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Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings

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ABSTRACT

This report highlights details on a pregnant case of COVID-19 who unfortunately did not survive. This 27-year-old woman at her 30 and 3/7 weeks' gestation was referred to our center with fever, myalgia, and cough. The laboratory investigations showed leukopenia and lymphopenia as well as increased creatinine and CRP levels. The first chest X-ray (faint bilateral patchy opacities) and CT scan (some faint subpleural ground-glass opacities associated with pleural thickening) were not typical for initial COVID-19 pulmonary infection, however, the treatment for COVID-19 was started. Due to respiratory distress, she was intubated and put under mechanical ventilation. After a while, the fetus was born with Apgar score of 0 and did not react to the neonatal cardio-pulmonary resuscitation protocol. Finally, due to deterioration in the clinical and imaging findings, the patient was expired as a result of multi-organ failure. Following the death, autopsy was performed and the histo-pathologic evaluations of the lungs showed evidence of viral pneumonia (viral cytopathic effect and a mild increase in alveolar wall thickness) and ARDS (hyaline membrane). Also, reverse transcription-polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection in the lungs. To our knowledge, this is the first report of maternal death with confirmed COVID-19 infection.

1. Introduction

In December 2019, an outbreak caused by a new coronavirus was started in Wuhan, Hubei province of China that led to a pandemic emergence according to the World Health Organization (WHO) on March 11, 2020 [1]. According to the phylogenetic studies, the pathogen was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease was called coronavirus disease 2019 (COVID-19). Reports have shown different signs among the patients with COVID-19 among which fever and cough were most common [2]. According to the data, several clinical outcomes such as sepsis, respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, coagulopathy, acute cardiac injury, and acute kidney injury are significantly (all P-values < 0.0001) higher in non-survivor patients compared to survivors. Thus, these outcomes have been suggested to be monitored more cautiously among the admitted patients [3]. So far, few reports have provided information on the clinical and imaging follow up of pregnant patients with COVID-19. Although, no mortality has been reported among their patients [4–6].

Herein, we report a pregnant patient diagnosed with COVID-19 who, unfortunately, did not survive. This report is going to address the data from admission until after the autopsy.

2. Case presentation

A 27-year-old woman at 30 and 3/7 weeks (gravida 2, para 1-0-0-1 [1 delivery, 0 premature delivery, 0 abortion, and 1 living child]) of pregnancy suffering respiratory distress was referred to our hospital

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Table 1
Laboratory results of the patient during hospitalization.

	Day 1, 8 PM	Day 2, 2 AM	Day 2, 10 AM	Day 2, 9 PM	Day 3, 9 AM
Leukocytes × 10^9/L	3	5.4	7.3	7.4	13.5
Lymphocytes, %	7.2	6.9	6	14.9	22.1
Neutrophils, %	91.9	89.2	92.8	82.8	70
Platelets × 10^9/micL	40	29	22	39	67
Hemoglobin, gr/dL	9.9	10.4	8.6	8.9	10.3
ESR, mm/h	54	N/A	N/A	N/A	34
CRP, mg/L	31	N/A	N/A	N/A	83
Creatinine, mg/dL	0.7	N/A	1.6	N/A	2.8
BUN mg/dL	17.5	22.8	N/A	N/A	41.1
Na, mEq/L	139	137	N/A	N/A	136
Ka, mEq/L	3.7	3.6	N/A	N/A	3.7
Protein (U/A)	2^+	2^+	N/A	N/A	N/A
Blood (U/A)	2^+	2^+	N/A	N/A	N/A
WBCs, hpf (U/A)	10–12	10–12	N/A	N/A	N/A
RBCs, hpf (U/A)	Many	Many	N/A	N/A	N/A
Albumin, g/L	3.1	N/A	N/A	N/A	N/A
AST, U/L	52	N/A	N/A	N/A	N/A
ALT, U/L	68	N/A	N/A	N/A	N/A
LDH, U/L	727	N/A	N/A	N/A	923
D-Dimer (μg/mL)	> 10,000	N/A	N/A	N/A	N/A
CPK U/L	N/A	N/A	N/A	N/A	371
CK-MB U/L	N/A	N/A	N/A	N/A	13
PT, seconds	14	15	16.5	N/A	13
PTT, seconds	69	54	41	N/A	33

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase; CPK: Creatine phosphokinase; CK-MB: Creatine kinase-MB PT: Pro-thrombin time; PTT: Partial thromboplastin time.

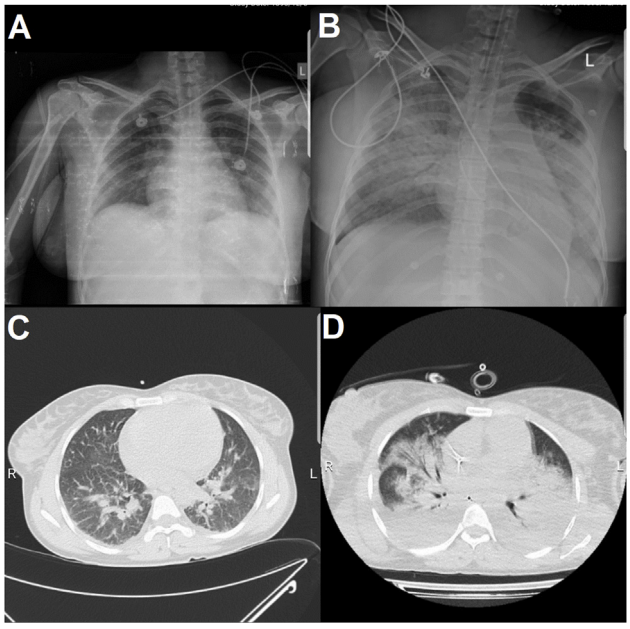

Fig. 1. Imaging finding of the patient. A and B: Anteroposterior chest X-ray of the patient at; A: the first hospital which shows faint bilateral patchy opacities. B: after intubation which shows bilateral central opacities. C and D: Chest CT scan (Lung window) of the patient; C: in the first hospital which shows faint subpleural ground-glass opacities and mild pleural thickening. D: after intubation which shows bilateral central consolidation and pleural effusion.

from a maternity hospital due to fever, cough, and myalgia for 3 days. The patient had no underlying disease and declared no specific issue in her medication and family history (occupation: housekeeper). She noted no contact with anyone diagnosed with COVID-19 as well as no recent travel history (inside or outside of Iran) in the past two weeks. All the previous pregnancy scheduled screening tests had been performed to the date and all were normal. As mentioned in the maternity hospital summery sheet, early examinations showed respiratory rate (RR) = 34/min, heart rate (HR) = 110/min, body temperature (BT) = 39 °C, blood pressure (BP) = 100/60 mmHg, O_2 saturation = 93%, and fetal heart rate (FHR) = 170/min. Also, it was noted on the summery sheet that patient had received oseltamivir, azithromycin, and ceftriaxone for less than 24 h. Also, results of vaginal examination and fern test stated to be normal by the maternity hospital. Due to tachypnea, she was transferred to the intensive care unit (ICU) and some laboratory tests were requested (Table 1). Also, a chest X-ray (Fig. 1-A) was performed that showed faint bilateral patchy opacities. Considering the CXR findings, azithromycin, oseltamivir, and ceftazidime were started for the patient. Also, based on the CXR findings and after confirming with her gynecologist, a computed tomography (CT) scan was performed (using abdominal shield) which revealed faint subpleural ground-glass opacities as well as pleural thickening (Fig. 1-*C*). According to the published data to that date, the mentioned findings were not completely in concordance with COIVD-19 [3,7–9]. However, due to the abnormal imaging findings, the patient was transferred to our center. At the first moment of arrival, she seemed ill and toxic and her examinations showed RR = 37/min, HR = 130/min, the BT = 39.5 °C, BP = 135/85 mmHg, and O_2 saturation = 92% (pulse oximetry). She was immediately transferred to the ICU and a full laboratory test was requested (Table 1) which most importantly showed leukopenia and thrombocytopenia accompanied with elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels. Soon after, the fever increased up to 40 °C and RR to 55/min accompanied by suprasternal and intercostal retraction. Immediate blood tests showed metabolic alkalosis while the patient was under non-invasive ventilation. Finally, she was intubated and put under mechanical ventilation (Mode: SIMV(VC) + PSV, FiO_2: 100%, rate 18/min, VT: 350 ml, and O_2 saturation 85%). Following another portable CXR, infectious service consult, and suspicion of COVID-19, oseltamivir, lopinavir/ritonavir, hydroxychloroquine, meropenem, and vancomycin were started (azithromycin and ceftazidime were discontinued in our center). The bedside trans-thoracic echocardiography was ordered which results showed severe right ventricle and atrium enlargement, severe right side systolic dysfunction, and tricuspid valve regurgitation (systolic pulmonary artery pressure = 70 mmHg), with an ejection fraction (EF) ratio of 50% (other issues were not notable). Also, an hour after intubation, BP was decreased to (80/60 mmHg) for which, 5 mcg/kg/min of epinephrine drip was started until BP raised up to 100/60 mmHg. On the early morning next day, the nurses reported body movement under sedation and then following spontaneous contractions, a cyanotic fetus was delivered vaginally with Apgar score of 0 (first and 5th minute of the birth). This score did not change after neonatal cardiopulmonary resuscitation (CPR). Following NVD, O_2 saturation was increased up to 90%; so, another CXR was requested that showed alveolar infiltration as bilateral patchy opacities (Fig. 1-B). Following the findings of the new CXR and since the clinical status of the patient was improved, another CT scan was requested for her which illustrated bilateral central consolidation and pleural effusion as new signs. Accordingly, possible ARDS or alveolar hemorrhages were suspected (Fig. 1-*D*). However, regarding the nonspecific findings on the CT scan such as the presence of bilateral pleural effusion (Fig. 1-*D*), increased Cr levels and proteinuria (Table 1), thrombocytopenia (Table 1), and evidence of alveolar hemorrhage (bloody mucosal secretions, one session, in the theracheal tube 12 h after intubation, probably due to either alveolar hemorrhage or intubation trauma accompanied with coagulation disorder), our internal medicine team suspected an acute collagen vascular autoimmune disease. Thus, the patient received corticosteroid pulse (methylprednisolone: 1gr) and a single session of emergent plasmapheresis with replacement of 2 L fresh frozen plasma. Following these actions, both neutrophil (count) and lymphocyte (count and ratio) were increased. Although, around afternoon, BP was decreased again and despite 40 mcg/kg/min epinephrine, the systolic pressure did not exceed

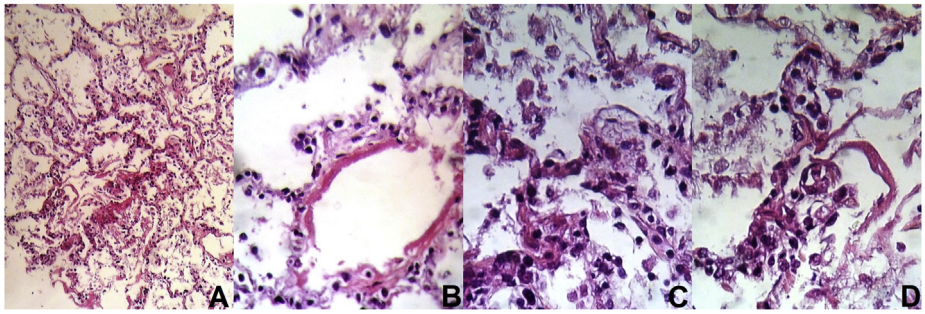

Fig. 2. A: Alveolar tissue showing mild increased wall thickness on low power. B: Hyaline membrane noted consistent with acute respiratory distress syndrome. C and D: Viral cytopathic effect seen (C and D).

90–100 mmHg. After several hours, O_2 saturation was decreased (70–75%) which, despite following all ARDS protocols, did not reach higher than 75% and unfortunately, the patient passed away due to multi-organ failure (ARDS, acute kidney injury, and septic shock).

Based on the atypical presentations, the patient underwent sample collection for real-time reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS-COVID-2 which was confirmative for COVID-19. Also, she underwent autopsy of lungs. The histologic findings of paraffin embedded lung tissue showed alveolar spaces with focal hyaline membrane, pneumocyte proliferation, and metaplastic changes. Also, viral cytopathic effect including multinucleation and nuclear atypia were noted. The most inflammatory cells present in the background were mononuclear cells composed of lymphocytes and macrophages (Fig. 2).

3. Discussion

Since 2000, two other outbreaks of coronaviruses have occurred other than COVID-19: Severe Acute Respiratory Syndrome (SARS) [10] and Middle East Respiratory Syndrome (MERS) [11]. Through the evaluations performed in the previous coronavirus outbreaks (SARS and MERS), pregnant women have been shown to be at increased risk of mortality, spontaneous miscarriage, preterm parturition, and intrauterine growth restriction. As it has been evaluated, the fatality rate of SARS and MERS among pregnant patients was 25% and 40%, respectively [10,11]. To our knowledge, this case is the first maternal death reported for pregnant patients diagnosed with COVID-19 so far. However, some studies have evaluated pregnancy outcomes of COVID-19.

Herein, we reported a case of COVID-19 in her late pregnancy who expressed atypical presentations in the mentioned imaging modalities. According to the released data to that date and considering the imaging findings on COVID-19 patients, results belonging to this patient were nonspecific for early stages of COVID -19 pneumonia. In the first CT scan, we found some small patchy ground glass opacities with subpleural distribution. Regarding the early initiation epidemic of COVID-19 in Iran, we decided to consider COVID-19 pneumonia as the main diagnosis. However, we also noticed a bilateral pleural thickening in the CT scan. As it has been mentioned, pleural effusion or thickening might be detected in the subacute phase of the disease but not on initial investigations [9,12]. Although, regarding the clinical findings as well as patchy ground-glass opacities in CT scan, the patient received the antiviral therapy.

An early study mentioned that the mean time from onset to ICU admission and mechanical ventilation was about 10.5 days [13]. However, unfortunately, a rapid progression to consolidative opacities and pleural effusion occurred in our patient that only took 30 h. Due to the worsening of results from clinical and imaging findings, it seems that the patient could be considered a “radiographic deterioration” as Shi et al. have presented [9]. Some studies have mentioned pleural effusion as a pertinent negative finding [12]; although, in some other studies, trace amounts or mild pleural effusion in the course of the disease has been noted in some patients [9,14,15]. Our patient, on the other hand, had moderate amount of pleural effusion which could have been attributed to the worsening of pulmonary involvement. Regarding the released radiologic findings on COVID-19 by the time our patient exhibited (especially about the presence of pleural effusion) and considering her fever, thrombocytopenia, proteinuria, suspicious bloody mucosal secretions, it was not easy to rule out serositis as one of the criteria of the collagen vascular disease for our internal team.

An early study has evaluated the outcome of nine pregnant patients with COVID-19 without any specific underlying diagnosed diseases (all gestational ages $\geq$36 weeks). Among them, 78%, 44%, 33% and 11% had fever (on admission), cough, myalgia, and dyspnea, respectively. Our patient on the other hand, presented all these symptoms at the same time. In laboratory investigations, they found that none of their patients had leukopenia while 56% of them had only lymphopenia ($< 10^9$ cells/L). Also, elevated CRP, aspartate aminotransferase (AST)/alanine aminotransferase (ALT), and positive RT-PCR for SARS-CoV-2 were observed in 75%, 33%, and 100%, respectively. No IUFD, stillbirth, severe neonatal asphyxia or maternal mortality was observed. However, in neonatal outcomes, 44% and 22% were preterm and had low birthweight, respectively. Among the nine reported cases, 89% of them had typical signs of viral infection and only one presented “right-sided subpleural patchy consolidation”. This patient was a 29-year-old woman in her 36 week of gestation with fever, caught, and myalgia for three days. In the laboratory tests, she had leukocytosis and lymphopenia at the same time. Also, her CRP level was stated to be missing data. She underwent a C-section and this premature delivery led to a birthweight of 2460 gr (low birthweight) [6].

Another study evaluated 13 pregnant patients (two cases < and 11 cases$\geq$ 28 week of gestation) diagnosed with COVID-19. They claimed the most common presentation among them to be fever (77%). Of these 13 patients, 23% were discharged before labor and they continued their pregnancy normally. On the other hand, 77% undergone cesarean section due to several reasons including fetal distress (3/10), premature rupture of the membrane or PROM (1/10), and stillbirth (1/10). Also, preterm labor was observed in 46% of all patients. One patient faced different complications such as multiple organ dysfunction. Due to the ARDS, she was intubated and put under mechanical ventilation in ICU. Also, she was diagnosed with acute kidney injury, acute hepatic failure, and septic shock. It is noteworthy to mention that this patient also had a stillbirth and according to the authors’ statement, “Patient 6 was still in the support of Extracorporeal Membrane Oxygenation” (unavailable in our center) and no further information was given on the outcome of this patient [16].

Also, a study has evaluated the risk factors related to the mortality among survivor and non-survivor patients diagnosed with COVID-19. Authors have stated that sepsis, respiratory failure, ARDS, heart failure, septic shock, coagulopathy, acute cardiac injury, and acute kidney injury were significantly higher (p-values < 0.00001) in non-survivors compared to those discharged. Also, they have shown that the

administration of corticosteroids in non-survivors was significantly higher than in survivor group. However, some other findings in their study such as non-invasive mechanical ventilation, high-flow nasal cannula oxygen therapy, and invasive mechanical ventilation were also significantly higher in non-survivors compared to the survivors (p-values < 0.00001). It is clear that taking these actions are all necessary in critically ill patients with COVID-19 and doesn't represent the worse outcome due to their action [3].

Taken together, there is not enough published evidence on COVID-19 (especially in pregnant patients) which help us to find the exact cause of death in this patient. Although, we have discussed the prominent findings of the patient (such as leukopenia, lymphopenia, elevated CRP, atypical imaging findings, and multi-organ failure) which have been known to associate with mortality in other published articles [3]. Regarding the treatment plan, the only treatment which has been mentioned to relate to mortality was corticosteroids which data has been published only after our patient received this drug. Although the low-dose corticosteroid therapy was a part of treatment strategy in our country, the intention beyond this treatment for the case was the clinical suspicion of a collagen-vascular disease. Altogether, considering the multi-organ failure, it is difficult to identify the definite cause(s) of death in this case and it needs more investigations in such cases.

4. Conclusion

As far as we know, no case of pregnancy mortality due to COVID-19 has been reported to this date. This patient was referred to our center with atypical presentations of the disease in imaging modalities. This case with the mentioned clinical, imaging, and laboratory data was the first report of COVID-19 pregnancy mortality. Further published data have shown that the subpleural ground-glass opacity was observed in the cases with more complications [6]. However, other than this finding, the case had different other findings associated with poor maternal outcome.

Ethical statement

Despite the consent form which the patient has kindly signed at the administration moment, her heirs signed a form as acceptance to use these data for publication. This report was approved by Medical Ethic Committee of Zanjan University of Medical Sciences.

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Declaration of competing interest

Authors declare no actual or potential conflict of interest related to this study.

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