CASE REPORT

Haemophagocytic lymphohistiocytosis presenting as HELLP syndrome: a diagnostic and therapeutic challenge

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal, haematological disorder, which can be clinically challenging to diagnose and manage. We report a case of HLH in a previously healthy 33-year-old primigravida. The patient presented at 22 weeks gestation with dyspnoea, abdominal pain, anaemia, thrombocytopenia and elevated liver enzymes suggestive of HELLP syndrome. HELLP, a syndrome characterised by haemolysis, elevated liver enzymes and low platelets is considered a severe form of pre-eclampsia. Despite delivery of the fetus, her condition deteriorated over 3–4 days with high-grade fever, worsening thrombocytopenia and anaemia requiring transfusion support. A bone marrow biopsy showed haemophagocytosis and a diagnosis of HLH was made. Partial remission was achieved with etoposide-based chemotherapy and complete remission following bone marrow transplantation. Eleven months post-transplant, the disease aggressively recurred, and the patient died within 3 weeks of relapse.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathological immune activation characterised by signs and symptoms of extreme inflammation.¹ This disease can be divided into primary HLH and secondary HLH. Primary HLH refers to a familial form where defects in perforin function and other cytosolic pathways are attributed to disease. Secondary HLH refers to a sporadic or acquired form, which has been attributed to a variety of autoimmune syndromes, rheumatological diseases, immunodeficiencies and infections, particularly viruses such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV).^{2–5} Its diagnosis is based on the Histiocyte Society HLH Study group, which requires either a genetic mutation associated with HLH (PRF1, UNC13D, STXBP1, RAB27A, STX11) or five of the following: (1) fever ($>38^{\circ}\text{C}$), (2) splenomegaly, (3) cytopenia affecting at least two lineages in the peripheral blood, (4) hypertriglyceridaemia and/or hypofibrinogenaemia, (5) haemophagocytosis in the bone marrow, spleen, lymph nodes or liver, (6) low or absent natural killer cell activity, (7) ferritin $>500\text{ mg/L}$ and (8) soluble CD25 (soluble interleukin 2 (IL-2) receptor) $>2400\text{ IU/mL}$.⁶ HLH is rarely described during pregnancy and clinical management appears

inconsistent across 17 published cases (table 1). Here, we report a case of pregnancy-related HLH, which was initially successfully treated with delivery, etoposide-based chemotherapy and allogenic bone marrow transplantation. Following 11 months in remission, the disease aggressively recurred and the patient died within 3 weeks of relapse.

CASE PRESENTATION

A previously healthy 33-year-old primigravida presented at 22 weeks gestation with 1 week history of dyspnoea along with epigastric, shoulder and back pain. The patient's medical and family history was unremarkable. She was afebrile, tachycardic (142 beats/min), normotensive (124/80 mm Hg) and tachypnoeic (24 breaths/min) with an oxygen saturation of 96% on room air. Physical examination did not reveal any rash, arthritis, lymphadenopathy or organomegaly. Laboratory studies showed a mild anaemia (haemoglobin 11.3 g/dL), moderate thrombocytopenia (platelet count of $86 \times 10^9/\text{L}$), elevated liver enzymes (alanine aminotransferase (ALT) 105 IU/L) and raised D-dimers (1.78 mg/L). Her lactate dehydrogenase (LDH) was slightly elevated at 305 IU/L. Peripheral blood smear showed a hypochromia and a CT pulmonary angiogram was normal. Her condition continued to deteriorate requiring oxygen therapy to maintain O_2 saturations of 96%. She developed severe epigastric pain. Platelet count fell to $62 \times 10^9/\text{L}$ and haemoglobin to 9.4 g/dL. Clinical suspicion was high for an atypical hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome and urgent delivery of the fetus was indicated. Labour was medically induced and the patient delivered a live female infant who died within minutes of delivery. Over the next 24 hours, she developed a high-grade fever and was commenced on intravenous broad spectrum antibiotics.

INVESTIGATIONS

A chest X-ray revealed a right basal pneumonia and she became increasingly oedematous with an albumin level of 12 g/L. Further laboratory investigations showed a rising LDH level (777 IU/L), hyperferritinaemia (3815 ng/mL), progressive thrombocytopenia to $25 \times 10^9/\text{L}$ and anaemia of 9.5 g/dL requiring transfusion support. She was also noted to have low levels of schistocytes in her blood film (1.7%). A CT of the abdomen revealed

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Table 1 Haemophagocytic lymphohistiocytosis in pregnancy

Author	Age (years)	Gestational age (weeks)	Associated diagnosis	Clinical presentation	Treatment	Outcome	Mode of delivery
Nakabayashi <i>et al</i> ¹⁶	30	21	Pre-eclampsia	Fever, pancytopenia, elevated LDH, ferritin	Antibiotics and Ig Antithrombin concentrate	Failed Remission	29 weeks CS
Yamaguchi <i>et al</i> ¹⁷	—	—	HSV2	Fever, pancytopenia, elevated ferritin, triglycerides, sIL-2R	Corticosteroids Ciclosporin A	Failed Remission	Term VD
Hanaoka <i>et al</i> ¹⁸	33	21	B-cell lymphoma	Fever, hepatosplenomegaly, pancytopenia, elevated ferritin, TG, LDH, sIL-2R	R-CHOP chemotherapy and emergent CS	Remission	28 weeks CS
Dunn <i>et al</i> ¹⁰	41	19	Still's disease	Rash, fever and headache, anaemia, elevated ferritin, TG, LDH	High-dose corticosteroids and delivery	Remission	30 weeks CS
Mayama <i>et al</i> ¹⁹	28	19	Parvovirus B19	Fever, pancytopenia, elevated ferritin, LDH	Corticosteroids	Remission	37 weeks VD
Teng <i>et al</i> ¹¹	28	23	AIHA	Fever, anaemia, thrombocytopenia, elevated ferritin, TG, LDH, sIL-2R	Steroids Termination of pregnancy	No response Remission	29 weeks CS (fetal death at delivery)
Kim <i>et al</i> ²⁰	29	12	SLE	Fever, pancytopenia, elevated ferritin, TG, LDH	Splenectomy	Remission	14 weeks TOP
Chmait <i>et al</i> ⁴	24	29	EBV	Routine check-up: pancytopenia	Ig, acyclovir, delivery at 30th week	Death: DIC, multiple organ failure	30 weeks CS
Klein <i>et al</i> ³	39	30	EBV	Pancytopenia, elevated ferritin, sIL-2R	Steroids, ciclosporin A, etoposide, rituximab	Death: multiple organ failure, sepsis	31 weeks CS
Ota <i>et al</i> ²¹	26	23	Liver abscess	Fever, thrombocytopenia, elevated ferritin, TG, LDH, sIL-2R	None	Death: cardiopulmonary arrest	—
Pérard <i>et al</i> ²²	28	22	SLE	Fever, pancytopenia, elevated ferritin, TG	Corticosteroids IVIg	Failed Remission	30 weeks VD
Chien <i>et al</i> ²³	28	23	—	Fever, anaemia, thrombocytopenia, elevated TG	CS delivery	Remission	CS
Tumian and Wong ⁵	35	38	CMV	Fever, anaemia, jaundice, elevated ferritin, TG, LDH, sIL-2R	CS delivery, steroids and ciclosporin A	Death: multiple organ failure	CS
Arewa and Ajadi ²⁴	31	21	HIV	Jaundice, fever, abdominal pain, anaemia, thrombocytopenia	HAART and delivery	Remission	Term VD
Shukla <i>et al</i> ²⁵	23	10	—	Fever, pancytopenia, elevated ferritin, TG	Corticosteroids Spontaneous abortion	Failed Remission	—
Samra <i>et al</i> ⁹	36	16	—	Fever, pancytopenia, elevated ferritin, TG	Corticosteroids	Remission	Term VD
Mihara <i>et al</i> ²	32	16	EBV	Fever, pancytopenia, elevated ferritin, LDH, sIL-2R	Corticosteroids, acyclovir IVIg	Failed Remission	35 weeks VD
Our patient	33	22	—	Dyspnoea, abdominal pain, anaemia, thrombocytopenia, raised ferritin, LDH	Corticosteroids Delivery, etoposide, BMT	Failed Remission	22 VD (fetal death at delivery)

AIHA, autoimmune haemolytic anaemia; BMT, bone marrow transplantation; CMV, cytomegalovirus; CS, caesarean section; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; HAART, highly active antiretroviral therapy; HLH, haemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; sIL-2R, soluble interleukin-2 receptor; SLE, systemic lupus erythematosus; TOP, termination of pregnancy; TG, triglycerides; VD, vaginal delivery.

hepatosplenomegaly and moderate volume ascites. A bone marrow aspirate and trephine biopsy was ordered 14 days post-partum, which revealed haemophagocytosis in the bone marrow. MRI of the brain was performed, which revealed an incidental pineal cyst. Results of genetic testing showed a normal perforin expression and granule release assay. Viral serology studies were also negative for EBV and CMV.

DIFFERENTIAL DIAGNOSIS

Our patient had fever, splenomegaly, cytopenia affecting two lineages in the peripheral blood (haemoglobin <9 g/dL and platelets <100×10⁹/L), haemophagocytosis in bone marrow and ferritin >500 µg/L fulfilling five out of eight criteria set out in the HLH 2004 trial. This supports a diagnosis of HLH.⁶ Given the patient's age, secondary HLH was most likely. The acquired form can develop at any age and is usually secondary to

infections (mycobacterium, EBV, CMV, HIV, herpes and protozoal infections), drug exposure (immunomodulatory drugs), autoimmune inflammatory disease (systemic lupus erythematosus, rheumatoid arthritis, Still's disease) and malignancies (eg, leukaemia, lymphoma, multiple myeloma, hepatocellular carcinoma and germ-cell tumours).^{7,8}

TREATMENT

Initial treatment consisted of dexamethasone and ciclosporin as per the HLH-2004 protocol.⁶ She deteriorated a week later with profound hypotension, tachycardia and sudden worsening cytopenias (haemoglobin 7.7 g/dL; platelets 16×10⁹/L), hypofibrinogenemia (0.3 g/L) and a rising prothrombin time (12.2 s). She developed shock, required inotropes and transfer to intensive care unit. Once stabilised, she continued her chemotherapy for 8 weeks. Her albumin improved to 37 IU/L and her transfusion

Figure 1 Timeline of platelet and ferritin levels over the course of the disease.

requirement diminished over weeks. Once her platelet count improved, a lumbar puncture was performed with intrathecal methotrexate administration as per protocol.⁶ Repeat bone marrow biopsy showed partial remission. Following this, her anaemia and thrombocytopenia remained stable but her ferritin continued to rise ($>15\,000$ IU/L) requiring admission again for further chemotherapy (figure 1). Her ferritin level reduced to 5041 IU/L following further etoposide-based therapy. Given the likely histiocyte cell burden reflected by her ferritin levels, the patient underwent allogeneic bone marrow transplant with curative intent 3 months later.

OUTCOME AND FOLLOW-UP

The patient went into remission following transplant and had a good quality of life. However, 11 months post bone marrow transplant, her condition deteriorated with falling platelet ($<10 \times 10^9$ /L), white cell (1.0×10^9 /L) and haemoglobin (9.3 g/dL) counts. An initial bone marrow biopsy showed no trace of HLH. However, 2 weeks later in the face of worsening cytopenia, the patient became symptomatic and a further biopsy showed over 60% infiltration with HLH cells and haemophagocytosis. At this time, she developed systemic symptoms of severe oedema, fatigue, malaise and severe pain in her right knee and hip. She was treated with methylprednisolone, etoposide and cyclophosphamide for palliation. Following 3 days at home with her family, she died of her disease.

DISCUSSION

Pregnancy-associated HLH is a rare entity and to our knowledge only 17 case reports have been published to date (table 1). Fever with or without pancytopenia was the predominant clinical finding in HLH cases described in pregnant women.⁹ For a pregnant patient who presents with fever, low platelet counts and elevated liver enzymes, a differential diagnosis of HELLP syndrome, sepsis, cholestasis of pregnancy and acute fatty liver of pregnancy should always be considered. Following delivery, the clinical features of HELLP syndrome typically resolve while the available case reports of pregnancy-related HLH suggest it follows a more progressive course.^{4 10 11} Haemophagocytosis on histology is often a late feature and is not necessary for a diagnosis as per HLH criteria. Ferritin levels greater than $500 \mu\text{g/L}$ (in the absence of other causes of hyperferritinaemia) have a sensitivity of 84% and greater than $10\,000 \mu\text{g/L}$ have 90% sensitivity and 96% specificity.^{12 13} Therefore, a pronounced hyperferritinaemia in the setting of systemic signs and symptoms along with a negative infection screen should raise suspicions of HLH.

There is no established treatment guideline for pregnancy-related HLH to date. In general, the treatment of secondary HLH includes three main components: (1) identification and treatment of the underlying cause; (2) inhibition of T-cell activation and proliferation and (3) inhibition of cytokine secretion and production. The treatment regime outlined in the HLH-94 protocol consists of 8 weeks of etoposide-based chemotherapy along with dexamethasone, cyclosporin and intrathecal methotrexate for those with CNS involvement.¹⁴ The HLH-94 protocol is currently recommended as the study results of the revised 2004 protocol have yet to be published.⁶ The HLH-94 regime achieved $\sim 75\%$ clinical remission after 8 weeks of treatment. At a median follow-up of 3.1 years, the estimated 3-year probability of survival overall was 55%.¹⁴ Of the 17 reported cases of pregnancy-associated HLH, at least 6 achieved complete remission following cessation of pregnancy. Kourtis *et al*¹⁵ recently challenged the long-held belief that pregnancy is a state of immunosuppression and suggests it should be viewed as a modulated immunological condition. While the specific role of pregnancy in HLH has not been elucidated, it is likely that the cellular and humoral immune mediators in HLH are subject to pregnancy-related alterations.

Learning points

- ▶ A pronounced hyperferritinaemia in the setting of systemic signs and symptoms along with a negative infection screen should raise suspicions of haemophagocytic lymphohistiocytosis (HLH).
- ▶ To our knowledge, this is the first known case of pregnancy-related HLH treated with allogeneic bone marrow transplant, which achieved 11 months of complete remission.
- ▶ The aggressive pace of the relapse in the post-transplant period signifies the aggressive nature of the condition and disease control or reinduction post allograft failure was not expected.

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REFERENCES

- 1 Jordan MB, Allen CE, Weitzman S, *et al*. How I treat hemophagocytic lymphohistiocytosis. *Blood* 2011;118:4041–52.
- 2 Mihara H, Kato Y, Tokura Y, *et al*. [Epstein-Barr virus-associated hemophagocytic syndrome during mid-term pregnancy successfully treated with combined methylprednisolone and intravenous immunoglobulin]. *Rinsho Ketsueki* 1999;40:1258–64.
- 3 Klein S, Schmidt C, La Rosée P, *et al*. Fulminant gastrointestinal bleeding caused by EBV-triggered hemophagocytic lymphohistiocytosis: report of a case. *Z Gastroenterol* 2014;52:354–9.
- 4 Chmait RH, Meimin DL, Koo CH, *et al*. Hemophagocytic syndrome in pregnancy. *Obstet Gynecol* 2000;95:1022–4.
- 5 Tumian NR, Wong CL. Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: a diagnostic and therapeutic challenge. *Taiwan J Obstet Gynecol* 2015;54:432–7.
- 6 Henter JJ, Horne A, Aricó M, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124–31.

- 7 Aryal MR, Badal M, Giri S, *et al.* Haemophagocytic lymphohistiocytosis mimicking septic shock after the initiation of chemotherapy for squamous cell carcinoma of the neck. *BMJ Case Rep* 2013;2013:bcr2013009651.
- 8 Deane S, Selmi C, Teuber SS, *et al.* Macrophage activation syndrome in autoimmune disease. *Int Arch Allergy Immunol* 2010;153:109–20.
- 9 Samra B, Yasmin M, Arnaout S, *et al.* Idiopathic Hemophagocytic lymphohistiocytosis during Pregnancy treated with steroids. *Hematol Rep* 2015;7:6100.
- 10 Dunn T, Cho M, Medeiros B, *et al.* Hemophagocytic lymphohistiocytosis in pregnancy: a case report and review of treatment options. *Hematology* 2012;17:325–8.
- 11 Teng CL, Hwang GY, Lee BJ, *et al.* Pregnancy-induced hemophagocytic lymphohistiocytosis combined with autoimmune hemolytic anemia. *J Chin Med Assoc* 2009;72:156–9.
- 12 Tsuda H, Shirono K. Successful treatment of virus-associated haemophagocytic syndrome in adults by cyclosporin A supported by granulocyte colony-stimulating factor. *Br J Haematol* 1996;93:572–5.
- 13 Ravelli A, Viola S, De Benedetti F, *et al.* Dramatic efficacy of cyclosporine A in macrophage activation syndrome. *Clin Exp Rheumatol* 2001;19:108.
- 14 Henter JL, Samuelsson-Horne A, Aricò M, *et al.* Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood* 2002;100:2367–73.
- 15 Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med* 2014;370:2211–8.
- 16 Nakabayashi M, Adachi T, Izuchi S, *et al.* Association of hypercytokinemia in the development of severe preeclampsia in a case of hemophagocytic syndrome. *Semin Thromb Hemost* 1999;25:467–71.
- 17 Yamaguchi K, Yamamoto A, Hisano M, *et al.* Herpes simplex virus 2-associated hemophagocytic lymphohistiocytosis in a pregnant patient. *Obstet Gynecol* 2005;105:1241–4.
- 18 Hanaoka M, Tsukimori K, Hojo S, *et al.* B-cell lymphoma during pregnancy associated with hemophagocytic syndrome and placental involvement. *Clin Lymphoma Myeloma* 2007;7:486–90.
- 19 Mayama M, Yoshihara M, Kokabu T, *et al.* Hemophagocytic lymphohistiocytosis associated with a Parvovirus B19 infection during pregnancy. *Obstet Gynecol* 2014;124(2 Pt 2 Suppl 1):438–41.
- 20 Kim JM, Kwok SK, Ju JH, Jh J, *et al.* Macrophage activation syndrome resistant to medical therapy in a patient with systemic lupus erythematosus and its remission with splenectomy. *Rheumatol Int* 2013;33:767–71.
- 21 Ota K, Kawahara K, Banno H, *et al.* Hemophagocytic Lymphohistiocytosis caused by pyogenic liver abscess during Pregnancy: a Case Report and Literature Review. *Open J Obstet Gynecol* 2016;06:287–92.
- 22 Pérard L, Costedoat-Chalumeau N, Limal N, *et al.* Hemophagocytic syndrome in a pregnant patient with systemic lupus erythematosus, complicated with preeclampsia and cerebral hemorrhage. *Ann Hematol* 2007;86:541–4.
- 23 Chien CT, Lee FJ, Luk HN, *et al.* Anesthetic management for cesarean delivery in a parturient with exacerbated hemophagocytic syndrome. *Int J Obstet Anesth* 2009;18:413–6.
- 24 Arewa OP, Ajadi AA. Human immunodeficiency virus associated with haemophagocytic syndrome in pregnancy: a case report. *West Afr J Med* 2011;30:66–8.
- 25 Shukla A, Kaur A, Hira HS. Pregnancy induced haemophagocytic syndrome. *J Obstet Gynaecol India* 2013;63:203–5.

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