The Journal of Obstetrics and Gynecology of India (September–October 2020) 70(5):390–392
https://doi.org/10.1007/s13224-019-01286-4

CASE REPORT

Pregnancy-Induced Hemophagocytic Lymphohistiocytosis: A Case Report

Luis A. Sánchez-Ato[1] · Flavia A. Cuestas-Quiroz[1] · Carla Agurto-Saldaña[2] · David Estela-Ayamamani[1,2]

Received: 23 June 2019 / Accepted: 28 September 2019 / Published online: 7 November 2019

Case Report

We present a 23-year-old pregnant woman gravida 3, para 1 27 weeks of gestation complaining of intermittent fever, hyporexia, and vomiting since one week. She had history of malar rash that increased with sun exposure since adolescence. Physical examination revealed fever, pulse of 99 beats per min, blood pressure of 80/50 mmHg, and breathing frequency of 19/min. She was pale, a maculopapular skin rash over both cheeks was observed. There was no lymphadenopathy or joint pain. The liver was palpable 2 cm below the right costal margin and tender; the spleen was not palpable. The uterus was gravid, normal tone, fetal heart rate was 158 beats per min, fetal movement was present, and uterine height was 23 cm. She was awake, oriented, and responsive. Laboratory results showed a hemoglobin of 11.1 g/dL, leukocytes of 6220/mm^3, a platelet count of 240,000/mm^3, and C protein reactive of 13.3 mg/L, urinary sediment showed leukocyturia without nitrites.

Luis A. Sánchez-Ato ia an assistant professor, Escuela de Medicina, Facultad de Ciencias de la Salud, Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru; Flavia A. Cuestas-Quiroz ia an assistant professor Escuela de Medicina, Facultad de Ciencias de la Salud, Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru; Carla Agurto-Saldana is a Gynecologist, Departamento de Obstetricia y Ginecología, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru; David Estela-Ayamamani is a Gynecologist, Escuela de Medicina, Facultad de Ciencias de la Salud, Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru and Departamento de Obstetricia y Ginecología, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru.

✉ Luis A. Sánchez-Ato
luisandressanch@gmail.com

[1] Escuela de Medicina, Facultad de Ciencias de la Salud, Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru

[2] Departamento de Obstetricia y Ginecología, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru

There was a suspicion of urinary tract infection; therefore, urinary and blood culture (both negative) were performed, and empiric antibiotic treatment was started using ceftriaxone. TORCH, HTLV I-II, and EBV serology tests were negative. An autoimmune disease was ruled out with negative ANA, anticardiolipin, ANCA MPO, and ANCA PR3. Tumor screening was negative according to abdominal CT, AFP, CEA, CA19-9, and CA-125. The patient presented with acute respiratory distress and was transferred to intensive care unit, with the chest skiagram showing diffuse infiltrates in both lung fields (Fig. 1). New laboratory test was performed 16 days after the admission, which was suggestive of hemoglobin 5.3 mg/dL, total leukocyte count 2240/mm^3, and platelets 38,000/mm^3. Renal function revealed an increase in creatinine to 1.74 and urea of 110 mmol/L. Liver biochemistry showed a raised serum TGO – 1345 U/L, TGP – 142 U/L, and hyperbilirubinemia (total 11.97 mg/dL, direct fraction 8.95 mg/dL). Serum LDH was raised to 9540 U/L. Ferritin measure showed a level of 1278 ng/mL. The echocardiogram was suggestive of moderate pericarditis with competent cardiac valves and no vegetations. Abdominal sonography was suggestive of hepatomegaly and splenomegaly, associated with diffuse hepatopathy. Liver biopsy showed chronic hepatopathy with steatohepatitis. HELLP syndrome was likely; nevertheless, the blood pressure was always normal.

The patient had persistent fever despite antibiotics; infectology suggested adding meropenem plus vancomycin due to probable sepsis of respiratory origin. Hematologist performed a bone marrow biopsy where hemophagocytosis was observed, which was suggestive of HLH. The result of a lipid profile demonstrated an increase in triglycerides of 369 mg/dl. At 29 weeks of gestation, intra uterine fetal demise was diagnosed, and the gynecology team elected accentuation and vaginal delivery of the stillborn, after which the patient showed clinical and laboratory improvement adding to the scheme of treatment with dexamethasone, etoposide, cyclosporine, and blood transfusions. Nonetheless, she acquired

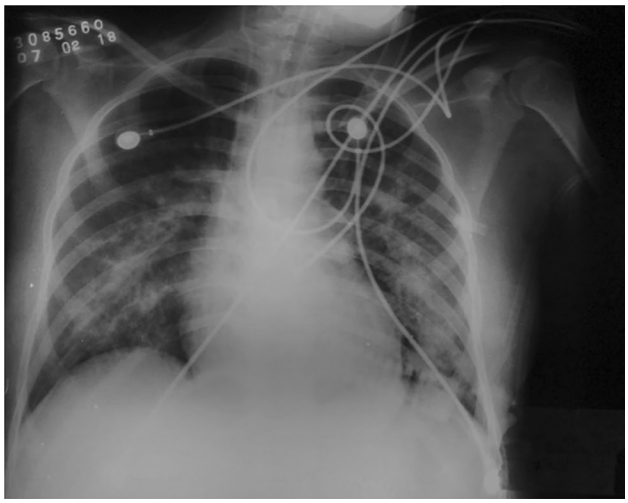

Fig. 1 X-chest ray. Diffuse infiltrates in both lung fields

a nosocomial infection leading to fatality 3 months after delivery.

Discussion

The diagnosis of HLH in this pregnant patient was made using the 2004 diagnostic and therapeutic guidelines for HLH, since five of the eight criteria were fulfilled [1–4]. The patient had fever, hepatosplenomegaly, cytopenias affecting two cellular lineages (hemoglobin < 9.0 mg/L, platelets < 100,000/mm^3), hypertriglyceridemia, and hemophagocytosis in the bone marrow. It is essential to consider HLH as a possible diagnosis in the context of a patient with persistent fever and general discomfort without apparent cause. In the laboratory analysis, the appearance of increased transaminases and triglycerides, anemia, thrombocytopenia, leukopenia, decreased fibrinogen, and an altered coagulation profile should also indicate HLH as a differential diagnosis [5–12].

Other pathologies that should be considered as differentials include HELLP syndrome in which arterial hypertension, anemia, thrombocytopenia, fever, and increased liver enzymes may be found [13]. Fatty liver of pregnancy is characterized by fever, jaundice, pain in the right upper quadrant, and central nervous system involvement [14]. Drug reaction with eosinophilia (DRESS) also has similarities to HLH such as dermatitis, fever, visceral organ involvement, and lymphadenopathy [15]. Sepsis should also be taken into consideration.

According to the study "Pregnancy-associated hemophagocytic lymphohistiocytosis secondary to NK/T cells lymphoma," there were 19 cases of HLH in pregnancy from 1991 to 2017, of these ten were associated with viral infections (Epstein–Barr infection the most common), two cases were induced by an autoimmune disease, six patients did not have a known cause and may have been induced by pregnancy, and one case was related to malignancies [16]. Our patient was diagnosed with a secondary HLH induced by pregnancy after negative TORCH and Epstein–Barr results, negative antibodies, and negative screening for malignancy (negative tumor markers and images). According to the literature, HLH related to pregnancy may be a common cause for this disease [16–18].

The pathophysiology is not well described during pregnancy. It seems to be similar to what occurs in preeclampsia, a rejection of fetal material which is taken as an antigen, caused by an exaggerated natural killer and T lymphocyte reaction [19]. The trafficking of feto-maternal antigens (fetal genetic material, cytotrophoblast, and syncytiotrophoblast cells) may then induce a severe systemic inflammatory response causing multiorgan failure. All these hypotheses are based on the already known fact that the placental barrier cannot completely evade the immune system. In the study of "Foreign fetal cells persist in the maternal circulation," the authors concluded that fetal cells persisted in maternal circulation years after delivery and they avoid destruction by host immune system with an unknown mechanism [20].

Treatment of HLH during pregnancy is not established; usually, there is an improvement in the maternal condition after the delivery. The management varies depending on several factors like the gestational trimester, clinical severity, state of the fetus, added complications, among others. When it occurs during the first trimester, it is more severe, and the mothers health is given priority since the fetus is less likely to survive. Then, the option to end the pregnancy should be considered as the choice of treatment. During the second trimester it is more difficult to decide whether or not to end the pregnancy, and the other factors previously mentioned should be taken into consideration. In the third trimester, the fetus and the mother have a better prognosis, and premature delivery is preferred. Drugs that will reduce inflammation and immune responses (corticosteroids, cyclosporine A, intravenous immunoglobulin, etoposide, etc.) should be utilized.

Conclusion

HLH in pregnancy is a challenge both in its diagnosis and in its treatment, especially because there are no established management guidelines. It is essential to investigate more about this condition to increase knowledge and facilitate decision making. HLH should be taken into account as a differential diagnosis when the patient presents with fever, cytopenias, hepatosplenomegaly, increased ferritin, and when hemophagocytosis is found in bone marrow aspiration. Making a quick decision regarding treatment can improve the prognosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This study is exempted from ethical approval by ethics committee of Hospital Nacional Edgardo Rebagliati Martins.

Research Involving Human Participants and/or Animals This article does not contain any studies with animals performed by any of the authors.

References

1. Henter J-I, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. J Clin Oncol. 2007;27(1):4169.
2. Larroche C. Hemophagocytic lymphohistiocytosis in adults: diagnosis and treatment. Jt Bone Spine. 2012;79(4):356–61.
3. Henter J, Elinder G, Soder O, Ost AKE. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Pizdiatr Scand. 1991;80(2):428–35.
4. Esumi N, Imashuku S. Hyperferritinemia in malignant histiocytosis, virus-associated hemophagocytic syndrome and familial erythrophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1989;5:268–70.
5. Bergsten E, Horne AC, Aricó 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. Niece JA, Rogers ZR, Ahmad N, Langevin A-M, MaClain KL. Hemophagocytic lymphohistiocytosis in texas: observations on ethnicity and race. J Clin Oncol [Internet]. 2010;27(1):4169.
7. Trottestam H, Horne AC, 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.
8. Ferreri AJM, Dognini GP, Campo E, Willemze R, Seymour JF, Bairey O, et al. Variations in clinical presentation, frequency of hemophagocytosis and clinical behavior of intravascular lymphoma diagnosed in different geographical regions. Haematologica. 2007;92(4):486–92.
9. Henter J, Elinder G. Haemophagocytic lymphohistiocytosis: an inherited primary form and a reactive secondary form. Br J Haematol. 1995;91:774–5.
10. Clementi R, Emmi L, Maccario R, Liotta F, Moretta L, Danesino C, et al. Adult onset and atypical presentation of hemophagocytic lymphohistiocytosis in siblings carrying PRF1 mutations. Blood. 2002;100(6):2266–7.
11. Henter JI, Aricò M, Elinder G, Imashuku S, Janka G. Familial hemophagocytic lymphohistiocytosis. Primary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am. 1998;12(2):417–33.
12. Janka GE. Familial hemophagocytic lymphohistiocytosis. Eur J Pediatr. 1983;140(3):221–30.
13. Jayawardena L, McNamara E. Diagnosis and management of pregnancies complicated by Haemolysis, Elevated Liver Enzymes and Low Platelets (HELLP) syndrome in the tertiary setting. Intern Med J. 2019. https://doi.org/10.1111/imj.14337.
14. Herath RP, Siriwardana SR, Ekanayake CD, Abeysekara V, Kodithuwakku SUA, Herath HP. Non-alcoholic fatty liver disease and pregnancy complications among Sri Lankan women: a cross sectional analytical study. PLoS ONE. 2019;14(4):1–15.
15. van Kester MS, Langeveld TJC, Bouwsma H, van Rees JB, Holman ER, Teng YKO, et al. A breathtaking DRESS due to amoxicillin–clavulanate presenting as polymorphic eruption of the pregnancy. J Eur Acad Dermatol Venereol. 2018;32(12):e436–7.
16. He M, Jia J, Zhang J, Beejadhursing R, Mwamaka Sharifu L, Yu J, et al. Pregnancy-associated hemophagocytic lymphohistiocytosis secondary to NK/T cells lymphoma. Medicine (United States). 2017;96(47):e8628.
17. Shukla A, Kaur A, Hira HS. Pregnancy induced haemophagocytic syndrome. J Obstet Gynecol India. 2013;63(3):203–5.
18. Sarkissian S, Khan Y, Farrell D, Constable D, Brem E. Hemophagocytic lymphohistiocytosis in the setting of HELLP syndrome. Clin Case Rep. 2018;6(12):2466–70.
19. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Pre-eclampsia: pathophysiology, diagnosis, and management. Vasc Health Risk Manag. 2011;7(1):467–74.
20. Williams Z, Zepf D, Longtine J, Anchan R, Broadman B, Missmer SA, et al. Foreign fetal cells persist in the maternal circulation. Fertil Steril. 2009;91(6):2593–5.

About the Author

Luis A. Sánchez-Ato is a 26-year-old Peruvian Medical Doctor at the Peruvian University of Applied Sciences (UPC), who was a junior researcher at the UPC Research Center part of a research on a biophysical platform with fluorescent ribosomal proteins for the study of new antibiotics. As part of the investigation, he made a rotation in the Laboratory of Camerino University in Italy. He is currently working as a Medical Doctor in Vista Alegre Clinic. He is a proactive doctor, with high investigative capacity and collaborator. He has proper interpersonal development to create and maintain a professional relationship, as well as an excellent doctor–patient relationship. He is interested in taking on tasks that involve new challenges for the improvement of health.