CASE REPORT

A case of haemophagocytic lymphohistiocytosis in pregnancy presented with pyrexia of unknown origin in Malaysia

Jonathan Heng Loke Tan, MD[1], Wee Fu Gan, MRCP[2], Hwee Cheng Chong, MRCP MMed[3], Nor Zaila Zaidan, MMed[4], Fatin Akmal Baharom, Mpath[5], Ngee Siang Lau, MRCP[6]

[1]Internal Medicine Department, Hospital Melaka, Malacca City, Malaysia, [2]Infectious Disease Unit, Hospital Melaka, Malacca City, Malaysia, [3]Rheumatology Unit, Hospital Melaka, Malacca City, Malaysia, [4]Infectious Disease Unit, Hospital Melaka, Malacca City, Malaysia, [5]Pathology Department, Hospital Melaka, Malacca City, Malaysia, [6]Haematology Unit, Hospital Ampang, Kuala Lumpur City, Malaysia

SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) in pregnancy is rare. Diagnosis is often elusive due to the rarity of this condition, potentially leading to high foetal and maternal mortality if misdiagnosed. We report a case of HLH in pregnancy whereby our patient presented with pyrexia of unknown origin in her third trimester. She was managed successfully with corticosteroids, intravenous immunoglobulin (IVIg), cyclosporin, and an expedited delivery.

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a rare but serious clinical syndrome, characterized by dysregulated and excessive immune activation due to various triggers.[1,2] The primary (genetic) form of HLH is caused by mutations affecting lymphocyte cytotoxicity and immune regulation, whereas the secondary (acquired) form more frequently diagnosed in adults, is triggered by infections, malignancies, autoimmune disorders, or rarely pregnancy.[3] In this report, we describe a case of HLH in pregnancy, the diagnostic challenges, treatment approach, and outcome.

CASE REPORT

A 31-year-old Indian lady Gravida 3, Para 2 at 32 weeks of gestation at 32 weeks of gestation, with gestational diabetes mellitus on diet control and anaemia in pregnancy, presented with a 1-week history of fever, chills, and rigor associated with lethargy, malaise and cough. She received initial treatment for presumed community-acquired pneumonia in a private hospital and subsequently transferred to our health facility due to financial constraints for further care.

Upon arrival, she was still febrile at 39.5°C but haemodynamically stable, not tachypnoeic and saturating well under room air. Physical examination was unremarkable with a gravid uterus corresponding to 30 weeks of gestation. A chest radiograph of the patient with abdominal shield was normal. However, there was pancytopenia on admission (haemoglobin 8.4 g/dL, total white cell count 2.5 x 10^9/L, absolute neutrophil count 1.56 x 10^9/L, platelet 57 x 10^9/L) with no circulating blasts or abnormal lymphoid cells on the peripheral blood smear.

Fever was persistent with high-grade temperatures reaching 40°C despite sequential courses of broad-spectrum antibiotics, which included coverage for atypical infection, given for a total of 21 days. As there was no positive yield from the repeated pan-cultures including fungal culture, empirical antibiotics were ceased and she was closely monitored. The temperature spikes continued but she was not septic-looking. Blood cultures taken during the antibiotic-free period were negative. Results of investigations for rheumatological disorders (Anti Nuclear Antibody, Extractable Nuclear Antigen panel, Rheumatoid Factor, Complement levels, Lupus Anticoagulant) and infections (Human Immunideficiency Virus, viral hepatitis, Parvovirus B19, Cytomegalovirus, Ebstein-Barr Virus, tuberculosis, dengue, malaria, mycoplasma, and COVID 19) were negative.

On the contrary, serial blood tests showed an increasing trend of C-reactive protein, lactate dehydrogenase, and ferritin, peaking at 141 mg/L, 1055 U/L, and 3798 µg/L, respectively. Triglyceride level was elevated at 6.11 mmol/L, associated with mildly elevated liver enzymes but no hypofribrinogenaemia to suggest HELLP syndrome. Several imaging modalities, specifically transthoracic echocardiogram, abdominal ultrasonogram (USG), contrast enhanced computed tomography (CECT) of thorax (with abdominal shield), and magnetic resonance imaging (MRI) of abdomen were performed to thoroughly investigate for the cause of PUO in our patient. The only significant abnormality detected was hepatosplenomegaly on both USG and MRI (liver span at 25.1 cm, spleen at 14.5 cm).

HLH was considered in view of persistent fever, pancytopenia, hepatosplenomegaly, and high inflammatory markers. A bone marrow aspirate and trephine biopsy (BMAT) was carried out which demonstrated haemophagocytosis with increased erythrophagocytosis, on a background of reactive marrow without evidence of malignancy (Figure 1(A) and (B)). Polymicrobial growth of gram negative organisms (*Acinetobacter sp.* and *Klebsiella pneumoniae*) was isolated from

This article was accepted: 25 September 2022
Corresponding Author: Jonathan Tan Heng Loke
Email: jonathantanhengloke@gmail.com

Table I: HLH-2004 diagnostic criteria

The diagnosis of HLH can be established if Criterion 1 or 2 is fulfilled.
1. A molecular diagnosis is consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
   - Fever
   - Splenomegaly
   - Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood)
     - Haemoglobin <90 g/L
     - Platelets <100 x10^9 /L
     - Neutrophils <1.0 x10^9 /L
   - Hypertriglyceridemia and/or hypofibrinogenemia
     - Fasting triglycerides ≥ 3.0 mmol/L (ie, ≥265 mg/dL)
     - Fibrinogen ≤1.5 g/L
   - Haemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy
   - Low or no natural killer cell activitiy (according to local laboratory reference)
   - Ferritin ≥500 µg/L
   - sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

Table II: Parameters and points in the HScore

Parameter	Number of Points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (℃)	0 (<38.4), 33 (38.4-39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias§	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (µg/L)	0 (<2000), 35 (2000-6000), or 50 (>6000)
Fibrinogen (g/L)	0 (>2.5) or 30 (≤2.5)
Aspartate aminotransferase (U/L)	0 (<30) or 19 (≥30)
Haemophagocytosis on bone marrow aspirate	0 (no) or 35 (yes)

*HIV positive or receiving long-term immunosuppressive therapy (i.e. glucocorticoids, cyclosporine A, azathioprine).
§ Defined as a haemoglobin level of 9.2 g/L and/or a leukocyte count ≤5 x10^9/L and/or a platelet count ≤110 x10^9/L

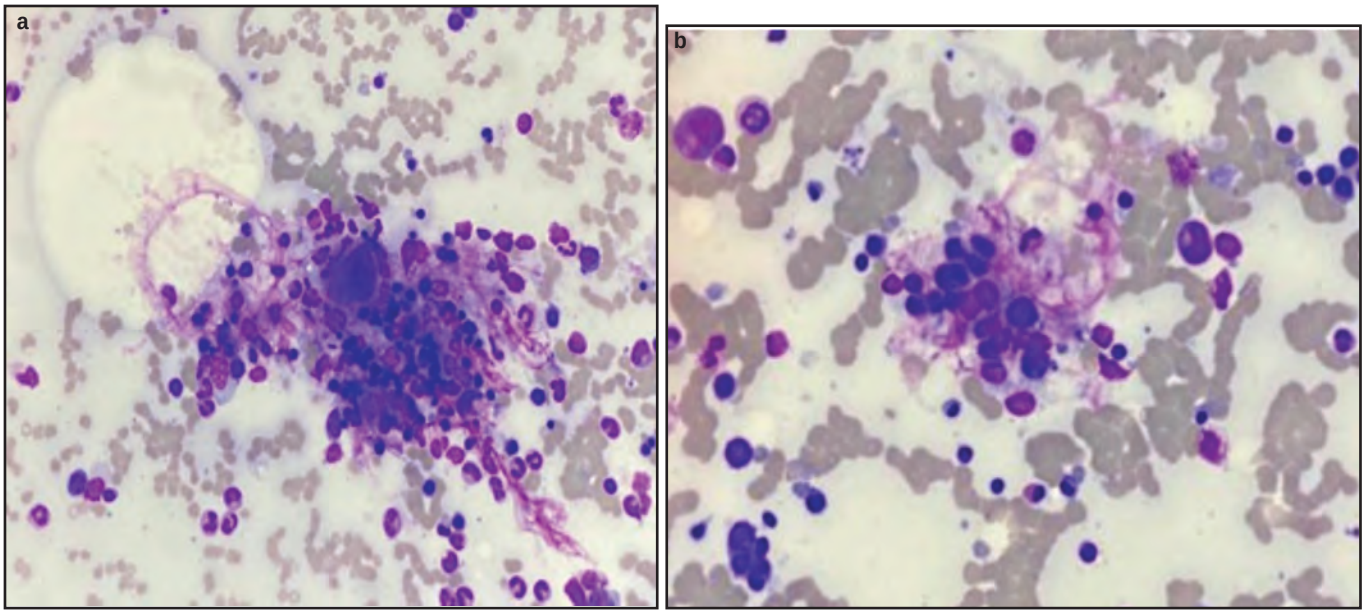

Fig. 1: Hypercellular marrow with increased haemophagocytic activities seen in bone marrow aspirate. (A) at low-powered field (B) at high-powered field.

the bone marrow aspirate and antibiotics were re-initiated to treat for possible superinfection in our patient. In retrospect, the organisms were likely contaminants as they were not isolated from paired culture samples taken during BMAT and from peripheral blood. Consequent to the BMAT findings, she was commenced on corticosteroids and IVIg before transfer to a tertiary haematology centre for specialized care. Fever promptly resolved soon after and she underwent an elective lower Caesarean section (LSCS) delivery at 36 weeks of pregnancy. She was thereafter started on cyclosporin with gradual normalisation of the blood counts.

DISCUSSION

Interest on acquired HLH in adults has increased over the years with improved awareness.[3] However, HLH in pregnancy is very seldom encountered as it remains a rare entity.[1] Diagnosis of HLH is not easy and it becomes all the more challenging when it develops in pregnancy due to a low index of suspicion and additional difficulties faced whilst searching for an aetiology that trigger the disease. Our patient presented with PUO and despite extensive investigations with mostly unremarkable results, a few features fortunately prompted the suspicion of HLH. Our patient fulfilled the HLH-2004 criteria (Table I) with 6 out of 8 criteria in addition to an elevated HScore (Table II) of 274, giving an above 99% probability of HLH.[4,5,6]

The pathophysiology of pregnancy-related HLH remains unclear.[1] In a systematic review by Teng et al., it is hypothesized that the placenta produces the most cytokines during pregnancy, causing a systemic inflammatory response which may induce or exacerbate HLH.[7] Another author postulated that the immature placenta releases syncytiotrophoblast components, fetal-derived soluble RNA and DNA, and cytotrophoblast cells which enter the maternal circulation causing various immune disorders and systemic inflammatory responses.[7,8] EBV infection remains a commonly identified aetiology for HLH regardless of pregnancy, followed by rheumatological diseases and malignancies.[9] Based on findings of the many examinations performed, we concluded that our patient had either an idiopathic HLH or HLH triggered by pregnancy. It is possible that less common viral triggers were missed due to unavailability of the diagnostic tests in our health facility. Diagnosing HLH is challenging as the majority of the clinical and laboratory parameters are merely supportive and not specific for the disorder. A delay in diagnosis prevents early initiation of therapy, leading to worse outcomes. HLH in pregnancy necessitates urgent attention and prompt action to arrest the inflammation, which may otherwise become uncontrolled, causing maternal mortality and foetal demise.[1] Our patient responded well to IVIg, dexamethasone and an expedited delivery. The delivery was uneventful and she was discharged well with an appointment under haematology clinic with improving ferritin levels.

CONCLUSION

Workup to reach a diagnosis of HLH especially in pregnancy is arduous due to the complexity and rarity of this condition. Albeit rare, HLH should always be considered as a cause of PUO in pregnancy. Multidisciplinary input is essential for appropriate investigations, early diagnosis, and timely management to ensure a favourable obstetric outcome.

ACKNOWLEDGEMENT

We would like to acknowledge Obstetric and Gynaecology colleagues from Hospital Melaka and Hospital Ampang for co-managing.

REFERENCES

1. Liu L, Cui Y, Zhou Q, Zhao H, Li X. Hemophagocytic lymphohistiocytosis during pregnancy: a review of the literature in epidemiology, pathogenesis, diagnosis and treatment. Orphanet J Rare Dis 2021; 16: 281.
2. Birndt S, Schenk T, Heinevetter B, Brunkhorst FM, Maschmeyer G, Rothmann F, et al. Hemophagocytic lymphohistiocytosis in adults: collaborative analysis of 137 cases of a nationwide German registry. J Cancer Res Clin Oncol. 2020;146:1065–1077.
3. La Rosee P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Am Soc Hematol 2019; 133(23): 2465.
4. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014; 66(9): 2613-20.
5. Bergsten E, Horne A, Arico M, Astigarraga I, Egeler RM, Filipovich AH, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 2017; 130(25): 2728-38.
6. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007; 48: 124-31.
7. Teng CL, Hwang GY, Lee BJ, Wang RC, Chou MM. Pregnancy-induced hemophagocytic lymphohistiocytosis combined with autoimmune hemolytic anemia. J Chin Med Assoc 2009; 72(3): 156-9.
8. Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response—a review. Placenta 2003; 24(Suppl A): S21-7.
9. Rousselin A, Alavi Z, Le Moigne E, Renard S, Tremouilhac C, Delluc A, et al. Hemophagocytic syndrome in pregnancy: case report, diagnosis, treatment, and prognosis. Clin Case Rep 2017; 5(11): 1756-64.