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

Jacqueline Potts,1 Brittney Gaudet,2 Danielle Durie,3 Joanne Quinones3

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 precluding the COVID-19 pandemic. A 33-year-old, gravida 2, para 1 at 27 weeks' gestation presented with fever, transaminisits, 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 multispeciality team at our tertiary care facility, she and her baby came over 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.2 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 stimulant,3 although the actual mechanism of pregnancy-induced HLH is still unknown.4 HLH can occur in pregnant women with other inciting stimuli as the primary cause (eg, Epstein-Barr virus (EBV), cytomegalovirus, systemic lupus erythematosus (SLE)).5 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.6 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 x 109/L, reference range 140–450 x 109/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 acetylsalicylic acid 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, 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 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 x 109/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.
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. 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 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 carbo prost tromethamine for uterine atony. Estimated blood loss was 700 mL. Immediately following delivery, intramuscular carbo prost tromethamine for uterine atony. Estimation was made to wait until the patient was stable to attempt to delay the need for veno-venous extracorporeal membrane oxygenation (VV ECMO). She received additional carbo prost tromethamine for uterine atony 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. 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 cholecystography, 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. 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. 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. In pregnancy, HLH presents a diagnostic challenge as this condition can masquerade as other pregnancy-related or haematological diagnoses, including SIRS, TTP9 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, a 2019 review published by Song et al suggested that etoposide was necessary to achieve remission of HLH in most published cases.11 Theoretical toxicity to fetus and the severe bone marrow suppression in the patient limit the use of etoposide in pregnancy-related HLH. 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
organomegaly and COVID-19 disease and multiorgan failure and specific laboratory abnormalities. 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.

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, 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 timely 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.

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

| Parameter                                      | 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 and 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 ≤5x10^9/L or platelet count of ≤110x10^9/L.

Contributors JQ and DD were involved in the case that is reported here and initiated the project. JP and BG performed the literature search and drafted the paper. DD and JQ edited and revised the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ’s website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iD

Jacqueline Potts http://orcid.org/0000-0001-7350-4822

REFERENCES

1 Yıldız H, Vandercam B, Thissen X, et al. Hepatitis during pregnancy: a case of haemophagocytic lymphohistiocytosis. Clin Res Hepatol Gastroenterol 2018;42:e49–55.
Case report

2 Al-Samkari H, Berliner N. Hemophagocytic lymphohistiocytosis. Ann Rev Pathol 2018;13:27–49.
3 Parrott J, Shilling A, Male HJ, et al. Hemophagocytic lymphohistiocytosis in pregnancy: a case series and review of the current literature. Case Rep Obstet Gynecol 2019;2019:9695367:1–8.
4 Opolska-Winiarska V, Grywalska E, Rolinski J. Could hemophagocytic lymphohistiocytosis be the core issue of severe COVID-19 cases? BMC Med 2020;18:2:14.
5 Allan PE, Osborn EC, Chung KK, et al. High-Frequency percussive ventilation revisited. J Burn Care Res 2010;31:510–20.
6 Henter JI, Aricò M, Egeler RM, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH Study group of the histiocyte Society. Med Pediatr Oncol 1997;28:342–7.
7 Campo M, Berliner N. Hemophagocytic lymphohistiocytosis in adults. Hematol Oncol Clin North Am 2015;29:915–25.
8 Nasser MF, Sharma S, Albers E, et al. Pregnancy-Related hemophagocytic lymphohistiocytosis associated with herpes simplex virus-2 infection: a diagnostic dilemma. Cureus 2018;10:e2352.
9 Teng C-L, Huang G-Y, Lee B-J, et al. Pregnancy-Induced hemophagocytic lymphohistiocytosis combined with autoimmune hemolytic anemia. J Chin Med Assoc 2009;72:156–9.
10 Kerley RN, Kelly RM, Cahill MR, et al. Hemophagocytic lymphohistiocytosis presenting as HELLP syndrome: a diagnostic and therapeutic challenge. BMJ Case Rep 2017;2017:bcr-2017-219516.
11 Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31.
12 Samra B, Yasin M, Arnaout S, et al. Idiopathic hemophagocytic lymphohistiocytosis during pregnancy treated with steroids. Hematol Rep 2015;7:6100.
13 Song Y, Wang Z, Hao Z, et al. Requirement for etoposide in the treatment of pregnancy related hemophagocytic lymphohistiocytosis: a multicenter retrospective study. Orphanet J Rare Dis 2019;14:50.
14 Hamizi K, Aouidane S, Belaibouzi G. Etoposide-based therapy for severe forms of COVID-19. Med Hypotheses 2020;142:109826.
15 M MB, IB, IA, et al. Etoposide treatment adjunctive to immunosuppressants for critically ill COVID-19 patients. J Infect 2020;81:452–82.
16 Media B. COVID Clinical. Smfm.org, 2021. Available: https://www.smfm.org/covidclinical [Accessed 23 Mar 2021].
17 Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 2014;66:2613–20.
18 National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Available: https://covid19treatmentguidelines.nih.gov [Accessed 12 Aug 2021].

Copyright 2021 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit https://www.bmj.com/company/products-services/rights-and-licensing/permissions/ BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:
► Submit as many cases as you like
► Enjoy fast sympathetic peer review and rapid publication of accepted articles
► Access all the published articles
► Re-use any of the published material for personal use and teaching without further permission

Customer Service
If you have any further queries about your subscription, please contact our customer services team on +44 (0) 20711 1105 or via email at support@bmj.com.
Visit casereports.bmj.com for more articles like this and to become a Fellow.