(A) Patient 1and her newborn; (B) Patient 2 and her newborn; (C) Patient 3 and her newborn.

Figure 1

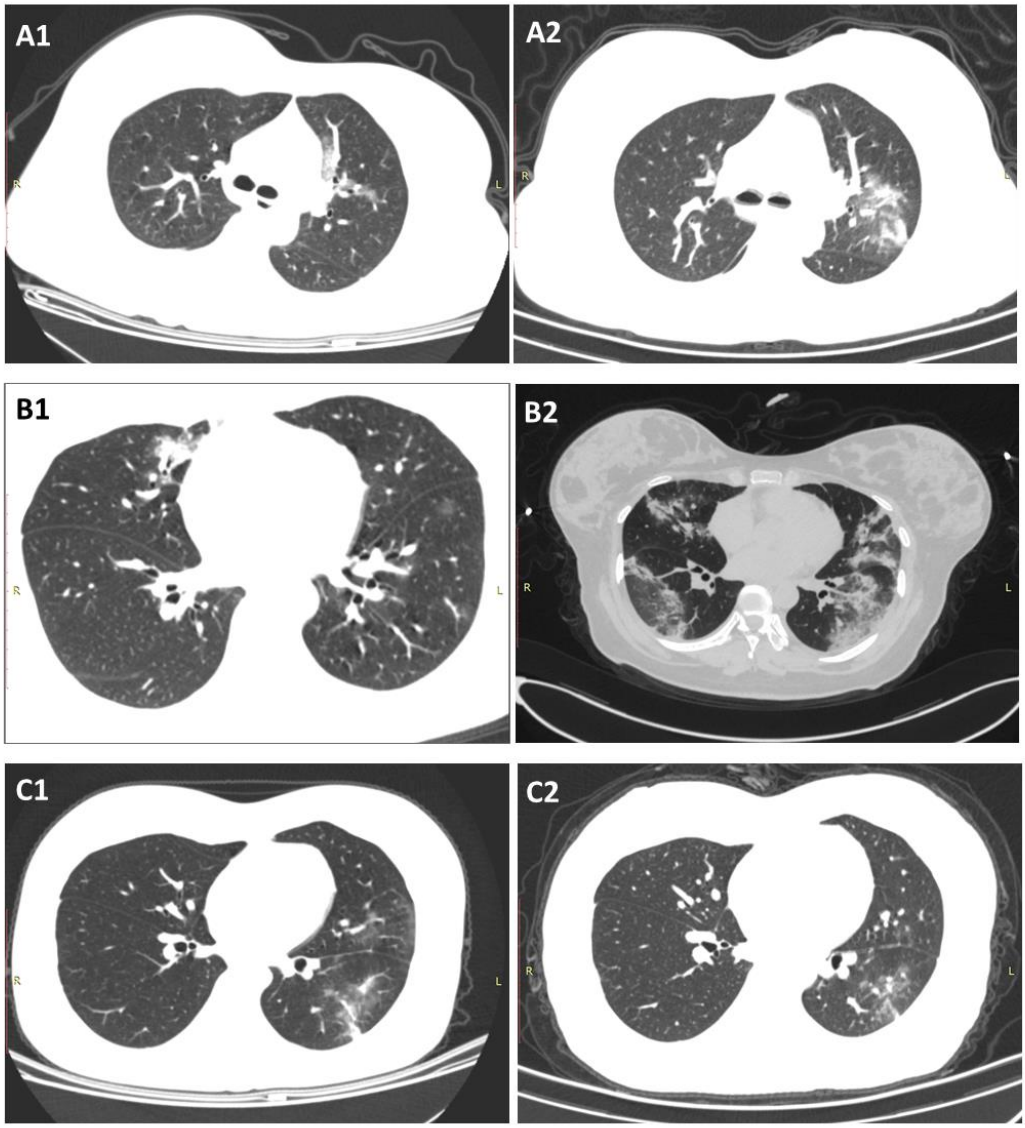

Figure 2