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Multisystem inflammatory syndrome in children (MIS-C) in pregnancy can mimic new-onset pre-eclampsia: A case report

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ABSTRACT

Introduction: Pregnant women affected by coronavirus disease 2019 (COVID-19) are at increased risk of severe disease, admission to an intensive care unit, and adverse pregnancy outcomes. In contrast, children typically experience a mild form of COVID-19. Nonetheless, there is a risk of multisystem inflammatory syndrome in children (MIS-C) following a SARS-CoV-2 infection.
Case: A healthy 16-year-old, G1P0, presented with MIS-C in the second trimester and was treated with intravenous immunoglobulin. She subsequently developed transient mild hypertension, proteinuria, and transaminitis, which ultimately was thought to be secondary to MIS-C rather than pre-eclampsia.
Discussion: MIS-C is an important COVID-19 complication in pediatric patients. This case offers guidance on expectant management of hypertension, transaminitis, and proteinuria during an episode of MIS-C in pregnant patients, as opposed to preterm delivery for a misdiagnosis of severe pre-eclampsia.

1. Introduction

Since its emergence in 2019, the novel coronavirus variant SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), which causes coronavirus disease 2019 (COVID-19), has spread quickly, resulting in a pandemic [1]. In 2020, the US reported 400,000 laboratory-confirmed cases in women of reproductive age, and studies have shown that pregnant women are at increased risk of severe disease, admission to an intensive care unit (ICU), requirement for mechanical ventilation or extracorporeal membrane oxygenation, and adverse pregnancy outcomes [2]. The proportion of cases of SARS-CoV-2 infections in children approaches 5%, with the 15–17-year age group comprising a third of infections; this includes reproductive-age adolescents who may become pregnant [3,4]. Fortunately, pediatric cases rarely require admission to the pediatric intensive care unit (PICU) [4].

Although acute COVID-19 episodes in children are usually mild, recent evidence has shown that children may suffer a complication of COVID-19 characterized by a widespread inflammatory response first identified in April 2020 [5]. This systemic response has been termed the multisystem inflammatory syndrome in children (MIS-C), defined as serious illness leading to hospitalization in patients under 21 years of age, with persistent fever, laboratory evidence of inflammation, multisystem (≥2) organ involvement, and current or recent SARS-CoV-2 infection or COVID-19 exposure within 4 weeks prior to onset of symptoms, without any alternative diagnoses [6,7].

The characteristics of MIS-C have been described in detail in large patient populations [6]. The temporal relationship between the symptom onset and hospitalization for MIS-C is approximately 25 days. Almost a third of patients test negative for SARS-CoV-2 infection at the time of MIS-C diagnosis, but do have detectable antibodies. Most patients present with tachycardia, tachypnea, gastrointestinal symptoms, rash, and conjunctival injection, and all patients present with fever. Those with worse symptoms have elevated levels of C-reactive protein (CRP), D-dimer, erythrocyte sedimentation rate (ESR), ferritin, troponin, cardiac b-type natriuretic peptide (BNP), liver enzymes, and others. They can also exhibit anemia, thrombocytopenia, and neutrophilia. The vast majority of MIS-C patients require admission to the ICU and 62% receive vasopressor support, with a median length of hospital

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stay of 6 days. Most patients affected by MIS-C are treated with intravenous (IV) immunoglobulin (IVIG) and almost half receive glucocorticosteroids [6].

Although the amount of data on MIS-C in the general pediatric population and data on COVID-19 in the adult pregnant population are growing, there is limited data on MIS-C in the pregnant pediatric population. To date, there are no published reports of MIS-C in pregnancy (according to a MEDLINE search with the following terms: "multi- system inflammatory syndrome children", "MIS-C", "pediatric multisystem inflammatory disease", "pregnant", "pregnancy", "pediatric(s)", "pediatric patient", "teen; teen pregnancy", and "juvenile; juvenile pregnancy"). This report describes management of a patient in her second trimester of pregnancy during an acute MIS-C episode.

2. Case Presentation

The patient was a previously healthy 16-year-old, G1P0, who presented to the Emergency Department (ED) at 25 + 2 weeks with fever, shortness of breath, and diarrhea. In the ED, she had an overall unremarkable work-up, including a negative COVID-19 test, although a computerized tomography (CT) angiogram showed bilateral pulmonary ground-glass opacities without evidence of pulmonary emboli. The patient had significant improvement of her symptoms with IV hydration and anti-pyrectics. Given complete resolution of her symptoms and stable vital signs, she was discharged home at that time with close follow-up, with a discharge diagnosis of upper respiratory infection and fever. She represented at 26 + 1 weeks' gestation with persistent fever and worsening shortness of breath. The patient was ill-appearing, tachypneic, tachycardic, and febrile. Although she continued to saturate well on room air without need for oxygen support (98–100% SpO2), her tachycardia reached a maximum of 140 bpm, fever peaked at 102.9 F, and she had low-normal blood pressure readings (ranging from systolic 105–132 mmHg and diastolic 53–83 mmHg). Laboratory tests showed a significant leukocytosis (WBC 41.1 × 10 [3]/μL [normal range 6–16 × 10 [3]/μL]), anemia (hemoglobin 9.0 g/dL [normal range 10-15 g/dL]), and an elevated D-dimer level (3.85 μgFEU/mL [normal range 0.05–0.73 μgFEU/mL]) [8]. Other acute phase reactants were significantly elevated (CRP >30.0 mg/dL [normal range 0.15–1.5 mg/dL], ESR 127 mm/h [normal range 7–47 mm/h], and ferritin 486 ng/mL [normal range 7–130 ng/mL]) [8]. Her renal and hepatic function tests were normal. A respiratory pathogen panel was sent and a chest X-ray was unremarkable. An echocardiogram showed normal ejection fraction, no wall motion abnormalities, normal coronary artery dimensions without evidence of aneurysms, and a trivial pericardial effusion. Fetal monitoring showed fetal tachycardia, minimal variability without accelerations or decelerations, and she exhibited uterine irritability on the tocometer. While in the ED, the patient's status worsened. She became increasingly hypotensive with systolic blood pressure readings ranging from 93 to 104 mmHg and diastolic from 41 to 57 mmHg, with mean arterial pressure (MAP) values dropping, ranging from 53 to 68 mmHg (normal range for second trimester: 77 ± 6 mmHg) [9]. This change in clinical status required initiation of pressor support with norepinephrine at an initial dose of 3 μg/min, initiation of broad-spectrum IV antibiotics with ceftriaxone (2 g q24h) and vancomycin (loading dose 1500 mg) while blood and urine cultures were pending, and she was admitted to the PICU for further management.

In the PICU, patient was continued on pressor support, and started on anticoagulation on admission (enoxaparin 0.5 m/kg every 12 h per institution protocol) as well as IV steroids (methylprednisolone 30 mg twice daily). She was maintained on pressor support, reaching a maximum dose of norepinephrine 7 μg/min at 24 h after presentation to the ED. Her BNP increased and peaked at 2180 pg/mL on hospital day (HD) 3 (Fig. 1), despite findings of a normal repeat echocardiogram on day 2 of admission. The respiratory pathogen panel returned negative for COVID-19 ORF1, COVID-19 *E*-gene, influenza, RSV, parainfluenza, SARS-CoV-2 ORF1ab, other coronaviruses, rhinovirus, and atypical pneumonia pathogens; it did, however, detect SARS-CoV-2 (M) which corresponds to the viral membrane glycoprotein M. In the setting of a diffuse inflammatory response and now proven prior COVID-19 infection, the decision was made to administer IVIG (a one-time dose of 2 g/kg) for treatment of MIS-C.

Following these interventions, the patient's course significantly improved; her fever resolved with use of cooling blankets and acetaminophen, and she was weaned off pressors for a total of 48 h. Her laboratory results continued to downtrend, including acute phase reactants and BNP, and blood and urine cultures were negative. She was transferred to the antepartum care unit for further management and fetal monitoring. On HD 4, the patient was noted to have mild hypertension (systolic pressure ranging from 141 to 155 mmHg and diastolic 91 to 94 mmHg), which prompted the collection of a 24-h urine for

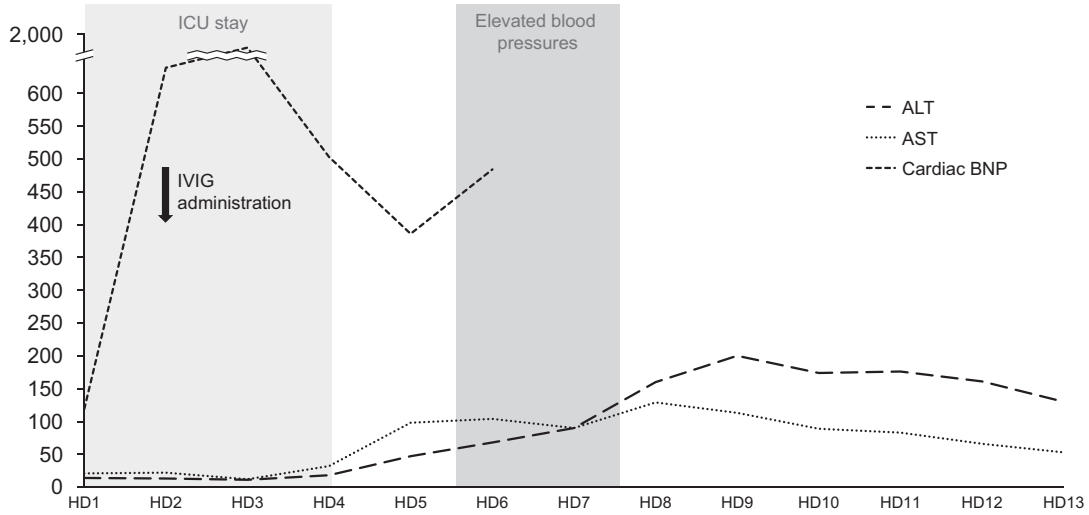

Fig. 1. Laboratory value trends during patient's hospital stay. Patient was admitted to the ICU for three days, receiving a dose of IVIG on hospital day 2. Patient's cardiac BNP peaked at 2180 pg/mL on hospital day 3. She developed mild hypertension on admission days 6 and 7, with a subsequent rise in liver function tests, which peaked 3–4 days after the onset of elevated blood pressures. Her inflammatory markers and liver function tests continued to improve towards her discharge. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; HD, hospital day; ICU, intensive care unit; IVIG, intravenous immunoglobulin.

protein assessment. The urine protein content was elevated to 326 mg/d, and, concurrently, her ALT and AST began to rise, peaking on HD 8 and HD 9 at 200 [IU]/L and 135 [IU]/L, respectively (Fig. 1). Initially, it was unclear whether this was development of a new-onset pre-eclampsia or transient transaminitis secondary to MIS-C. To exclude other causes of transaminitis, a right upper quadrant ultrasound scan, coagulation studies, complete hepatitis virus A, B, C, and E panel, and other less common causes of transaminitis in children [anti-nuclear antibodies, anti-LKM-1 (liver kidney microsome type-1) antibodies, anti-smooth muscle antibodies, ceruloplasmin levels, alpha-antitrypsin phenotype] were collected. Anti-nuclear antibodies returned as positive (titer 1:40) but clinically insignificant, given findings of normal smooth muscle antibodies and normal LKM-1 antibodies. Other hepatitis results were unremarkable. To exclude atypical HELLP syndrome, LDH, haptoglobin, peripheral smear were also drawn and were not consistent with hemolysis.

The patient had spontaneous resolution of her mild hypertension and her LFTs continued to improve after peaking on HD 8 and 9. She was discharged on HD 13 with close follow-up with maternal-fetal medicine, infectious diseases, and pediatric cardiology. Fetal growth at time of hospitalization at 27 + 2 weeks showed an appropriately grown fetus measuring 992 g (45%ile), with a normal fluid level. After discharge, the patient was followed weekly for laboratory studies and amniotic fluid index assessment, which showed complete resolution of transaminitis and she continued to have reassuring fetal assessments. Her proteinuria resolved by 3 weeks after discharge, as seen by a follow-up 24-h urine protein, which returned with 95 mg. The patient completed her course of oral steroids ten days after discharge; her overall steroid administration included initial dexamethasone 6 mg every 12 h for two doses (chosen for fetal lung maturity in the event of need for early delivery and potential treatment of COVID-19), followed by methylprednisolone 30 mg twice daily for 5 days (with overlapping 2 doses of betamethasone 12 mg every 24 h), followed by an oral prednisone taper (15 mg every 12 h for 5 days, then 15 mg daily for 5 days). The patient was followed every 7–10 days in the clinic between 28 and 38 weeks with serial biophysical profiles and growth ultrasound scans. She was diagnosed with fetal growth restriction (FGR) at 33 weeks of gestation, with estimated fetal weight (EFW) 25% and abdominal circumference (AC) 7%, umbilical artery Doppler pulsatility index (PI) 90%ile. Her FGR persisted and she was, therefore, scheduled for induction of labor at 38 weeks. She delivered a healthy infant, weighing 2535 g (small for gestational age, 5%) *via* an uncomplicated vaginal delivery. Both mother and baby were doing well at the time of this report. Patient consent was obtained to describe the above findings in the case report in accordance with local legislation.

3. Discussion

In this report, we present a pediatric patient in the second trimester of pregnancy who developed MIS-C in the setting of a SARS-CoV-2 infection. She presented with significant multi-organ (cardiac, hematologic, hepatic, and renal) involvement, accompanied by markedly elevated inflammatory markers. Interestingly, during her stay she also developed mild hypertension, which temporally coincided with significant transaminitis and proteinuria. This was concerning for the development of pre-eclampsia with severe features. Transaminitis peaked on HD 8 and 9, then continued to improve and resolved completely by 3 weeks after onset. Her blood pressure returned to normal prior to discharge, and proteinuria completely resolved by 4 weeks after diagnosis. She proceeded to develop FGR in the third trimester, for which she was induced, and delivered a healthy neonate at term.

The multi-organ involvement during MIS-C in setting of COVID-19 made the potential diagnosis of pre-eclampsia unclear and difficult to manage in this case. The patient had mild hypertension, proteinuria, and transaminitis, which created concern for development of pre-eclampsia with severe features, but it was suspected that this was confounded by the clinical manifestations of MIS-C. No reports of MIS-C in a pregnant pediatric patient seem to be available for comparison. Studies published regarding COVID-19 in pregnancy illustrate that pregnant women are at increased risk of severe disease and complications from COVID-19 [10]. Interestingly, a study by Medoza et al. described a pre-eclampsia-like syndrome in 6 out of 8 women diagnosed with severe COVID-19 [11]. These patients developed elevated blood pressure, a rise in LFTs to more than twice normal, and proteinuria to $\geq$300 mg/d; only one of 6 severe COVID-19 cases had an abnormal sFLT-1/PlGF (soluble fms-like tyrosine kinase-1 to placental growth factor) ratio and uterine artery dopplers, suggestive of placental insufficiency. This suggested that the physiologic changes during COVID-19 were not due to pre-eclampsia, which often does lead to placental dysfunction. The sFLT-1/PlGF ratio was not tested in our study because the facilities were not available. While the Medoza study offers potential strategies for diagnosing pre-eclampsia and HELLP in pregnancies affected with COVID-19, this study did not encompass pediatric patients with MIS-C.

Acute hepatitis has been reported in patients affected by MIS-C. Cantor et al. reviewed 44 cases of MIS-C and found that 43% of them had laboratory evidence of hepatitis, defined as elevation of ALT >40 [UI]/L and AST >50 [UI]/L. [12] Most commonly, liver enzymes were highest on admission (63% of patients); however, in the rest of the cases, they peaked on days 1 to 4 of hospitalization. Only 26% of the patients with hepatitis had confirmed evidence of SARS-CoV-2 infection. This supports our speculation that the transaminitis in our patient was secondary to MIS-C as opposed to pre-eclampsia, although the temporal relationship of the peak of transaminitis in our case was notably later (days 8 to 9). It is important to note that exclusion of acute hepatitis or auto-immune hepatitis does not exclude the diagnosis of pre-eclampsia in this case, but only assists with eliminating other causes of transaminitis.

Our case can be used to offer guidance on expectant management of transaminitis and proteinuria in a pregnant pediatric patient with mild hypertension in the setting of MIS-C diagnosis. The case illustrates the complete resolution of these symptoms by 3–4 weeks after diagnosis. Management with a multi-disciplinary care team, including maternal-fetal medicine, pediatric gastroenterology, intensivists, and infectious diseases specialists, is critical to managing the varied and nuanced clinical course of these patients. Strategies to differentiate between complications of COVID-19/MIS-C and pre-eclampsia include evaluation of hemolysis to exclude HELLP, hepatitis panel and other hepatic function tests to exclude causes of congenital and auto-immune hepatitis, and review of medications and their side-effects to exclude drug-induced liver injury. The use of sFLT-1, PlGF and other soluble angiogenic factors was also suggested by some authors as a potential tool for predicting the likelihood of pre-eclampsia or differentiating COVID-related transaminitis and other symptoms which can complicate the diagnosis of pre-eclampsia in this patient population [11,13,14]. Serial laboratory studies for resolution of inflammation and transaminitis as well as ultrasound scans to evaluate fetal growth and amniotic fluid volume can be considered in such cases. A thoughtful and cautiously conservative approach was useful in this case and helped to avoid unnecessary iatrogenic preterm birth, which carries significant maternal complications as well as neonatal morbidity and mortality associated with prematurity. Further reports and studies are needed to understand the relationship between COVID-19 and the body's subsequent immune response in pregnant pediatric patients. This is critically important with the rise of new SARS-CoV-2 variants and the likelihood that pediatric pregnant patients will continue to be infected.

Contributors

Khrystyna Levytska was responsible for the conception and design of the study, interpretation of data, drafting and revising the article to the final form as submitted; she was also involved in the patient's care during hospitalization and outpatient follow-up.

Lorene Temming was responsible for the conception and design of the study, interpretation of data, revising the article to the final form as submitted and direct involvement in patient care during hospitalization.

Jason Dranove was directly involved in the patient's care during hospital admission as a consultant, as well as conception and design of the study, interpretation of data, and revising the manuscript.

Ngina Connors was involved in the conception and design of the study, interpretation of data, drafting and revising the article to the final form as submitted.

Rebecca Pollack was responsible for the conception and design of the study, interpretation of data, revising the article to the final form as it is submitted and direct involvement in patient care during hospitalization.

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Patient consent

Obtained.

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This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors have no conflicts to disclose which could have inappropriately influenced this work.

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