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Case Report

Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: A diagnostic and therapeutic challenge

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ABSTRACT

Objective: Hemophagocytic lymphohistiocytosis (HLH) is a disorder characterized by uncontrolled mature histiocyte proliferation, hemophagocytosis, and hypercytokinemia. We describe a previously healthy pregnant patient who presented in the third trimester of pregnancy with HLH.

Case Report: A 35-year-old woman presented at 38 weeks' gestation with pyrexia, jaundice, severe anemia, elevated liver enzymes, and lactate dehydrogenase suggestive of HELLP (hemolysis, elevated liver enzyme, low platelet) syndrome. Unfortunately, her condition deteriorated and she was ventilated in the intensive care unit despite delivery of the baby and administration of dexamethasone. She developed microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment suggestive of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. However, she was refractory to plasma exchange, intravenous immunoglobulin, and broad-spectrum antibiotics. HLH was eventually diagnosed from biochemical and bone marrow findings. An extensive search for possible causes yielded negative results. She improved significantly with intravenous dexamethasone and cyclosporine A and was transferred out of the intensive care unit. Unfortunately, she developed cytomegalovirus disease 2 weeks later, which improved transiently with intravenous ganciclovir; later, however, she succumbed to multidrug-resistant nosocomial infections, rapidly progressive cytomegalovirus disease, and multiorgan failure.

Conclusion: This case highlights the challenges and difficulties involved in the diagnosis and management of pregnancy-related HLH. Immunosuppressive treatment for HLH can precipitate life-threatening opportunistic infections, which need to be promptly diagnosed and treated.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare yet potentially fatal clinicopathological entity because of uncontrolled immune system activation. It results in histiocytic proliferation with significant hemophagocytic activity in the bone marrow and massive release of inflammatory cytokines [1]. Its diagnosis is based on the HLH-2004 criteria, which requires at least five of the following manifestations: fever $\geq$ 38°C, splenomegaly, cytopenia affecting at least two lineages in the peripheral blood, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen, lymph nodes or liver, low or absent natural killer cell activity, ferritin $\geq$ 500 ng/mL, and elevated sCD25 [2]. Its incidence worldwide is not known. According to Ishii et al [3], the annual incidence of HLH in Japan is approximately one in 800,000.

HLH can be classified as either primary or secondary. Primary HLH is an autosomal recessive disorder, also termed familial HLH. It commonly occurs in infancy and childhood, but can also present later and is often fatal when untreated [4]. Defects in a number of genes have been linked to familial HLH: Perforin (PRF1), Munc 13-4 (UNC13D), Syntaxin 11 (STX11), and Munc 19-2 (STXBP2) [2]. Secondary HLH can be triggered by a variety of diseases such as infections, immunodeficiency syndromes, hematological malignancies, and autoimmune diseases. This classification is not always

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straightforward because primary HLH can present at any age. An underlying genetic mutation is found in only 40% of all primary HLH patients, and both types could be triggered by a variety of infections [4]. However, it is useful in long-term management, as mortality is generally higher in primary HLH unless it is treated by hematopoietic stem cell transplant.

To date, there are few reported cases of pregnancy-related HLH that are associated with significant morbidity and mortality [5–18]. The majority of cases occurred during the second trimester of pregnancy (Table 1). The diagnosis of HLH in pregnancy can be extremely challenging as some of the clinicopathological features may mimic the presentation of other common conditions exclusive to pregnancy such as HELLP (hemolysis, elevated liver enzyme, low platelet) syndrome and acute fatty liver of pregnancy. There are no established guidelines for the management of pregnancy-related HLH.

We report our experience in managing a previously healthy pregnant patient who presented in the third trimester of pregnancy with HLH. This case highlights the complexity of pregnancy-related HLH and identifies some key areas in the management of this disease that should be addressed in order to improve survival in this potentially fatal disease.

Case Report

A 35-year-old woman presented with a 2-day history of vomiting, jaundice, pruritus, and dark-colored urine at 38 weeks' gestation. Antenatally, she was diagnosed with gestational diabetes, which was diet-controlled. During her first pregnancy, she had an emergency cesarean section for severe preeclampsia at 32 weeks' gestation. She denied any abdominal pain, diarrhea, joint pain, alopecia, malar rash, or bleeding tendency. There was no history of recent travels, and she was not on any medication. On examination, she looked pale and jaundiced. She was apyrexial with a blood pressure of 125/72 mmHg and a heart rate of 100 beats/min. An abdominal examination revealed a gravid uterus without organomegaly. Examination of other systems yielded unremarkable results, and there was no evidence of lymphadenopathy.

Table 1
Summary of reported cases of pregnancy-related HLH.

No.	Age (y)	Period of gestation (wk)	Cause/associated factor	Treatment	Outcome of pregnancy		Study
					Maternal	Fetal	
1	28	23	Autoimmune hemolytic anemia (AIHA)	Steroids—no response, Termination of pregnancy	Alive	Delivered at 29 wk of gestation—died from pulmonary distress	Teng et al [5]
2	32	16	EBV	Methylprednisolone 1 g/d for 3 d + IV immunoglobulin 20 g/d for 3 d + acyclovir 750 mg/d + gabexate mesilate 2 g/d Maintenance: oral prednisolone 5 mg/d + camostat mesilate 600 mg/d	Alive	Delivered at 35 wk of gestation—alive	Mihara et al [6]
3	33	23	B cell lymphoma	Steroids—no response Six cycles of R-CHOP, then autologous peripheral blood stem cell transplantation	Alive	Delivered at 28 wk of gestation - alive	Hanaoka et al [7]
4	[a]	2nd trimester	HSV-2	Acyclovir (750 mg/d) & prednisolone (30 mg/d) → transient reduction in fever IV pulse methylprednisolone followed by full-dose prednisolone & later cyclosporine A	Alive	Delivered at 37 wk of gestation—alive	Yamaguchi et al [8]
5	24	29	Necrotizing lymphadenitis—EBV	IV immunoglobulin 60 g/d for 3 d & IV acyclovir 750 mg every 12 h	Death	Delivered at 30 wk gestation—alive	Chmait et al [9]
6	41	19	Twin pregnancy, history of Still's disease	High-dose corticosteroids	Alive	Delivered at 30 wk of gestation—alive	Dunn et al [10]
7	28	22	SLE	IV immunoglobulin 1 g/kg/d for 2 d then IV methylprednisolone 1 g/d for 3 d followed by oral prednisone 0.5 mg/kg/d Another 2 doses of IVIg given at 28 wk & 30 wk of gestation, respectively	Alive	Delivered at 30 wk of gestation—alive	Perard et al [11]
8	31	21	HIV & malaria	Antimalaria treatment (amodiaquine) & HAART	Alive	Delivered at term—alive	Arewa & Ajadi [12]
9	[a]	21	Preeclampsia	Antibiotics + immunoglobulin given but failed Antithrombin concentrates	Alive	Alive	Nakabayashi et al [13]
10	30	9 d after delivery	Human parvovirus B19	[a]	[a]	[a]	Tsuda et al [14]
11	29	21	Systemic lupus erythematosus	[a]	[a]	[a]	Hannebicque-Montaigne et al [15]
12	36	38 d after delivery	Primary Sjogren's syndrome	Oral prednisolone 1 mg/kg/d	Alive	Alive	Komaru et al [16]
13	33	After delivery	SLE	Oral prednisolone 55 mg/d	Alive	Alive	Yoshida et al [17]
14	[a]	Second trimester	—	High-dose IV Ig	Alive	[a]	Gill et al [18]

EBV = Epstein-Barr virus; HAART = highly active antiretroviral therapy; HLH = hemophagocytic lymphohistiocytosis; HSV-2 = herpes simplex virus 2; IVIg = intravenous immunoglobulin; R–CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy regimen; SLE = systemic lupus erythematosus.
[a] Information not available.

A full blood count showed hemoglobin (Hb) of 7.1 g/dL (mean cell volume 67.4 fL), white cell count of 15 $\times$ 10^9/L with predominantly neutrophils (82.8%), and platelet count of 151 $\times$ 10^9/L. Peripheral blood film showed hypochromic microcytic red blood cells, anisocytosis, polychromasia, and target and pencil cells. Spherocytes and a few atypical lymphocytes were present, but no fragmented red cells were noted. Results of the liver function test was abnormal: elevated bilirubin of 164 μmol/L (predominantly conjugated); alanine transaminase, 341 U/L; aspartate transaminase, 397 U/L; alkaline phosphatase, 389 U/L. The renal profile revealed an elevated creatinine of 153 U/L and a slightly low sodium level of 131 mmol/L. Lactate dehydrogenase was elevated at 1190 U/L. Coagulation was abnormal with an elevated prothrombin time of 31.3 seconds (control 12.7 seconds) and an activated partial thrombin time of 79.3 seconds (control 38.7 seconds). Urine dipstick showed proteinuria 2+.

She subsequently underwent an emergency cesarean section owing to evidence of fetal distress. As there was severe anemia and coagulopathy, she was transfused with 4 units of packed red blood cells and 4 units of fresh frozen plasma prior to surgery. Postoperatively, her Hb and platelet counts dropped further to 4.1 g/dL and 84 $\times$ 10^9/L, respectively, within 6 hours. The direct Coombs test result was negative, and her abdominal ultrasound showed normal size and echogenicity of the liver and spleen. At this point, the overall clinical picture was suggestive of HELLP syndrome. Despite delivery of the baby, she developed disseminated intravascular coagulopathy, hypovolemic shock, and acute kidney injury with severe metabolic acidosis requiring ventilator support and continuous venovenous hemodialysis in the intensive care unit (ICU). Intravenous dexamethasone 10 mg daily was administered with minimal improvement.

She received multiple blood product support owing to persistent cytopenias and coagulopathy. On Day 4 postpartum, she suddenly developed hemoptysis and acute respiratory distress approximately 2 hours following transfusion with blood products. Her chest X-ray results showed diffuse ill-defined opacities at both lower lung zones, which were most probably attributable to transfusion-related acute lung injury. She was treated supportively with oxygen, and her clinical condition stabilized. Although her Hb level was initially maintained for a few days, she developed a fever on Day 7 postpartum that was associated with worsening anemia and thrombocytopenia. Repeat blood film showed features consistent with microangiopathic hemolytic anemia. As blood and tracheal aspirate culture grew *Klebsiella* ESBL, the clinical picture was more suggestive of infection-induced thrombotic thrombocytopenic purpura. She was commenced on intravenous broad spectrum antibiotics and underwent four cycles of plasma exchange. She was also treated with intravenous immunoglobulin (IVIg) 10 g twice a day for 3 days. Despite these measures and massive blood product support (26 units of packed red blood cells, 45 units of fresh frozen plasma, 16 units of platelets, and 30 units of cryoprecipitate), her condition continued to deteriorate.

Extensive infection screening including blood, urine, and sputum cultures yielded negative results. Serial full blood count showed persistent severe anemia (Hb, 5.5 g/dL), severe thrombocytopenia (platelet count, 32 $\times$ 10^9/L), and leukocytosis. The result of her liver function test was persistently abnormal with an alanine transaminase of 158 U/L and aspartate transaminase 74 U/L. Lactate dehydrogenase was significantly elevated at 2692 U/L and C-reactive protein was 1.18 mg/L. The immunoglobulin panel showed normal IgM, IgG, and IgA levels. A bone marrow biopsy showed prominent hemophagocytosis with some atypical smear cells (Figure 1).

On Day 14 postpartum, a diagnosis of HLH was eventually made that was supported by other blood parameters including low

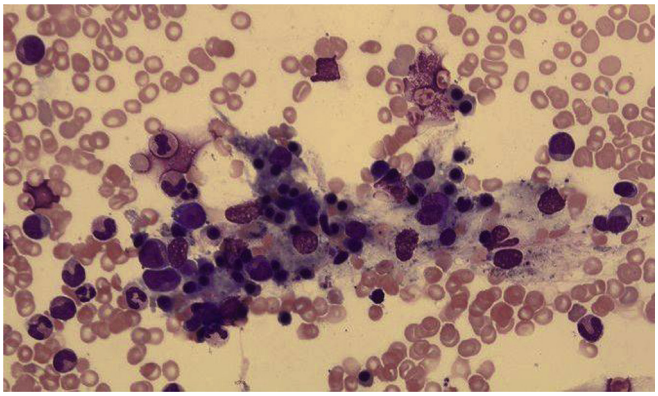

Figure 1. Photomicrograph of bone marrow aspirate showing macrophages with hemophagocytic activity (May–Grunwald stain, ×20, original magnification).

fibrinogen (0.9 g/L), elevated D dimer (19.8 μg/mL), elevated triglyceride (3.45 mmol/l), and elevated ferritin (4506 μg/L). Extensive investigations to search for the underlying cause of HLH were performed. Autoimmune screening including antinuclear, antidouble-stranded DNA, anticardiolipin antibody, and rheumatoid factor was negative. Serological investigations showed no evidence of active Epstein-Barr virus (EBV), cytomegalovirus disease (CMV), herpes simplex, dengue, leptospira, hepatitis B, hepatitis C, VDRL, and Human immunodeficiency virus (HIV). Chest X-ray was normal and abdominal computed tomography showed no hepatosplenomegaly or lymphadenopathy. As there was no obvious evidence of an infectious cause, she was initially treated with intravenous dexamethasone (16 mg daily) together with intravenous cyclosporine (75 mg twice a day). She improved dramatically,

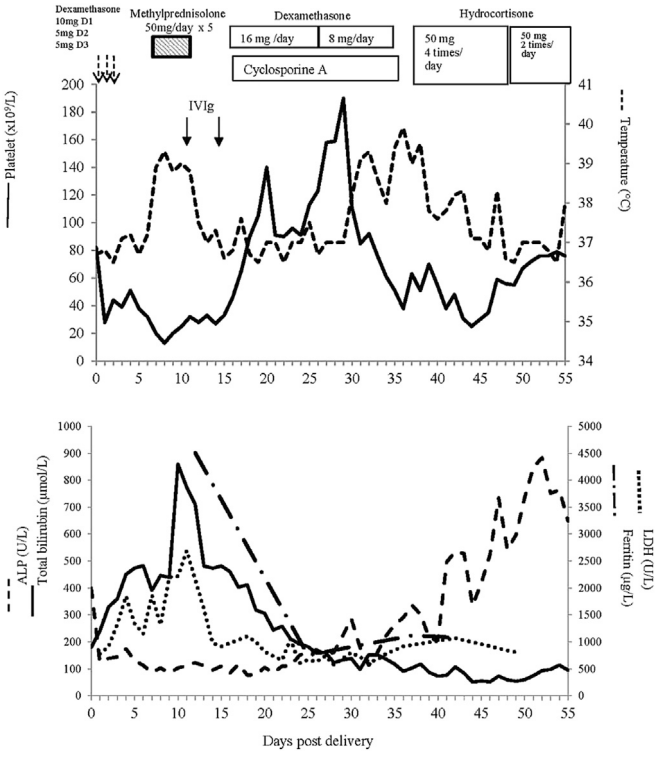

Figure 2. Timeline of the clinical course, laboratory results (platelet, ALP, total bilirubin, LDH and ferritin) and treatments. Timing of administration and doses of medications are shown. ALP = alkaline phosphatase; LDH = lactate dehydrogenase.

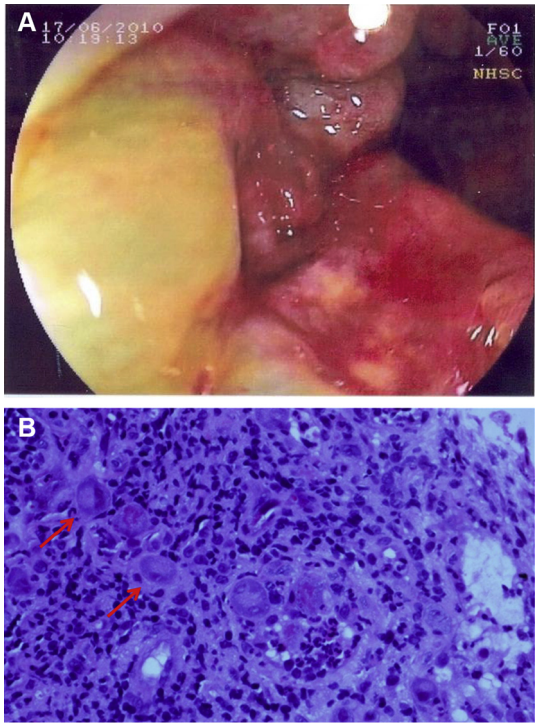

Figure 3. (A) Colonoscopy findings showing erythematous rectal wall with ulcers and bleeding areas. (B) Photomicrograph of colon biopsy showing giant cells with inclusion body (arrow) characteristic of cytomegalovirus colitis (hematoxylin and eosin staining, ×20, original magnification).

was extubated, and transferred out of the ICU. Within 2 weeks, complete clinical and biochemical improvement was observed. The dose of steroids was therefore slowly tapered down, and cyclosporine A was changed to 75 mg twice a day orally (Figure 2).

On Day 31 postpartum, she developed several episodes of fresh per rectal bleeding from multiple rectal ulcers (Figure 3A) that required multiple colonoscopies and surgical intervention in an attempt to control the bleeding. A biopsy of the rectal ulcers showed CMV inclusion bodies (Figure 3B). Although there was an absence of anti-CMV IgM antibody, quantitative CMV polymerase chain reaction from the blood showed a high viral load of > 1 million copies/mL. She also had severe lymphopenia with lymphocyte counts ranging between 0.2×10^9/L and 0.4×10^9/L. As the HLH was well controlled and in view of the CMV infection, cyclosporine was stopped and she was treated with intravenous ganciclovir. On Day 40 postpartum, she developed coarse tremors of her upper limbs, followed by reduced consciousness level. Magnetic resonance imaging of the brain showed bilateral occipital cortical and subcortical hyperintensities, which was suggestive of posterior reversible leukoencephalopathy. Cerebrospinal fluid analysis showed normal result. Electroencephalogram did not show any epileptic discharges. She was reintubated and transferred back to the ICU. Despite treatment with ganciclovir, she developed rapidly progressive CMV disease including pneumonitis (Figures 4A and 4B) and hematuria due to hemorrhagic cystitis. She succumbed a few days later after developing severe hospital-acquired multidrug-resistant *Acinetobacter* sp. and *Klebsiella* sp. pneumonia resulting in septic shock and multiorgan failure.

Discussion

This case illustrates the diagnostic and therapeutic challenges in the management of HLH in a pregnant lady. According to the

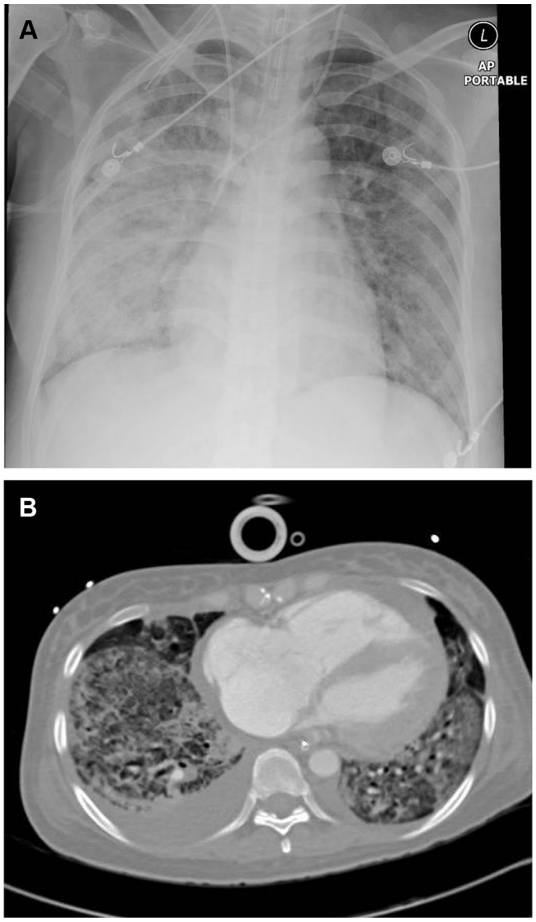

Figure 4. (A) Chest radiograph showing patchy opacities at both lung fields, mainly on the right lung. (B) Computed tomography (CT) of the thorax showing right pleural effusion and extensive ground glass and interstitial opacities over both lungs.

revised diagnostic criteria guideline of the HLH-2004 protocol, HLH is diagnosed if either a genetic finding consistent with HLH or five or more out of eight criteria are fulfilled [2]. The clinical and laboratory features of HLH are attributable to organ infiltration and damage and also massive release of proinflammatory cytokines including interferon-γ, interleukin-18 and -6, and tumor necrosis factor α [19]. The organs commonly involved are bone marrow, liver, spleen, lymph nodes, and central nervous system. This patient had persistent pyrexia despite treatment with broad-spectrum antibiotics with negative cultures, bicytopenia (anemia and thrombocytopenia), hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, elevated liver enzymes, and hemophagocytic activity in her bone marrow. None of these features are specific for HLH. However, fever is almost always present in HLH [19]. Nearly all patients have bicytopenia (usually anemia and thrombocytopenia) or pancytopenia and elevated serum ferritin (often > 1000 ng/mL with < 20% as the glycosylated form) [19]. Features suggestive of HLH are progressive organ involvement, worsening cytopenia, significantly higher than expected ferritin level in inflammatory syndrome or sepsis, worsening liver function, and abnormal coagulation [20]. Bone marrow and other lymphoid tissues (such as liver, spleen, and lymph nodes) may show hemophagocytic activity. Although biopsy-proven hemophagocytosis is regarded as the gold standard for HLH, it may be absent in the early stage of the disease [19]. The timing of biopsy from the onset of hemophagocytosis and the extent of different organ involvement at a particular time during the course of the disease will influence the histology results.

Therefore, repetitive biopsies are sometimes required for diagnosis especially when there is a high index of suspicion. Once a diagnosis of HLH is established, it is crucial to promptly search for an underlying genetic disorder, rheumatological disease, malignancy, and a triggering infective cause.

Without treatment, the mortality of patients with HLH is high, particularly in primary HLH and those related to malignancy. Those with active familial HLH have a survival of ~2 months without treatment [21,22]. Takahashi et al [1] reported that HLH associated with lymphomas had a significantly higher mortality compared to HLH because of infections and autoimmune diseases (overall survival, 8% vs. 83%). Ishii et al [3] reported a 5-year overall survival rate of 82.7% for EBV–HLH and 89% for other infection-associated HLH in pediatric and adult patients in Japan. The lowest survival rate was in T/natural killer cell lymphoma-associated HLH [3].

A comprehensive search of the literature on pregnancy with HLH was performed using MEDLINE and PubMed databases, and the findings were tabulated (Table 1). Ten out of 14 cases occurred during the second trimester with a range of 16–29 weeks' gestation. Our patient presented with symptoms in her third trimester. The pathophysiology of pregnancy-related HLH is not known. It is not clear whether the pregnancy itself is responsible for or predisposes the mother to HLH. In HLH, $CD8^+$ T cells undergo unregulated polyclonal expansion and permanent activation after stimulation by a virus or other factors [19]. This will lead to excessive macrophage activation and, subsequently, hemophagocytosis. In a normal pregnancy, maternal T helper lymphocytes typically shift from Th1 predominance to Th2 in order to adapt to the growing fetus in the body [23]. This will result in relatively decreased cell-mediated immunity (CMI) by Th1 cells with increased susceptibility to viral infections [23]. Yamaguchi et al [8] hypothesized that the decreased CMI may allow the overactivation of hemophagocytes as the first immune response to infection instead of Th1 immune response. These stimulated and uncontrolled macrophages also rapidly produce tissue necrosis factor α, which initiates the inflammatory effector pathway. Teng et al [5] hypothesized that fetomaternal trafficking was the key element in pregnancy-related HLH and its cytokine storm. Failure of maternal T lymphocytes to recognize fetomaternal human lymphocyte antigens and release of trophoblast debris and cytotrophoblast cells into maternal circulation may induce an overwhelming systemic inflammatory response, mimicking pregnancy-related HLH [5]. It is possible that the deterioration of the patient's clinical condition was aggravated by abnormal fetomaternal cell trafficking-induced cytokine storm, which was unfortunately refractory to the various treatment modalities given.

Similar to other anecdotal reports, the diagnosis of pregnancy-related HLH was not suspected in this patient during her initial presentation because of its rare occurrence and the fact that other common obstetric emergencies also needed to be considered. In general, the presence of pyrexia, anemia, thrombocytopenia, and elevated liver enzymes in a pregnant woman should always raise the suspicion of HELLP syndrome, acute fatty liver in pregnancy, or even sepsis. The absence of hypertension and proteinuria has been documented in HELLP syndrome. Although the clinical features of pregnancy-related HLH and HELLP syndrome are similar, their natural course varies. Following delivery of the baby, HELLP syndrome usually improves within several days, but HLH may have a progressive course [9]. Partial HELLP syndrome was the provisional diagnosis in this patient during the early course of the illness. However, the subsequent deterioration of her condition despite delivery of the baby made the diagnosis unlikely. Among the factors implicated in reported cases of pregnancy-related HLH were viruses such as EBV, HSV-2, and HIV, B cell lymphoma, and systemic lupus erythematosus (Table 1).

There is no established treatment guideline for pregnancy-related HLH to date. The aim of treatment in secondary HLH is to suppress the life-threatening inflammatory process driving the HLH and treat the underlying cause. It is imperative to start treatment as soon as possible. According to the reviewed literature, treatments included high dose steroids alone [5,10,16,17], steroids and acyclovir [8], IVIg, steroids and acyclovir [6], IVIg and steroids [11], IVIg and acyclovir [9], IVIg alone [18], chemotherapy followed by hematopoietic stem cell transplantation [7], antimalarial and Highly active antiretroviral therapy (HAART) [12], or antithrombin [13]. In this patient, high dose dexamethasone and cyclosporine helped to control her condition. Although steroids are almost always the choice of treatment in pregnancy-related HLH (Table 1), it was found to be ineffective in inducing remission in four cases when given as a monotherapy initially [5–8]. Steroids help to control the life-threatening hyperinflammation as it is cytotoxic to lymphocytes and inhibits expression of cytokines and differentiation of dendritic cells [24]. In patients with predominant neurological manifestations, dexamethasone is recommended as it is able to cross the blood–brain barrier [18]. Matsuda and Koyasu [25] reported that the potential effect of cyclosporine A on HLH is likely inhibition of T cell activation and normalization of the Th2/Th2 balance. The presence of calcineurin in macrophages/histiocytes made these cells susceptible to direct inhibition of cyclosporine A [25]. Treatment with IVIg was found to be ineffective in this patient. IVIg probably acts via cytokine- and pathogen-specific antibodies. IVIg has been shown to improve the outcome of virus-associated HLH [18,26]. Etoposide is a chemotherapeutic agent that is highly active in monocytic and histiocytic diseases [24]. However, it was not administered to our patient because of the risk of worsening cytopenias, as well as liver and renal impairment. Immunosuppressive treatment in patients with HLH is a huge challenge as one has to weigh the balance between controlling the hyperinflammatory process and the risk of opportunistic infection, worsening cytopenias, and organ impairment as a result of the treatment itself.

To our knowledge, this is the first reported case of pregnancy-related HLH with subsequent CMV reactivation and infection. The absence of CMV IgM in the blood and CMV inclusion body in the bone marrow in the early course of her illness makes it unlikely as the triggering cause for HLH in this case. The mechanism of CMV reactivation in this patient was likely to be multifactorial. She received multiple blood transfusion and had severe lymphopenia resulting in reduced CMI. This predisposed her to CMV infection, which was later confirmed by polymerase chain reaction and the presence of inclusion bodies in the rectal biopsy. Interestingly, serial CMV serology tests were all negative for both IgM and IgG. Yamashita et al [27] reported that the mean interval from the beginning of corticosteroid therapy until the initial detection of CMV-positive antigenemia was 33 days. In a few published cases of CMV-associated HLH, the treatment approaches included IVIg alone [26], ganciclovir monotherapy [28], and combination of IVIg and ganciclovir [29]. All patients survived.

Although HLH is invariably known as a life-threatening disease, there was only one reported mortality in the reviewed cases of pregnancy-related HLH (Table 1). However, it has been found to cause significant obstetrics complications to both mother and fetus. Two had severe preeclampsia, in which one was further complicated with eclampsia, meningeal hemorrhage, and cerebral hemorrhage [11]. One patient developed HELLP syndrome and died in the postpartum course because of coagulopathy and multiorgan failure [9]. Seven patients had preterm labor, in which four patients had to undergo emergency cesarean section owing to fetal distress, reduced fetal movements, and breech presentation [5–7,9–11,13].

The overall prognosis of pregnancy-related HLH is not known because of its rare occurrence.

In conclusion, HLH should be suspected in a pregnant patient who has persistent pyrexia, significant cytopenias, and organ enlargement and/or dysfunction with worsening clinical condition despite delivery of the baby. Secondary causes must be explored thoroughly, and repeated investigations should be performed as deemed relevant clinically. Prompt diagnosis and treatment is extremely essential and should be balanced with the risks of secondary infections. A different treatment approach may be required in pregnancy-related HLH; however, this needs to be confirmed in a larger number of patients.

Conflicts of interest

The authors have no conflict of interests relevant to this article.

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