International Journal of Research in Medical Sciences
Rajendran A et al. Int J Res Med Sci. 2017 Aug;5(8):3758-3766
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20173603

Case Report

Triple threat: pregnancy, SLE, EBV as potential triggers in secondary hemophagocytic lymphohistiocytosis

Aiswarya Rajendran*, Akil Adrian Sherif, Arun Divakar, Sandeep Surendran, Jyothi Visalakshy, Madhavan Pillai Gopalakrishna Pillai

Department of Medicine, Amrita Institute of Medical Sciences, Kerala, India

Received: 14 June 2017
Accepted: 08 July 2017

***Correspondence:**
Dr. Aiswarya Rajendran,
E-mail: aiswarya.rajendran04@gmail.com

ABSTRACT

We present a case of hemophagocytic lymphocytosis (HLH) that occurred secondary to a combination of Epstein Barr virus (EBV) infection and systemic lupus erythematosus (SLE) in early pregnancy. A 29-years-old lady presented with complaints of fever, vomiting and loose stools. She underwent successful in-vitro fertilization (IVF) and embryo transfer 20 days prior to the onset of these symptoms. Her blood investigations revealed anemia, neutropenia, hyperferritinemia and hypertriglyceridemia, eventually resulting in a diagnosis of HLH further substantiated by bone marrow examination. Additional investigations revealed positive anti-dsDNA and EBV IgM antibodies amongst other findings, adding SLE and EBV to the diagnoses. They were considered potential triggers for HLH. However, the occurrence of these events following IVF poses the question of whether pregnancy played a role in the development of HLH. Our patient responded well to pulse steroid therapy and has had an uneventful course till date.

Keywords: Hemophagocytic lymphohistiocytosis, Immunological changes in pregnancy, Macrophage activation syndrome

INTRODUCTION

HLH is a poorly diagnosed condition that can be fatal if not promptly recognized. Diagnosing this condition is wrought with challenges in the form of ambiguous clinical features, lack of specific diagnostic tests and the relative rarity of the condition resulting in it being missed in many differential lists. In addition, HLH is seen to occur secondarily in a wide variety of clinical scenarios where the immune system is compromised or modulated.

In present case report, we bring attention to such a case that occurred in the background of three other conditions viz; SLE, EBV infection and pregnancy. While all three conditions have been described in literature to trigger HLH, we failed to find reports of these conditions occurring simultaneously in a patient. A systematic review of literature led us to 23 cases of HLH in pregnancy reported worldwide, none of which have a co-occurrence of both EBV and SLE (Table 4). We examine these cases and discuss the immunomodulation seen in pregnancy that may potentially render the patient susceptible to this condition along with a brief review of the HLH syndrome and our case in specific.

CASE REPORT

A 29-years-old lady with no known comorbidities presented to us with complaints of fever with chills and rigors of 3 days' duration. The patient had undergone IVF and embryo transfer 20 days prior to the onset of these symptoms. The fever was sudden in onset and high grade in intensity with no diurnal variation. It was associated with 3-4 episodes of non-bilious, non-blood-stained vomiting and 4-5 episodes of loose stools per day, devoid

of any blood or mucus. There was no associated abdominal pain. Upon examination, she was conscious and oriented with a temperature of 38.5˚C, heart rate of 110/minute, respiratory rate of 21/minute and had pallor of the palpebral conjunctiva.

Systemic examination was within normal limits. She was admitted for further evaluation and management. On the day of admission, her blood investigations revealed bicytopenia with hemoglobin of 8.9 g/dl, RBC count of 3.4 x 1012 cells/L and WBC count of 0.9 x 109 cells/L (Table 1). Her peripheral blood smear examination revealed dimorphic anemia with microcytosis and leukopenia. A provisional diagnosis of neutropenic sepsis was made and she was started on antibiotics empirically. Despite therapy her neutropenia persisted and hence a bone marrow study was sought which revealed evidence of hemophagocytosis (Figure 1). At this point, a differential of HLH was considered and further work up for the same was initiated. Investigations revealed transaminitis, hyperferritinemia, hypertriglyceridemia and elevated LDH as outlined in Table 2. This was consistent with the HLH-2004 guidelines with 5 out of the 8 criteria being present resulting in a diagnosis of HLH.[1] The 'HScore', a diagnostic scoring system developed in France that aids diagnoses of hemophagocytic syndrome, was calculated as well and found to be 207 (92% probability of having HLH).[2]

Without further delay, she was started on Methylprednisolone pulse therapy at a dose of 1g/day.Attempting to delineate the etiology, a panel of tests including autoimmune and viral markers were run. Her autoimmune work up returned positive ANA, positive anti-dsDNA, low C3, C4 and a positive direct Coomb's test suggesting hemolytic anemia. A new diagnosis of SLE was established based on SLICC criteria according to which she met 4 out of the 17 criteria.[3]

Table 1: Routine blood investigations, day 0-14.

Investigation	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Hemoglobin (g/dl)	8.9	8.7	9.1	8.5	8.7	7.45	8.39	7.9	7.9	8.3	8.5	8.9	8.9	9.6	9.4
RBC (x 1012/L)	3.4	3.5	3.8	3.6	3.6	3.35	3.6	3.8	2.93	3.4	3.4	3.6	3.5	3.45	3.8
Platelet (x 109/L)	185	110	163	132	191	155	135	203	225	290	233	287	270	219	259
WBC (x 109/L)	0.903	0.7	0.7	0.6	0.5	1.27	1.30	1.8	2.64	3.1	3.3	4.2	4.9	5.1	4.6
Neutrophil (%)	49.6	51.9	38.4	31.3	16.3	48.9	55.0	56.3	70.4	66.1	66.5	64.0	63.4	76.2	75.3
Lymphocyte (%)	37.1	34.1	45.8	52.8	70.5	37.8	29.1	33.5	20.8	19.4	20.6	21.0	21.6	16.1	16.6
Total bilirubin (mg/dl)	0.4				0.23			0.42							0.59
SGOT (IU/L)	241.4				228.9			101.1							78.3
SGPT (IU/L)	59.0				78.5			79.5							94.8
ALP (IU/L)	127.3				178.9			152.7							79.7
Serum albumin (g/dl)	2.83				3.14			2.77							3.09
Serum globuli (g/dl)	3.5				3.6			3.4							3.3

Viral markers showed IgM antibodies against EBV viral capsid antigen (VCA). Viral DNA quantification via PCR was not performed at the time, although retrospectively it would have been an ideal contribution to follow-up of the infection. Nonetheless, IgM antibodies to EBV VCA is highly sensitive and specific for acute infection and reactivation of a latent infection (Table 2).[4] With the additional diagnoses of SLE and EBV, HLH was believed to be secondary in etiology with either or both serving as triggers.

Table 2: Other investigations.

Investigation	Value	Day
ESR (mm/hr)	108	0
CRP (mg/L)	135	0
Creatinine (mg/dl)	0.65	0
Urine examination	Normal	0
Ultrasound abdomen	Normal	0
Serum ferritin (ng/ml)	3714.9	0
Beta-hCG (mIU/L)	10371.06	0
Fibrinogen (mg/dl)	296	1
Peripheral Smear	Dimorphic anemia with microcytes and leukopenia	1
LDH (IU/L)	1416.0	3
Coomb's test direct	Positive (+1)	3
Serum ferritin (ng/ml)	5493.3	3
Serum triglycerides (mg/dl)	374.5	3
Beta-hCG (mIU/L)	14339.37	3
Prothrombin time with INR	13.5/14.6/0.91	5
Activated partial thromboplastin time	29.3/32.2	5
APLA IgG (GPL U/ml)	3.15	5
APLA IgM (MPL U/ml)	3.85	5
Bone marrow aspiration*	Partly dilute marrow with increase in lymphocytes (30%) with evidence of hemophagocytosis.	6
C3 complement fraction	48.0	7
C4 complement fraction	4.36	7
Anti-dsDNA (IU/ml)	87	7
ANA screen (IFA)	Homogenous pattern (3+)	7
Anti Jo antibody (EU)	2.18 (negative)	7
Anti Scl 70 (EU)	2.95 (negative)	7
Anti SS-A antibody (EU)	2.16 (negative)	7
Anti SS-B antibody (EU)	2.67 (negative)	7
Anti RNP antibody (EU)	1.62 (negative)	7
Anti Sm antibody (EU)	2.81 (negative)	7
IgM EBV (VCA)	0.22 (positive)	7
Serum ferritin (ng/ml)	20	28

Immunologic investigations limited to those described above. Tests for soluble IL-2 receptor alpha, flow cytometry, NK cell function, gene mutations and HLA typing were not performed.

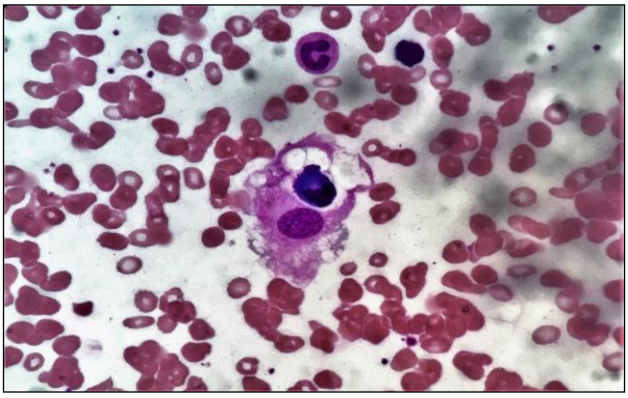

Figure 1: Bone Marrow aspirate of the patient showing evidence of phagocytosis with a histiocyte and containing an engulfed neutrophil and platelets on Wright-Giemsa stain.

Differential diagnosis

- Sepsis induced neutropenic syndrome / multi-organ dysfunction syndrome (MODS).[5]
- Hematological malignancies such as leukemias and lymphomas.[6,7]
- Autoimmune lymphoproliferative syndrome (ALPS).[6]
- Systemic lupus erythematosus (SLE).[7]
- HELLP syndrome.[8]

Treatment

In conjunction with the patient's initial presentation, a provisional diagnosis of neutropenic sepsis was made. She was treated with Ceftazidime empirically along with supportive therapy. However, her symptoms and counts failed to improve thereby warranting an escalation in her

antibiotic regimen to Meropenem and Micafungin for fungal cover.

Despite these measures, her neutropenia continued to persist prompting the need for a bone marrow study; this revealed evidence of hemophagocytosis and a diagnosis of HLH was eventually made.

Treatment guidelines for HLH remain complex, dynamic and continue to evolve with new evidence. While no established treatment protocol exists for adult HLH, those employed in the HLH-94 and 2004 clinical trials serve as guidelines. Our patient, being clinically stable was started on pulse steroid therapy with Methylprednisolone at a dose of 1g/day for five days as per the Histiocyte society HLH-94 treatment guidelines.[9]

The dose was decreased to 500mg/day for the next three days and then she was switched to oral steroids at a dose of 160 mg/day which was gradually tapered off over a course of 8 weeks.

Induction therapy as recommended by the HLH-94 guidelines is reserved for patients with a clinically deteriorating course, CNS involvement, steroid refractory cases, a recurrent disease or those patients being prepared for a hematopoietic stem cell transplant.[1,9]

Induction therapy includes various chemotherapeutic drugs such as Dexamethasone, Etoposide and intrathecal Methotrexate in various doses and combinations based on the patient's clinical profile. A targeted approach using anti-interferon gamma monoclonal antibodies called NI-0501 that emerged during the HLH-2004 trial and currently in phase II clinical trials appears promising, with better outcomes and fewer adverse effects.[10]

Table 3: Revised diagnostic guidelines for HLH, Henter et al. reproduced with permission from pediatric blood and cancer/John Wiley and Sons.[1]

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
A molecular diagnosis consistent with HLH
Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenia (affecting ≥ 2 of 3 lineages in the peripheral blood)
• Hemoglobin < 90 g/L (in infants < 4 weeks: hemoglobin < 100 g/L) • Platelets < 100 x 10^9/L • Neutrophils < 1.0 x 10^9/L
Hypertriglyceridemia and/or hypofibrinogenemia
• Fasting triglycerides 3.0 mmol/L (i.e., 265 mg/dl) • Fibrinogen ≤ 1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
New diagnostic criteria
• Low or absent NK-cell activity (per local laboratory reference) • Ferritin 500 mg/L • Soluble CD25 (i.e., soluble IL-2 receptor) 2,400 U/ml Co

Outcome and follow-up

The patient responded well to steroid therapy with resolution in her symptoms and an improvement in her counts. The patient was discharged in a hemodynamically stable and afebrile condition 14 days after her symptoms started.

Serum ferritin was repeated at follow up four weeks after initial presentation, and was found to be 20 ng/mL suggestive of disease remission.[11] She is now in the 26th week of gestation with a viable twin gestation without any symptoms or relapses upon follow up.

DISCUSSION

HLH is a relatively rare entity and is characterized by abnormal immune activation involving host lymphocytes and macrophages resulting in excessive inflammation and tissue destruction. Failure of the normal downregulation of activated lymphohistiocytes occurs, perpetuating an acute state of hypercytokinemia. Typically, the pathological picture associated with HLH may depict hemophagocytosis in the bone marrow, but this is not synonymous with HLH and either can occur in the absence of the other.[12,13] Mortality associated with HLH hovers around 42% unless recognized and treated in a

timely fashion wherein lies the importance of swiftly diagnosing this condition.[14]

HLH can occur in any age group and has been described in adults as old as 70. But it is commonly seen in infants and children, especially the familial form involving genetic mutations. HLH may be classified as primary or secondary. The former, also referred to as familial HLH, arises from one or more genetic mutations whereas secondary or sporadic HLH occurs in response to a clear trigger, in patients with no known predisposing genetic mutations. These triggers may be broadly classified as those leading to immune activation, usually infections and most commonly Epstein-Barr viral infections; and those resulting in immune suppression; these include inherited immune deficiency syndromes, malignancies, HIV infections and rheumatological disorders to name a few. Secondary HLH at times can resolve spontaneously on treatment of the underlying disorder and in general may not require chemotherapy. Primary HLH on the other hand can be rapidly fatal and usually necessitates use of the full regimen described in the HLH-2004 protocol. In adults, HLH may be suggestive of an underlying hematologic malignancy and in many cases, serves as a trigger for HLH as well.[15-19] Occasionally HLH tends to be discovered prior to the underlying malignancy.[20] Such cases tend to have a more turbulent clinical course with poorer outcomes and physicians must be wary of these possibilities while dealing with HLH.[21,22]

Table 4: Summary of cases of HLH in pregnancy (amended from Tumian et al and Kanako et al)[8,28]

Study	Age (years)	Gestational age at diagnosis (weeks)	Associated illness/trigger	Treatment	Outcome of pregnancy
Kim[7]	29	12	SLE	IVIG, Steroids, Splenectomy	Therapeutic abortion at 14 weeks
Gill et al[29]	30	18	No Trigger	High dose gamma-globulin	Delivery at term. Mother and baby alive.
Yamaguchi et al[26]	*NA*	Second trimester	HSV-2	Acyclovir (750 mg/d) and prednisolone (30 mg/d) / transient reduction in fever IV pulse methylprednisolone followed by full-dose prednisolone and later cyclosporine A	Delivered at 37 weeks. Mother and baby alive
Mihara et al[30]	32	16	EBV	Methylprednisolone 1 g/d for 3days, IVIG 20 g/d for 3 days, acyclovir 750 mg/d + gabexate mesilate 2 g/d. Maintenance: oral prednisolone 5 mg/d, camostat mesilate 600 mg/day	Delivered at 35 weeks. Mother and baby alive
Dunn et al[31]	41	19	Still's disease	Steroids	Delivered at 30 weeks. Mother and baby alive
Mayama et al[32]	28	19	Parvovirus B19	Steroids	Delivered at 37 weeks. Mother and baby alive
Arewa and Ajadi[33]	31	21	HIV and Malaria	Anti-malarial treatment (amodiaquine) and HAART	Delivered at term. Mother and baby alive
Nakabayashi et al[34]	30	21	Preeclampsia	Antibiotics + Immunoglobulin- No response	Delivered at term. Mother and baby alive
Hannebicque-Montaigne et al[35]	29	21	SLE	*NA*	*NA*
Pérard et al[36]	28	22	SLE	IVIG 1 g/kg/d for 2 d then IV	Delivered at 30 weeks. Mother and baby alive

				methylprednisolone 1 g/d for 3 d followed by oral prednisone 0.5 mg/kg/d Another 2 doses of IVIG given at 28 weeks and 30 week of gestation, respectively	
Teng et al[37]	28	23	Autoimmune hemolytic anemia (AIHA)	Steroid- unresponsive	Fetal demise at 29 weeks due to respiratory distress. Mother alive
Hanaoka et al[38]	33	23	B cell lymphoma	Steroids no response Six cycles of R-CHOP, then autologous peripheral blood stem cell transplantation	Delivered at 28 weeks. Mother and baby alive
Kanako et al[28]	26	23	Liver abscess	None	Death of mother and fetus.
Chien et al[39]	28	23	EBV	Steroids	Delivered at 30 weeks. Mother and baby alive
Goulding et al[40]	27	23	HSV	Steroids, Acyclovir.	Fetal demise at 23 weeks due to respiratory distress. Mother alive.
Zaibi et al[41]	33	24	SLE	Steroids	Pregnancy terminated at 33 weeks. Mother alive
Pawar et al[42]	30	24	Visceral Leishmaniasis	Steroids	Delivered at 38 weeks. Mother and baby alive.
Chmait et al[43]	24	29	EBV	IV immunoglobulin 60 g/d for 3 d and IV acyclovir 750 mg every 12 h	Delivered at 30 weeks. Maternal death due to coagulopathy and Multiorgan failure. Fetus alive
Klein et al[44]	39	30	EBV	Steroids, Cyclosporine A, Etoposide, Rituximab: No response	Maternal Death. Fetus alive
Tumian et al[8]	35	38	CMV	Steroids, Plasmapheresis, IVIG	Delivered at 38 weeks. Mother and baby alive
Yoshida et al[45]	33	After delivery	SLE	Steroids	Mother and baby alive
Tsuda et al[46]	30	9 days after delivery	Parvovirus B19	*NA*	*NA*
Komaru et al[47]	36	38 days after delivery	Primary Sjogren's syndrome	Steroids	Mother and baby alive

NA = information not available

The clinical manifestations seen in HLH usually begin as a febrile illness with a dysfunction of multiple organ systems. The clinical profile of such presentations may be generally described as an acutely ill patient with cytopenia of more than one cell line, abnormal liver function tests, neurological symptoms, coagulopathy with elevated D-dimers and multi-organ dysfunction. Other commonly encountered clinical features as described by the HLH-94 study include hepatomegaly, lymphadenopathy, rash, diarrhea, bleeding and neurological symptoms.[23] While many of the symptoms seen in this condition remain non-specific, some studies mention hepatitis with hepatomegaly as being extremely common.

Based on the HLH-2004 criteria, a positive diagnosis constitutes at least 5 out of 8 factors presented in Table 3. Regardless of diagnostic guidelines, one must have a high index of suspicion for HLH in clinically relevant situations, considering the high mortality associated with delayed treatment. Guidelines were developed for purposes of research and need not necessarily capture all cases of HLH within its description. Hence the modified diagnostic criteria were proposed which calls for a positive diagnosis if at least 3 of 4 clinical findings (fever, splenomegaly, cytopenias or hepatitis) and 1 of 4 immune markers (hemophagocytosis, hyperferritinemia, reduced NK function or increased sIL2Rα) are present.[9,24]

Pregnancy is a unique physiological state about the lack of an immune response to the developing fetus; 50% of which is foreign. Though pregnancy is not truly a state of immunodeficiency, there does exist a component of immune suppression. It has been suggested that maternal cell mediated immunity is suppressed while maintaining the humoral immunity intact as a mechanism to tolerate fetal antigens. This immune modulation may be attributed to the shift seen from Th1 to Th2 predominance expressed by the maternal T helper lymphocytes as an adaptation response to the growing fetus.[25] While these changes are believed to occur at the maternal-fetal interface, it does affect systemic immunity making the mother more susceptible to infectious agents.[8] This decrease in cell mediated immunity has been hypothesized to be responsible for the excessive activation of lymphohistiocytes, a Th2 response as opposed to the normal Th1 response.[26,27] This may lead to immune activation scenarios such as HLH.

Our patient, after presenting with HLH was subsequently diagnosed with an EBV infection and SLE on further workup. The temporal order of their occurrences is unknown. This brings up the possibility that, the backdrop of SLE and pregnancy may have predisposed the patient to a certain degree of immune compromise that allowed the development of an EBV infection that subsequently triggered HLH. While any of the alternatives remain viable possibilities, the occurrence of HLH following a positive pregnancy cannot be ignored.

A review of literature on MEDLINE and Cochrane databases using relevant 'MeSH' terms and keywords led us to compile 23 reported cases (Table 4) of HLH in pregnancy. It is important to note that 9 of the 23 (39%) cases were triggered by either SLE or EBV. We were also able to delineate that all the 23 cases occurred during or following the second trimester of pregnancy. The earliest occurrence of HLH in pregnancy was at 12 weeks.[7] Considering our patient's symptoms began merely 20 days following embryo transfer, it raises the dilemma of whether pregnancy was an inciting event that led to HLH or simply a coincidence. We cannot draw firm conclusions in the role of pregnancy being a potential trigger. Further research in areas of gestational immunology and HLH may shed more light on the matter.

Arriving at a diagnosis of HLH can be quite challenging due to the relative rarity of the condition, variability in presentation and the non-specificity of the features seen. While such challenges remain, it is imperative to diagnose this condition promptly and initiate therapy.

- HLH is a syndrome characterized by phagocytosis of host cells by macrophages and lymphocytes due to abnormal immune activation.
- A typical clinical profile of HLH is an acutely ill patient with cytopenia of more than one cell line, abnormal liver function tests, neurological symptoms and multi-organ dysfunction with hyperferritinemia and hypertriglyceridemia.
- In adults, secondary HLH is relatively more common and is usually triggered by a viral infection, autoimmune condition or malignancy. The primary form is commoner in children.
- Morbidity and mortality is high in the absence of therapy and hence treatment must not be delayed if the modified diagnostic criteria are satisfied.
- In a confirmed case of HLH, identification of underlying autoimmune, neoplastic and infectious triggers is important.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. 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(2):124-31.
2. 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 Hoboken NJ. 2014;66(9):2613-20.
3. Petri M, Orbai A-M, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-86.
4. Bruu A-L, Hjetland R, Holter E, Mortensen L, Natas O, Petterson W, et al. Evaluation of 12 Commercial Tests for Detection of Epstein-Barr virus-specific and Heterophile antibodies. Clin Diagn Lab Immunol. 2000;7(3):451-6.
5. Castillo L, Carcillo J. Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes

on a spectrum of inflammation. Pediatr Crit Care. 2009;10(3):387-92.
6. Spergel AR, Walkovich K, Price S, Niemela JE, Wright D, Fleisher TA, et al. Autoimmune lymphoproliferative syndrome misdiagnosed as hemophagocytic lymphohistiocytosis. Ped. 2013; 1;132(5):e1440-4.
7. Kim JM, Kwok SK, Ju JH, Park KS, Park GS, Kim HY, 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(3):767-71.
8. Tumian NR, Wong CL. Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: A diagnostic and therapeutic challenge. Taiwan J Obstet Gynecol. 2015;54(4):432-7.
9. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041-52.
10. Bracaglia C, Gatto A, Pardeo M, Lapeyre G, Ferlin W, Nelson R, et al. Anti-interferon-gamma (IFNγ) monoclonal antibody treatment in a patient carrying an NLRC4 mutation and severe hemophagocytic lymphohistiocytosis. Pediatr Rheumatol. 2015;13(S1):O68.
11. Lin TF, Ferlic-Stark LL, Allen CE, Kozinetz CA, McClain KL. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer. 2011;56(1):154-5.
12. Gupta A, Tyrrell P, Valani R, Benseler S, Weitzman S, Abdelhaleem M. The role of the initial bone marrow aspirate in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008;51(3):402-4.
13. Janka GE. Familial hemophagocytic lymphohistiocytosis. Eur J Pediatr. 1983;140(3):221-30.
14. Riviere S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, et al. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. Am J Med. 2014;127(11):1118-25.
15. Falini B, Pileri S, De Solas I, Martelli MF, Mason DY, Delsol G, et al. Peripheral T-cell lymphoma associated with hemophagocytic syndrome. Blood. 1990;75(2):434-44.
16. Ménard F, Besson C, Rincé P, Lambotte O, Lazure T, Canioni D, et al. Hodgkin lymphoma-associated hemophagocytic syndrome: a disorder strongly correlated with Epstein-Barr virus. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008;47(4):531-4.
17. Okuda T, Sakamoto S, Deguchi T, Misawa S, Kashima K, Yoshihara T, et al. Hemophagocytic syndrome associated with aggressive natural killer cell leukemia. Am J Hematol. 1991;38(4):321-3.
18. Miyahara M, Sano M, Shibata K, Matsuzaki M, Ibaraki K, Shimamoto Y, et al. B-cell lymphoma-associated hemophagocytic syndrome: clinicopathological characteristics. Ann Hematol. 2000;79(7):378-88.
19. Pastore RD, Chadburn A, Kripas C, Schattner EJ. Novel association of haemophagocytic syndrome with Kaposi's sarcoma-associated herpesvirus-related primary effusion lymphoma. Br J Haematol. 2000;111(4):1112-5.
20. Chang TY, Jaffray J, Woda B, Newburger PE, Usmani GN. Hemophagocytic lymphohistiocytosis with MUNC13-4 gene mutation or reduced natural killer cell function prior to onset of childhood leukemia. Pediatr Blood Cancer. 2011;56(5):856-8.
21. Nikiforow S, Berliner N. The unique aspects of presentation and diagnosis of hemophagocytic lymphohistiocytosis in adults. ASH Educ Program Book. 2015;2015(1):183-9.
22. Santhakumara RP, Boyella PK, Vidyadharan G, Indu RN, Munirathnam V, Rema G, et al. HLH, Lymphoma, CMV and HLH: Heterogeneous presentation of HLH in Lymphoma. Indian J Cancer Educ Res. 2015;3(2):71.
23. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood. 2011;118(17):4577-84.
24. Filipovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. ASH Educ Program Book. 2009;2009(1):127-31.
25. Luppi P. How immune mechanisms are affected by pregnancy. Vaccine. 2003;21(24):3352-7.
26. Yamaguchi K, Yamamoto A, Hisano M, Natori M, Murashima A. Herpes simplex virus 2-associated hemophagocytic lymphohistiocytosis in a pregnant patient. Obstet Gynecol. 2005;105(5):1241-4.
27. Whitacre CC, Reingold SC, O'looney PA, Blankenhorn E, Brinley F, Collier E, et al. A gender gap in autoimmunity. Sci. 1999;283(5406):1277-8.
28. Ota K, Kawahara K, Banno H, Nishijima K, Yoshida Y. Hemophagocytic lymphohistiocytosis caused by pyogenic liver abscess during pregnancy: a case report and literature review. Open J Obstet Gynecol. 2016;6(05):287.
29. Gill DS, Spencer A, Cobcroft RG. High-dose gamma-globulin therapy in the reactive haemophagocytic syndrome. Br J Haematol. 1994;88(1):204-6.
30. Mihara H, Kato Y, Tokura Y, Hattori Y, Sato A, Kobayashi H, et al. Epstein-Barr virus-associated hemophagocytic syndrome during mid-term pregnancy successfully treated with combined methylprednisolone and intravenous immunoglobulin. Rinsho Ketsueki. 1999;40(12):1258-64.
31. Dunn T, Cho M, Medeiros B, Logan A, Ungewickell A, Liedtke M. Hemophagocytic lymphohistiocytosis in pregnancy: a case report and review of treatment options. Hematol Amst Neth. 2012;17(6):325-8.

32. Mayama M, Yoshihara M, Kokabu T, Oguchi H. Hemophagocytic lymphohistiocytosis associated with a parvovirus B19 infection during pregnancy. Obstet Gynecol. 2014;124(2):438-41.
33. Arewa OP, Ajadi AA. Human immunodeficiency virus associated with haemophagocytic syndrome in pregnancy: a case report. West Afr J Med. 2011;30(1):66-8.
34. Nakabayashi M, Adachi T, Izuchi S, Sugisaki A. Association of hypercytokinemia in the development of severe preeclampsia in a case of hemophagocytic syndrome. Semin Thromb Hemost. 1999;25(5):467-71.
35. Hannebicque-Montaigne K, Le Roc'h A, Launay D, Coulon C, Deruelle P, Langlois S. Haemophagocytic syndrome in pregnancy: a case report. Ann Fr Anesth Reanim. 2012;31(3):239-42.
36. Pérard L, Costedoat-Chalumeau N, Limal N, Hot A, Cohen J, Vauthier-Brouzes D, et al. Hemophagocytic syndrome in a pregnant patient with systemic lupus erythematosus, complicated with preeclampsia and cerebral hemorrhage. Ann Hematol. 2007;86(7):541-4.
37. Teng CL, Hwang GY, Lee BJ, Wang RC, Chou MM. Pregnancy-induced hemophagocytic lymphohistiocytosis combined with autoimmune hemolytic anemia. J Chin Med Assoc JCMA. 2009r;72(3):156-9.
38. Hanaoka M, Tsukimori K, Hojo S, Abe Y, Mutou T, Muta K, et al. B-cell lymphoma during pregnancy associated with hemophagocytic syndrome and placental involvement. Clin Lymphoma Myeloma. 2007;7(7):486-90.
39. Chien CT, Lee FJ, Luk HN, Wu CC. Anaesthetic management for cesarean delivery in a parturient with exacerbated hemophagocytic syndrome. Int J Obstet Anesth. 2009;18(4):413-6.
40. Goulding EA, Barnden KR. Disseminated herpes simplex virus manifesting as pyrexia and cervicitis and leading to reactive hemophagocytic syndrome in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2014;180:198-9.
41. Zaibi H, Azzabi S, Ourari-Dhahri B, Ben Amar J, Ali Baccar M, Aouina H, et al. Rare cause of fever in pregnant women: Hemophagocytic syndrome. Tunis Med. 2015;93(5):331-2.
42. Pawar S, Ragesh R, Nischal N, Sharma S, Panda PK, Sharma SK. Unique triad of "Pregnancy, Kala Azar and Hemophagocytic Lymphohistiocytic Syndrome from a non-endemic region." J Assoc Physicians Ind. 2015;63(6):65-8.
43. Chmait RH, Meimin DL, Koo CH, Huffaker J. Hemophagocytic syndrome in pregnancy. Obstet Gynecol. 2000;95(6):1022-4.
44. Klein S, Schmidt C, La Rosee P, Pletz M, Harz S, Dirsch O, et al. Fulminant gastrointestinal bleeding caused by EBV-triggered hemophagocytic lymphohistiocytosis: report of a case. Z Für Gastroenterol. 2014;52(04):354-9.
45. Yoshida S, Takeuchi T, Itami Y, Hata K, Watanabe K, Shoda T, et al. Hemophagocytic syndrome as primary manifestation in a patient with systemic lupus erythematosus after parturition. Nihon Rinsho Meneki Gakkai Kaishi. 2009;32(1):66-70.
46. Tsuda H, Shirono K, Shimizu K, Shimomura T. Postpartum parvovirus B19-associated acute pure red cell aplasia and hemophagocytic syndrome. Rinsho Ketsueki. 1995;36(7):672-6.
47. Komaru Y, Higuchi T, Koyamada R, Haji Y, Okada M, Kamesaki T, et al. Primary Sjögren syndrome presenting with hemolytic anemia and pure red cell aplasia following delivery due to Coombs-negative autoimmune hemolytic anemia and hemophagocytosis. Intern Med. 2013;52(20):2343-6.

Cite this article as: Rajendran A, Sherif AA, Divakar A, Surendran S, Visalakshy J, Pillai MKG. Triple threat: pregnancy, SLE, EBV as potential triggers in secondary hemophagocytic Lymphohistiocytosis. Int J Res Med Sci 2017;5:3758-66.