

Haemophagocytic lymphohistiocytosis in pregnancy: a pertinent case during the COVID-19 pandemic

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is a rare, often fatal disease, and presents a diagnostic challenge in the pregnant patient. This challenge is particularly relevant during the current COVID-19 pandemic. We present a case of HLH in a pregnant woman presenting with fever predating the COVID-19 pandemic. A 33-year-old, gravida 2, para 1 at 27 weeks' gestation presented with fever, transaminitis, thrombocytopenia and elevated ferritin. After treatment according to the HLH-94 protocol, caesarean delivery and weeks of intensive care, the patient recovered fully. With prompt diagnosis and a multispecialty team at our tertiary care facility, she and her baby overcame a dire prognosis. HLH should be considered in pregnant patients presenting with a febrile illness. Particularly in cases of severe COVID-19, secondary HLH must be considered as an associated diagnosis.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal disease.¹ Symptoms of HLH are non-specific and often confounded with other more common disorders of pregnancy, presenting a diagnostic challenge. Published observations to date have reported death in 3 of 20 (15%) cases in pregnancy.¹ Primary, or familial, HLH can be inherited as an autosomal recessive or X-linked condition. Secondary HLH (sHLH) can be infectious, malignant or autoimmune related. Pregnancy itself has been proposed as an inciting immune stimulus,² although the actual mechanism of pregnancy-induced HLH is still unknown.³ HLH can occur in pregnant women with other inciting stimuli as the primary cause (eg, Epstein-Barr virus (EBV), cytomegalovirus, systemic lupus erythematosus (SLE)).³ A more recent concern is the risk of the development of sHLH as a result of infection with SARS-CoV-2 and its associated subsequent cytokine storm and resultant multiorgan failure.⁴ In light of the current COVID-19 pandemic due to SARS-CoV-2, where HLH as a condition may become more prevalent, we present a case of a pregnant woman with HLH and highlight the diagnostic criteria, clinical features and management of this condition.

CASE PRESENTATION

A 33-year-old, gravida 2, para 1001, was admitted to the perinatal unit at 27 weeks' gestation with a febrile illness and thrombocytopenia. She reported a history of malaise, headache, fevers, epigastric pain and decreased appetite for 4 days prior to admission. She had a sick contact, her 2-year-old daughter, who had experienced a febrile illness 1 week prior to presentation. She

reported fevers of 103°F at home. She had initially been admitted to a rural hospital, and then was transferred to our tertiary care centre after her initial evaluation identified mild transaminitis (aspartate aminotransferase (AST) 89 U/L, reference range less than 41 U/L; alanine aminotransferase 90 U/L, reference range less than 56 U/L), thrombocytopenia (platelet count $89 \times 10^9/L$, reference range $140-450 \times 10^9/L$), elevated bilirubin (2.8 mg/dL, reference range 0.2–1.0 mg/dL), and elevated lactate dehydrogenase (387 U/L, reference range 100–250 U/L). Fibrinogen was within normal limits at 270 mg/dL (reference range 200–400 mg/dL). At the outside hospital, her fever was treated with acetaminophen. She received the first dose of betamethasone for fetal lung maturity, and she was started on intravenous ampicillin–sulbactam. Blood cultures and 24-hour urine for total protein quantification were collected. On arrival to our hospital, initial history and physical manifestation noted that the patient was afebrile and appeared 'ill and fatigued with intermittent chills during examination with conjunctival erythema, heart rate in the low 100s and dry mucosa'.

Several hours after admission, the patient developed symptoms consistent with systemic inflammatory response syndrome (SIRS) with tachycardia, hypotension and ongoing fever as high as 103.9°F. A chest radiograph was notable for left lower lobe density, small pleural effusion and possible pulmonary oedema. Echocardiogram showed a hyperdynamic left ventricle, no valvular abnormalities and preserved right ventricle function. Left ventricular ejection fraction was 70%. She was transferred to the intensive care unit (ICU). The broad-spectrum antibiotics cefepime, vancomycin and metronidazole were initiated. Nasal high-flow oxygen therapy was required to maintain her oxygen saturation rate above 95%. The condition highest in the differential diagnosis at that time was thrombotic thrombocytopenic purpura (TTP), whether primary or secondary to infection; with haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome less likely.

During the initial assessment and management period, the fetal heart rate tracing was intermittently category II secondary to fetal tachycardia and variable decelerations. Due to maternal acuity of illness and her early gestational age, delivery was to be considered only for a persistent category III fetal heart rate tracing.

On hospital day 2, worsening respiratory failure required the patient to be intubated. Central venous access was obtained. Her platelet count decreased to $40 \times 10^9/L$ and serum creatinine increased to 2.4 mg/dL. Supportive care, furosemide and broad-spectrum antibiotics were continued. Repeat comprehensive respiratory panel was negative.



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On hospital day 3, the patient's respiratory status continued to decline. The decision was made to proceed with volumetric diffusive respiration (VDR) in an attempt to delay the need for veno-venous extracorporeal membrane oxygenation (VV ECMO) and the heparin bolus required to initiate ECMO. VDR and nitrous oxide also provide oxygenation at lower peak pressures than typical mechanical ventilators, so there was theoretically less risk of ventilator-associated lung injury in our patient with persistent hypoxemia.⁵ During this transition, the fetus experienced prolonged bradycardia with absent variability. An emergent classic caesarean delivery was performed at the bedside in the ICU. She delivered a live-born male infant weighing 1170 grams with Apgar scores of 3 and 5 at 1 and 5 minutes, respectively. Intraoperatively, the patient received two units of packed red blood cells, two units of platelets, intravenous oxytocin and intramuscular carboprost tromethamine for uterine atony. Estimated blood loss was 700 mL. Immediately following delivery, the patient was unable to ventilate effectively despite intubation and VDR. She was taken to the operating room for initiation of VV ECMO. She received additional carboprost tromethamine at that time due to concern for bleeding with administration of intravenous heparin required to initiate ECMO.

INVESTIGATIONS

Comprehensive respiratory virus panel was negative. Infectious disease evaluation was notable for positive EBV, parvovirus and adenovirus viral serologies, suggestive of recent or past infection. Adenovirus nasal PCR was negative. Atypical infectious workup, including *Anaplasma*, Lyme, *Ehrlichia*, West Nile virus and Q-fever, was negative.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses at the time of presentation included HELLP syndrome, viral infection, TTP, SLE, sepsis, pneumonia, disseminated intravascular coagulation and antiphospholipid antibody syndrome. This case predates the current COVID-19 pandemic. At the time of delivery, the workup for her underlying disease was still ongoing, and the possibility of HLH as a diagnosis was raised. Several abnormal findings were noted including significantly elevated ferritin (10 226 ng/mL, reference range less than 291 ng/mL), elevated triglycerides (1981 mg/dL, reference range <150 mg/dL), as well as splenomegaly on CT imaging. She underwent a bone marrow biopsy on the day of delivery. HLH was the presumed diagnosis at that time.

TREATMENT

On the day of delivery, empirical treatment for HLH was initiated. The patient was treated with dexamethasone per the HLH-94 protocol.⁶ There was hesitancy to start etoposide, a strong chemotherapy agent, when the differential was still so broad and included infection. The patient initially improved clinically with dexamethasone alone. We wanted to avoid further immunosuppression and avoid use of etoposide while the patient was on ECMO. When the patient's clinical status plateaued after 10 days of dexamethasone alone, the decision was made to start treatment with etoposide. By this time, a definitive diagnosis of HLH had been made based on bone marrow biopsy results. She remained on etoposide until her ferritin normalised, and then was managed with tacrolimus for 6 months. Regarding the remainder of her hospital course, she required intensive care and infusion of vasopressor agents for septic shock due to left lower lobe pneumonia, presumed to be due to prior adenovirus infection. She underwent thoracotomy on postpartum day 6 due to

continued bleeding from the thoracostomy tube site resulting in prolonged disseminated intravascular coagulation. She returned to the operating room 15 days after delivery for caesarean wound exploration when a soft tissue separation and haematoma were noted. The following day, she developed fevers and was started on empirical antibiotics. Etoposide was continued during this time despite suspected infection. Laboratory studies were significant hyperbilirubinaemia as well as transaminitis. Gastroenterology was consulted and recommended cholecintigraphy, which was notable for intrahepatic cholestasis. Sixteen days after delivery, she underwent percutaneous cholecystotomy catheter placement for suspected cholecystitis.

OUTCOME AND FOLLOW-UP

The pathology from the bone marrow biopsy showed histiocytes with intracytoplasmic platelets, nucleated red cells and occasional neutrophils, consistent with haemophagocytosis, thus confirming the diagnosis of HLH. On the day of delivery, the patient was transferred from the medical ICU to cardiac ICU for continuation of ECMO, and decannulation of ECMO occurred 10 days later. On hospital day 21, she was extubated. When the patient was stable for transfer out of the ICU, she was transferred to the medical-surgical unit. Over the course of the next 4 weeks, the patient continued to make clinical improvements and was discharged home. Her post-delivery course was also complicated by an abdominal wound haematoma requiring evacuation followed by prolonged wound care and negative pressure wound therapy. After discharge, she underwent genetic testing for familial HLH, which was negative.

DISCUSSION

HLH is a rare but often fatal disease involving uncontrolled proliferation and activation of histiocytes with phagocytosis of normal haematopoietic cells and impaired cytolytic function of natural killer cells and cytotoxic T cells which normally identify and kill target cells.⁷ This results in an ongoing fulminant cytokine response. sHLH is a form of HLH that develops in response to an inciting event such as infection, autoimmune disorders or malignancy.⁸ In pregnancy, HLH presents a diagnostic challenge as this condition can masquerade as other pregnancy-related or haematological diagnoses, including SIRS, TTP^{8 9} or HELLP syndrome.¹⁰ Prompt diagnosis of HLH will allow the medical team to manage the patient according to the HLH-2004¹⁰ or HLH-94 protocol.¹¹ Treatment of HLH in pregnancy using these treatment protocols involves treatment with cytotoxic medications such as etoposide, and presents a challenge due to the risks of treatment on the fetus. Although case reports of HLH in pregnancy have shown an adequate response to high-dose steroids,¹² a 2019 review published by Song *et al* suggested that etoposide was necessary to achieve remission of HLH in most published cases.¹³ Theoretical toxicity to fetus and the severe bone marrow suppression in the patient limit the use of etoposide in pregnancy-related HLH.^{14 15} Fortunately, in the case presented here, the patient underwent delivery of the infant prior to initiation of etoposide.

Although our patient presented with HLH before the current COVID-19 pandemic, this case highlights the importance of keeping a high index of suspicion for the diagnosis of HLH in a patient presenting with a febrile illness. We wanted to highlight the similarities in the diagnostic challenge that both COVID-19 and HLH present. During the current pandemic, it is sometimes difficult to see beyond the most likely diagnosis and test for other rarer causes. In this case, timely diagnosis was

Table 1 H-score for secondary haemophagocytic lymphohistiocytosis (sHLH)* parameters¹⁶ (modified from reference)

	Score
Temperature	
<38.4°C	0
38.4°C–39.4°C	33
≥39.5°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly <i>and</i> splenomegaly	38
Number of cytopenias†	
1 lineage	0
2 lineages	24
3 lineages	34
Triglycerides	
<133 mg/dL	0
133–354 mg/dL	44
>354 mg/dL	64
Fibrinogen	
>250 mg/dL	0
≤250 mg/dL	30
Ferritin	
<2000 ng/mL	0
2000–6000 ng/mL	35
>6000 ng/mL	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression	
No	0
Yes	18

*The H-score generates a probability for the presence of sHLH. Scores greater than 169 are 93% sensitive and 86% specific for sHLH. This scoring system has not been validated in the pregnant population.

†Cytopenia is defined as haemoglobin ≤92 g/L, leucocyte count of ≤5×10⁹/L or platelet count of ≤110×10⁹/L

crucial, thus we felt that it is important to be familiar with HLH in pregnancy as it has a very specific treatment regimen. If this case had presented during the current SARS-CoV-2 pandemic, it likely would have been initially treated as severe COVID-19 pneumonia. Fevers in any patient raise an alarm for the pervasive SARS-CoV-2 respiratory virus. The Society of Maternal Fetal Medicine released guidelines for the management of pregnant patients with COVID-19,¹⁶ where they describe clinical criteria that raise concern for possible sHLH. These clinical signs include unremitting fever, hepatosplenomegaly, elevated ferritin and cytopenia. Using a tool known as the H-score (table 1), which has only been validated outside of pregnancy, one can determine if a pregnant patient warrants inpatient monitoring. The H-score is comprised of nine factors, which include temperature, organomegaly, number of cytopenias, triglyceride level, fibrinogen level, ferritin level, serum AST, presence of haemophagocytosis on bone marrow aspirate and known immunosuppression. A diagnostic pathway has also been proposed, which would lead providers to consider a diagnosis of HLH based on worsening COVID-19 disease and multiorgan failure and specific

laboratory abnormalities.¹⁷ It should be noted that severe COVID-19 is more responsive to different treatment protocols than HLH. Most COVID-19 treatment protocols recommend using antibody-based therapies, interleukin 6 pathway inhibitors and remdesivir in addition to steroids.¹⁸

For the obstetrician, the COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has created a new possible inciting factor for HLH, and even a new confounding diagnosis when treating patients with a febrile illness. A delay in diagnosis of sHLH in the setting of COVID-19 or another viral illness can lead to adverse outcomes for both the patient and the fetus. There are yet to be published data on sHLH in pregnancy induced by SARS-CoV-2 infection, but this is certainly a possibility given the prevalence of the virus in the population. As demonstrated in this case report, diagnosis and management of pregnant patients with HLH require a multispecialty approach including rheumatology, haematology, infectious disease, anaesthesia, neonatology and critical care. A critical step in the diagnosis of this patient was the decision of the outside hospital to transfer her to a tertiary care centre. When caring for critically ill pregnant patients, access to resources is paramount. The input of multiple specialties is needed for timing of delivery to be planned. Having access to a level 4 neonatal ICU allows for the best outcome for infants, especially those that require preterm delivery. The ability to have multiple specialists caring for this patient was crucial in establishing a timely diagnosis and a positive outcome for the patient and her infant.

Learning points

- ▶ Although rare, haemophagocytic lymphohistiocytosis (HLH) is a diagnosis that must be on the differential for every patient with continuous fevers of unknown origin or worsening clinical status due to COVID-19 infection.
- ▶ In pregnancy, HLH can mimic other pregnancy-related or haematological diagnoses, including systemic inflammatory response syndrome; haemolysis, elevated liver enzymes, low platelet count syndrome; thrombotic thrombocytopenic purpura; systemic lupus erythematosus and antiphospholipid antibody syndrome.
- ▶ HLH is treated using the HLH-2004 or HLH-94 protocol. However, a risks-versus-benefits discussion must be done when considering the use of cytotoxic medications such as etoposide in pregnant patients.

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