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Diagnostic challenges for severe infection with severe acute respiratory syndrome coronavirus 2 in pregnancy: a case report

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Abstract

Background Diagnosis of severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019) proved challenging during the initial waves of the pandemic owing to false-negative diagnostic tests. Maternal patients with conditions such as preeclampsia and thromboembolism presented with overlapping symptoms with coronavirus disease 2019.

Case presentation A 44-year-old South Asian mother in the third trimester presented with respiratory symptoms and preeclampsia. Two successive rapid antigen tests for coronavirus disease 2019 were negative. Treatment was started for lower respiratory tract infection and suspected thromboembolism (with a therapeutic dose of enoxaparin). With worsening respiratory distress, a chest X-ray was performed, which suggested severe coronavirus disease 2019. A repeated rapid antigen test was found to be positive. She was started on intravenous dexamethasone. She underwent an emergency caesarean section following reversal of enoxaparin with protamine and delivered a healthy baby. The mother was transferred to a tertiary care center for advanced intensive care. She was intubated 24 hours later and received a single dose of intravenous tocilizumab owing to increasing ventilatory supports. A computed tomography pulmonary angiogram excluded pulmonary embolism. She was extubated on day 5 and discharged home on day 15. On follow-up, she was found to be devoid of long-term sequelae coronavirus disease 2019 at 1 year. The false-negative rapid antigen test for coronavirus disease 2019 presented a diagnostic challenge to clinicians, especially when further supportive radiological investigations were unavailable in a low-resource setting. Maternal coronavirus disease 2019 bore nonspecific symptoms of other pregnancy-related conditions, further complicating the diagnostic and therapeutic process.

Conclusion Pandemics pose significant challenges to clinicians, particularly in the initial stages, owing to diagnostic difficulties. A high index of suspicion and early involvement of multidisciplinary teams may prove to be adjunctive to surrogate investigations.

Keywords SARS-CoV-2, COVID-19, Maternal, Rapid antigen testing, RAT, Case report

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in early 2020 [1]. Its rapid spread was met with inadequate diagnostic and therapeutic provisions, especially during the first wave of the pandemic. This was particularly true for low-resource centers. The maternal

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outcomes following COVID-19 infection have been significant, with 4.6% of mothers requiring intensive care admission and a mortality rate of 1.2% [2, 3]. This was much worse compared with the outcomes of the rest of the infected population [4]. The infection was diagnosed by a rapid antigen test (RAT) as a point-of-care test, while the reverse transcriptase polymerase chain reaction test (RT-PCR) was considered the gold standard [5]. The severity of the disease was assessed by clinical presentation and laboratory markers. Intubation and ventilation carried a high mortality rate during the first wave of the pandemic, with clinicians being cautious about the use of mechanical ventilation [6]. Thromboembolic phenomena complicated the clinical course. Studies illustrated a two-fold rise in thromboembolic phenomena in the infected maternal group compared with non-infected mothers [7]. Selective intravenous monoclonal antibody therapy and steroids were utilized for the treatment of severe infection, with later studies showing improved outcomes [8]. The abstract of this case report was presented at the Euroanaesthesia 2021 Congress as an eposter (abstract 7334).

Case presentation

A 44-year-old South Asian mother presented to the emergency treatment unit of a district general hospital in Sri Lanka with history of worsening cough and shortness of breath for 3 days during the first wave of the COVID-19 pandemic. Her body weight was 88 kg, and her body mass index was 33 kg/m^2. She was in her third pregnancy, and her two previous pregnancies were uncomplicated. In the current pregnancy, she was in her 37th week of amenorrhea. Up to now, it had been uncomplicated. Her past medical and surgical history was not significant. There was a recent history of immobility due to the current illness. She was a nonsmoker and a nonalcoholic. On examination, she was afebrile. There was mild pitting pedal edema. There was no calf swelling or redness. Her vitals were recorded as follows: respiratory rate 24/minute with vesicular breathing, bilateral occasional coarse crepitations, peripheral oxygen saturation of 93% in air, pulse rate 110/minute, and noninvasive blood pressure 145/88 mmHg. She was conscious and rational, and her neurological examination was routine, with normal tendon reflexes. The fetal assessment revealed a live fetus with appropriate fetal parameters. She had had contact with a COVID-19 patient.

Investigations

Given the prevailing pandemic, her contact history, and respiratory symptoms, she underwent a RAT of nasopharyngeal swabs for COVID-19. A doctor trained in RAT testing obtained samples. Two successive tests were negative. Owing to the high index of suspicion, a PCR test for COVID-19 was sent to the closest tertiary care center, as it was not available at our hospital. Blood and urine cultures were sent, given her high C-reactive protein level (CRP) (240 mg/dL) and white blood cell count (19.0×10^9/L, with neutrophils at 75% and lymphocytes at 18%). We were unable to obtain any sputum samples for initial testing. The portable X-ray was out of order, and computed tomography (CT) facilities were unavailable. Initial arterial blood gas analysis (while on high-flow nasal oxygen) revealed metabolic acidosis (pH 7.25, pCO_2 27, paO_2 66, (FiO_2 0.5), HCO_3 17, BE −7, lactate 4.5). Her urine protein qualitative test was positive (3+). The rest of the biochemistry, which included blood glucose, serum electrolytes, creatinine and urea, liver enzymes, and clotting profile, showed normal results. Lactate dehydrogenase and D-dimer levels were unavailable at our institution, and the limb venous duplex was not performed owing to technical difficulties. The electrocardiogram illustrated sinus tachycardia with no other abnormalities.

Differential diagnosis

Initial considerations included preeclampsia with pulmonary involvement and lower respiratory tract infection, which were the most likely diagnoses. Thromboembolism was also considered during the diagnostic workup. Peripartum cardiomyopathy and cardiac failure were considered unlikely. Once the PCR test results were available, COVID-19 was confirmed.

Treatment

Given her respiratory distress and pregnancy, she was admitted to the high-dependency unit for close observation. She was started on high-flow nasal oxygen therapy with initial settings of 50% fractional O_2 and 50 L/minute flow. Intermittent nebulization with 0.9% saline was commenced. She was started on intravenous 1.2 g 8-hourly Co-amoxiclav, 500 mg 12-hourly clarithromycin, and 150 mg oseltamivir 12 hourly to cover possible respiratory pathogens. Forty milligrams per day (prophylactic) enoxaparin was also commenced. She was allowed a light diet. Urine output was measured after urinary catheterization, and an input–output chart was generated. Oral 100 mg labetalol was prescribed every 8 hours to maintain blood pressure under 140/90 mmHg. As she did not have features of severe preeclampsia, intravenous magnesium therapy was not indicated. Six hours following admission, her respiratory distress progressively worsened, requiring maximum high-flow nasal oxygen therapy (90% O_2 and 70 L/minute). After a multidisciplinary team discussion, including the obstetrician, physician, and anesthetist, therapeutic enoxaparin

was commenced at a dosage of 40 mg 12 hourly as she was at high risk of thromboembolism (with multiple risk factors of obesity, pregnancy, preeclampsia, immobility, and underlying chest condition) and owing to the unavailability of unfractionated heparin. Two hours later, the X-ray was functional, and a chest X-ray was performed with the necessary precautions. It demonstrated severe COVID-19 infection (Fig. 1). As PCR results were unavailable, we repeated a RAT, which also came back positive. She was diagnosed with COVID-19. Her respiratory distress was further worsening, and she was commenced on bilevel positive airway pressure (BiPAP) therapy and 8 mg per day of intravenous dexamethasone. The enoxaparin dose was reduced to a prophylactic dose of 40 mg once daily. The patient was decided to be transferred to the closest tertiary care center for intensive care. Owing to the unavailability of a neonatal bed in the receiving hospital, it was agreed to proceed with an emergency caesarean section in our center after discussing with the obstetric, neonatal, and intensive care teams in the receiving hospital. As the patient had received her therapeutic dose of enoxaparin 4 h prior, the hematologist recommended reversal with 1 mg/kg intravenous protamine. The emergency caesarean section was conducted under single-shot subarachnoid anesthesia at L4–5 level by the consultant anesthetist, considering her high-risk status for general anesthesia. Anesthesia and surgery were uneventful, and a 2.8-kg single live fetus was delivered. The mother was transferred with supplementary oxygen to the tertiary care center. She was recommenced on BiPAP therapy, and 24 h later, she was intubated for lung-protective ventilation, as arterial blood gas showed deterioration (pH 7.2, pCO_2 43, pO_2 65 with FiO_2 1.0, HCO_3 14, BE −9, lactate 6). A CT pulmonary angiogram was performed, which excluded any major embolism, and the lung window confirmed severe COVID-19 acute respiratory distress syndrome (C-ARDS). Repeated CRP were elevated (350 mg/dl), and the procalcitonin levels were low (0.1mic/L). Her blood and urine cultures did not yield any growth. As she continued to be dependent on high ventilatory support, intravenous tocilizumab 8 mg/kg therapy was administered on the fifth day per the advice of the microbiologist. She was initiated on noradrenaline infusion via a femoral central venous line to keep the mean arterial pressure above 65 mmHg. The femoral line was chosen to avoid iatrogenic lung injury in the background of severe C-ARDS. She was later diagnosed with a deep vein thrombosis related to the femoral venous catheter and received therapeutic enoxaparin.

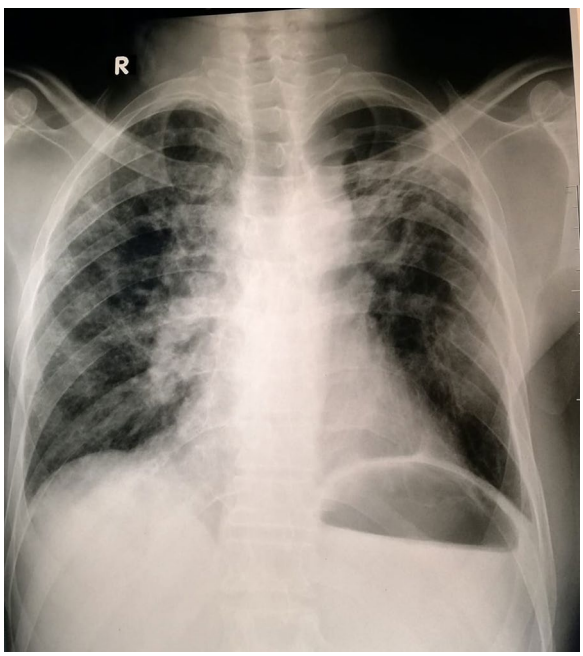

Fig. 1 Chest X-ray illustrating severe coronavirus disease 2019

Outcome and follow-up

The patient was monitored for any features suggestive of spinal hematoma, which she did not exhibit during her hospital stay. By day 5 of the intensive care stay, she was gradually weaned off the ventilator and vasopressors and extubated. She was discharged to the ward on day 8 and home on day 15. At 1-year follow-up, she did not have any residual respiratory symptoms, and her blood pressure was normalized. The baby was healthy and did not acquire the infection, as confirmed by a negative PCR test. The critical events following the admission timeline are illustrated in Fig. 2.

Discussion

The sensitivity and specificity of initial screening and diagnostic tests for COVID-19 have evolved since the pandemic began. The RT-PCR test, considered the gold-standard diagnostic modality, presented challenges in low-resource settings owing to the need for sophisticated technology and expertise, as well as increased costs and delays in results resulting from the increased sample burden [9, 10]. These delays in diagnosis complicated timely clinical decision-making [10]. In our setup, PCR test results were typically available 24–48 h after sample transfer owing to the high volume of samples received at the testing center. In contrast, RAT typically showed positive results during active infection. These were portable, low-cost, and quickly produced results, making them well suited for low-resource settings [11]. They also closed the diagnostic gap of delayed PCR results [12]. Still, their sensitivity was variable, and a pooled sensitivity of 69% suggested the possibility of false-negative

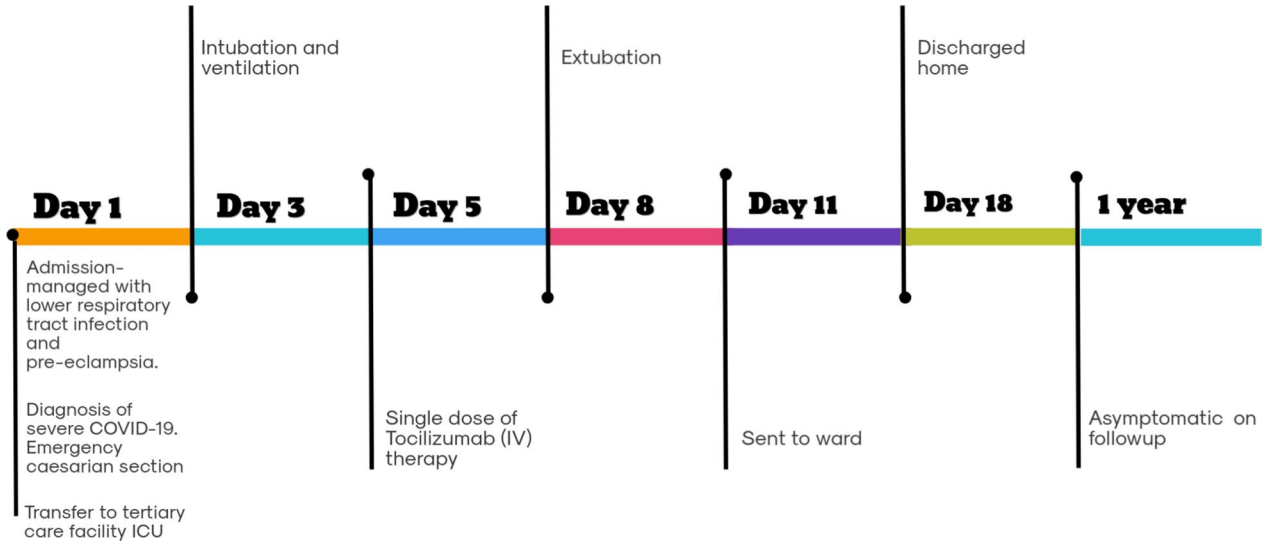

Fig. 2 Timeline from admission to 1-year follow-up

results, especially during the early stages of the disease, when patients are asymptomatic and the viral load is low [13]. In their systematic review, Arshadi *et al.* demonstrated that the subgroups of nasopharyngeal swabs (70%) and throat or saliva swabs (52%) showed differing sensitivities of diagnosis by RAT [12]. Similarly, operator competence, patient compliance, manufacturer, and variants of COVID-19 may also contribute to the outcome of test results [14]. In our setup, an initial negative RAT in symptomatic patients warranted a repeat RAT or PCR. Two negative RAT results were unusual in this case; however, this may be linked to low viral load, as the positive test was performed 8 hours after the two initial tests.

Misdiagnosis of non-COVID-19 conditions or underdiagnosis of COVID-19 was prevalent during the pandemic, particularly in maternal patients, where conditions such as preeclampsia and thromboembolism presented with overlapping symptoms [15–17]. Complications of COVID-19 in maternal patients were significant, including severe respiratory distress, thromboembolic events, and preterm delivery [18, 19]. Coexisting preeclampsia further complicated management, increasing the risk of maternal morbidity and mortality [20]. Marchand *et al.* found that 7% of infected mothers had coexisting preeclampsia [3]. Maternal and fetal outcomes in COVID-19-infected pregnancies varied, with some studies indicating higher rates of preterm birth and neonatal intensive care unit admissions [2]. A systematic review and meta-analysis demonstrated neonatal intensive care admission rates of 32.9% and a neonatal death rate of 3% [3]. The overall vertical transmission rate was 3.5% according to the same study. Maternal and fetal circumstances often dictated the mode of delivery. A significantly higher cesarean delivery rate (53.2%) was found among the infected cohort [3]. A clinically evident benefit over natural delivery has not been substantiated regarding improved maternal outcomes or reduced transmission of infection [4]. However, a heightened sense of urgency might have led to this trend globally. Subarachnoid anesthesia, as chosen in this case, has been reported to be safe and effective, reducing the risks associated with general anesthesia [15]. The administration of central neuraxial blocks in anticoagulated patients carries a varied risk, depending on the dosage and the time since the last dose of anticoagulation. In obstetric cohorts where the delivery may be expedited, unfractionated heparin is indicated owing to the short duration of action [21]. In our patient, the unavailability of the former led to the use of low-molecular-weight heparin (LMWH). The Association of Anaesthetists suggests a high risk associated with central neuraxial blocks if the last therapeutic dose was administered within the previous 6 h [21]. Severe respiratory distress and high oxygen requirements in our patient led to a multidisciplinary decision to proceed with subarachnoid block after the reversal of LMWH in preference to general anesthesia. However, it is imperative to monitor patients for the development of spinal hematoma in cases of high-risk central neuraxial blocks, particularly in the background of antiplatelet or anticoagulant use. Considering severe respiratory distress and preeclampsia, early delivery could have been performed operatively in our patient. However, the unavailability of neonatal high-dependency unit (HDU) beds, emergency operating theater (OT) beds, and the overwhelmed transport

facilities (unavailability of ambulances) and initial multidisciplinary decision to optimize the mother led to delayed delivery of the baby.

The commencement of the therapeutic dose of LMWH followed an in-depth discussion among a multidisciplinary team involved in the management of our mother. According to the 2019 European Society of Cardiology guideline, our patient belonged to the intermediate risk category of pulmonary embolism (PE) according to the 'Pretest' criteria [22]. They suggest performing a D-dimer test to assess the possibility further and, if positive, to proceed with a chest X-ray and compression ultrasonography to exclude proximal deep vein thrombosis (DVT). If DVT is detected, therapeutic anticoagulation is recommended. We faced multiple challenges owing to the unavailability of all the required tests, prompting us to make a clinical decision regarding therapeutic anticoagulation. Later, PE was excluded from the tertiary care center. The utility of lung ultrasound and the Wells score has been suggested for diagnosing PE in critically ill patients with COVID-19 [23].

An increased incidence of intensive care unit (ICU) admission, intubation, and ventilation was found among pregnant women with risk factors (for example, obesity, diabetes, and older age) [24]. During the pandemic, debate and resistance arose regarding the early intubation of critically ill patients with COVID-19. As found later, it was associated with poorer outcomes when intubated more than 24 h after admission to the ICU [25]. In our patient, intubation after 24 h was an elective decision. The judgment to administer intravenous tocilizumab was based on emerging evidence suggesting its efficacy in reducing inflammation and improving outcomes in severe COVID-19 cases [8, 9]. This, combined with dexamethasone, represented a targeted approach to managing the hyperinflammatory state associated with severe COVID-19 infection [8, 9]. The WHO recommends that patients be approached as if they have COVID-19 in cases of clinical suspicion. Considering the high false-negative rates of rapid antigen tests, clinical compatibility with COVID-19 and the high CRP and hemogram findings suggesting a viral infection, it should have been accepted as a COVID-19 infection from the beginning in this patient.

The current data suggest that vaccination against COVID-19 during pregnancy is associated with lower rates of infection, reduced disease severity, and lower maternal mortality, in the absence of worsened fetal outcomes [26, 27]. Apart from the discussed treatment modalities, sotrovimab, remdesivir, extracorporeal membrane oxygenation (ECMO), and ventilation in prone position are recommended therapies to be utilized on an individual basis [28].

Conclusion

Pandemics will inevitably emerge, presenting diagnostic challenges that will burden our healthcare system. Clinical judgment and multidisciplinary management will provide invaluable support to counterbalance such diagnostic difficulties, especially in this era of dependence on sophisticated investigations.

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Author contributions
Clinical management of the patient, concept, consent: B.M. Literature review, drafting of the initial and final manuscript, approval of the final manuscript: B.M.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Our institution does not require ethical approval to report individual cases or case series.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The author declared no potential competing interests concerning the research, authorship, and/or publication of this article.

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