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CASE REPORT

Hepatitis during pregnancy: A case of hemophagocytic lymphohistiocytosis

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KEYWORDS
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Summary Hemophagocytic lymphohistiocytosis (HLH) is a rare but severe and potentially fatal syndrome that can occur during pregnancy. A 36 years-old woman, at 29 weeks of gestation, presented with itchiness and jaundice since a week. On clinical examination she was apyrexial and frankly icteric. Laboratory data showed evidence of acute hepatitis. A complete work-up was made excluding viral hepatitis (HAV, HEV, HBV, HCV, HHV6, CMV, EBV) and autoimmune liver disease. Liver diseases related to pregnancy were not completely excluded. A liver biopsy was performed and firstly interpreted as showing features of acute hepatitis. The clinical situation worsened, she developed fever with signs of fetal distress and emergent delivery was done. A second look at the liver biopsy showed features compatible with HLH, which was also confirmed on bone marrow biopsy. Extensive work-up with exclusion of infectious and malignant diseases, lead us to the diagnosis of HLH secondary to pregnancy and short term steroid therapy was started. She then completely recovered and didn't present any relapse after 4 months of follow up. HLH during pregnancy is very rare and this is the first case of HLH presenting as acute hepatitis and diagnosed on a liver biopsy.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal disease due to uncontrolled immune system activation. The diagnosis is based on the HLH-2004 criteria [1]. It can be primary or secondary to infections, malignancies and rheumatologic diseases. Only few cases of pregnancy-related HLH are reported in the literature with various clinical presentations and no systematic liver and bone-marrow histological diagnosis confirmation. We report here a new case of HLH developing during pregnancy and take this opportunity to review the literature and present the main characteristics of these patients.

Case report

A 36 years-old woman presented to the department of gynecology for itchiness and jaundice since a week. She was at 29 weeks of gestation and her medication was based on antiretroviral treatment (darunavir, ritonavir, emtricitabine, tenofovir disoproxil fumarate) for an HIV infection diagnosed in 2014. It was her third pregnancy and she had no other past medical history. She didn't travel abroad and has not taken any drug, alcohol or herbs recently. On clinical examination she was apyrexial and frankly icteric with a blood pressure of 125/72 mmHg without clinical signs of chronic liver disease. Relevant laboratory data were: total bilirubin, 10.2 mg/dL (normal value [NV] < 1.2 mg/dL); conjugated bilirubin, 8.2 mg/dL (NV < 0.3 mg/dL); biliary acids: 232,8 (NV < 10 μmol/L), aspartate aminotransferase 4267 U/L (NV < 40); alanine aminotransferase 1245 U/L (NV < 40); gamma glutamyl transpeptidase 52 U/L (NV < 60); LDH, 1789 IU/L (NV < 250 UI/L); neutrophil count 4380/μL (NV 1600—7000/μL); hemoglobin 7.2 g/dL (NV 13—18 g/dL); platelet count 416,000/mm^3 (NV 150,000—350,000/mm^3); ferritin 853 (NV 13—150 μg/L); renal function and coagulation parameters were normal. Serologic tests for CMV, EBV, herpes virus, toxoplasma, parvovirus B19, hepatitis A, B, C and E were negative. Plasma HIV viral load and CD4 count were below 40 copies/mL and 604/μL respectively, compatible with well-controlled HIV infection. Antinuclear antibodies (ANA), rheumatoid factors, antiphospholipid antibodies were negative. Chest X-ray, liver and obstetric ultrasonography as well as urinalysis were normal. In this situation of hepatitis of unknown origin in the third pregnancy trimester, a liver biopsy was performed at 31 weeks 1/7 of pregnancy to rule out severe conditions imposing premature delivery and to look for a treatable disease. This biopsy was firstly interpreted as showing signs of acute hepatitis without evidence of intrahepatic cholestasis of pregnancy (Fig. 1A). A viral or drug induced hepatitis was suspected and antiretroviral treatments were stopped.

As the biliary acids were higher than 40 μmol/L, we considered a high risk for stillbirth. The delivery was programmed at 32 weeks of pregnancy with fetal pulmonary maturation and until then daily monitoring of the baby. Unfortunately, the patient developed temperature of 39 °C at 31 weeks 5/7 days and the monitoring showed signs of fetal distress. An emergency cesarean section was performed at 31 weeks 6/7 days. After surgery, the temperature remained high. Intravenous empirical antibiotherapy with

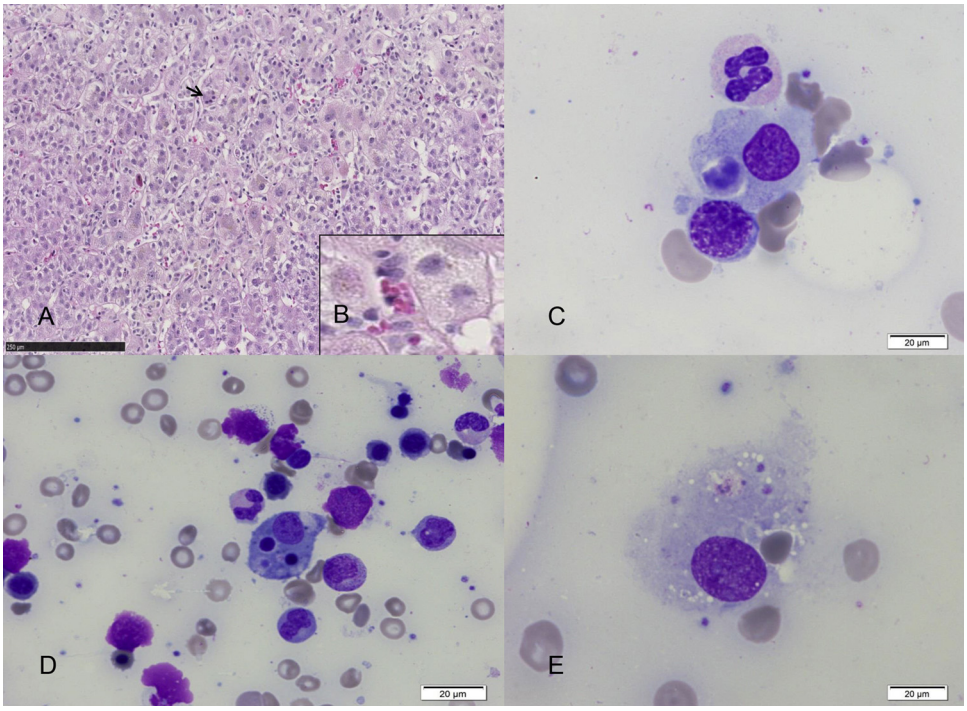

Figure 1 A. Liver biopsy-haematoxylin and eosin stain. The liver parenchyma showed severe lobular inflammation composed of lymphocytes and neutrophils associating with giant cell transformation of the hepatocytes (arrow). B. The liver parenchyma showed hemophagocytosis. C—E. Bone marrow. May—Grunwald Giemsa staining. Bone marrow showing signs of hemophagocytosis. A macrophage engulfing neutrophils, lymphocytes and red cells are shown on C, D and E.

Table 1 Characteristics of patient's cases reported in the literature with HLH during pregnancy.

Publication	Gestational age (weeks)	Associated disease	Clinical signs	Pertinent labs	Histology	Treatment	Outcome
Tsuda et al. (Jpn J Clin Hematol 1995) [3]	Post-partum	Parvovirus B19	Fever	Cytopenias	NA	NA	NA
Mihara et al. (Jpn J Clin Hematol 1999) [4]	16	EBV	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia, DIC	Bone marrow	Corticosteroids IVIG Aciclovir	Complete remission
Nakabayashi et al. (Semin Throm Hemost 1999) [5]	21	Preeclampsia	Fever, hepatosplenomegaly	Cytopenias, ferritine > 500 ng/mL, Hepatitis, DIC	Bone marrow	IVIG	Complete remission
Chmait et al. (Obstet Gynecol 2000) [6]	29	EBV	Routine checkup	Cytopenias, ferritine > 500 ng/mL	Bone marrow	Delivery at 30 weeks	Death
Yamaguchi et al. (Obstet Gynecol 2005) [7]	20	HSV-2	Fever	Cytopenias, ferritine > 500 ng/mL	Bone marrow	Corticosteroids Cyclosporin A	Complete remission
Perard et al. (Ann Hematol 2007) [8]	22	Systemic lupus erythematosus	Fever	Cytopenias, Ferritine > 500 ng/mL	Bone marrow	Corticosteroids IVIG 3 doses Premature Delivery	Complete remission
Hanaoka et al. (Clin Lymphoma Myeloma 2007) [9]	23	B-cell lymphoma	Fever, hepatosplenomegaly	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia, DIC	Bone marrow	R-CHOP chemotherapy Emergent C-section	Complete remission
Chien et al. (Int J Obstet Anesth 2009) [10]	23	No etiology	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia	Bone marrow	Cesarean delivery	Complete remission

Table 1 (*Continued*)

Publication	Gestational age (weeks)	Associated disease	Clinical signs	Pertinent labs	Histology	Treatment	Outcome
Teng et al. (J Clin Med Assoc 2009) [11]	23	Autoimmune hemolytic anemia	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia	Bone marrow	Corticosteroids Cesarean delivery at 29 weeks	Complete remission
Yoshida et al. (Jpn J Clin Immunol 2009) [12]	Post-partum	Systemic lupus erythematosus	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia, hepatitis	Bone marrow	Corticosteroids	Complete remission
Arewa et al. (West Afr J Med 2011) [13]	21	HIV	Fever, jaundice, abdominal pain	Cytopenias	Bone marrow	HAART Delivery at term.	Complete remission
Dunn et al. (Hematology 2012) [14]	19	Still's disease	Fever, rash, headache	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia	Bone marrow	Corticosteroids	Complete remission
Hannebique et al. (Ann Fr Anesth Reanim 2012) [15]	21	Systemic lupus erythematosus	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia	Bone marrow	Corticosteroids IVIG	Complete remission
Shukla et al. (Gynaecol India 2013) [16]	10	No etiology	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia	Bone marrow Liver	Corticosteroids Abortion	Complete remission
Komaru et al. (Intern Med 2013) [17]	Post-partum	Sjögren disease	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia, Hepatitis	Bone marrow	Corticosteroids	Complete remission

Table 1 (*Continued*)

Publication	Gestational age (weeks)	Associated disease	Clinical signs	Pertinent labs	Histology	Treatment	Outcome
Mayama et al. (Obstet Gynecol 2014) [18]	21	Parvovirus B19	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia	Bone marrow	Corticosteroids	Complete remission
Tumian et al. (Taiwan J Obstet Gynecol 2015) [19]	38	No etiology	Fever, jaundice	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia, hepatitis	Bone marrow	Corticosteroids Cyclosporine	Death
Samra et al. (Hematol Rep 2015) [20]	16	No etiology	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia	Bone marrow	Corticosteroids	Complete remission
Giard et al. (ACG Case Rep J 2016) [21]	13	Kikuchi Fujimoto lymphadenitis	Fever	Cytopenias, ferritine > 500 ng/mL, HYPER-TRIGLYCERIDEMIA, Hepatitis	Bone marrow Liver	Corticosteroids Etoposide Abortion	Death
Ikeda et al. (Rinsho Ketsueki 2017) [22]	11	EBV	Fever	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia	Bone marrow	Single dose dexamethasone Etoposide Cyclosporine	Complete remission
Our case	32	No etiology	Fever, jaundice	Cytopenias, ferritine > 500 ng/mL, hypertriglyceridemia, hepatitis	Bone marrow Liver	Corticosteroids	Complete remission

NA: not available; EBV: Ebstein Barr Virus; HSV-2: Herpes Simplex Virus type 2; HAART: highly active antiretroviral treatment; IVIG: intravenous immunoglobulin.

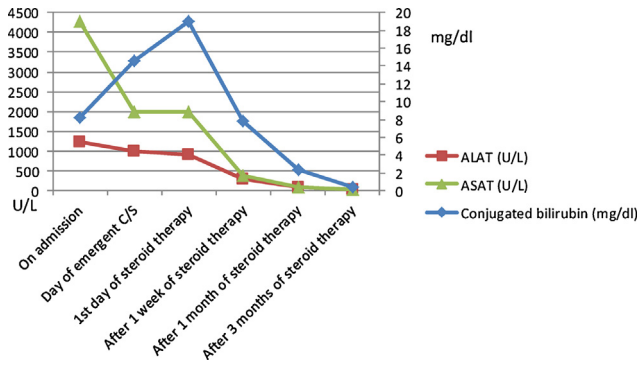

Figure 2 Evolution of liver tests before and after steroid therapy (C/S: cesarean section).

ceftriaxone (2 g/day) and metronidazole 500 mg t.i.d in the hypothesis of a chorioamnionitis were started. Blood and urine cultures were negative. There was no sign of gynecologic infection on endovaginal ultrasonography. After a week of antibiotherapy, fever persisted and so we decided to stop antibiotherapy. A second look at the liver biopsy (Fig. 1B) revealed signs of hemophagocytic lymphohistiocytosis (HLH). Ferritin level was controlled at day 3 after delivery and was very high at 10543 μg/L (NV below 150 μg/dL) with fasting triglyceride level at 466 (NV < 150 mg/dL). Liver tests were still high. A bone marrow biopsy was performed showing features of HLH but no immunophenotypic evidence of a lymphoproliferative disease by visual and flow cytometric analysis (Fig. 1C—E). An 18-FDG PET imaging didn't reveal any sign of infection, cancer or lymphoma. Direct examination and PCR for mycobacterium tuberculosis on bone marrow were negative. Serum PCR for EBV, CMV, HHV-6 and HHV-8 became negative as were serology for leishmania, bartonella, leptospirosis, dengue and histoplasma capsulatum. A diagnosis of HLH in the context of pregnancy was retained according to HLH-2004 trial. We started a treatment with intravenous methylprednisolone at dose of 80 mg daily during 7 days followed by a tapering dose orally. The patient's clinical condition improved after 3 days of therapy and no other immunosuppresive agent was added. Within 6 weeks, complete clinical and biological improvement was observed (Fig. 2).

Discussion

Secondary HLH is a rare disease associated with infection (virus, bacteria, mycosis, parasitic), cancer, lymphoma, autoimmune disease and drug but it is rare during pregnancy [2]. The diagnosis is based on HLH-2004 criteria. The absence of hemophagocytosis in the bone marrow does not exclude a diagnosis of HLH. In our case the diagnosis was not made at the initial presentation since the patient first presented with clinical and biological features of acute liver injury. We had first to rule out common obstetrical emergencies and pregnancy related liver diseases such as intrahepatic cholestasis, acute fatty liver of pregnancy, HELLP syndrome or preeclampsia.

A rapid diagnosis is important to reduce mortality. There are no clear guidelines for the treatment of pregnancy related HLH. Steroids constitute an integral part of the HLH protocols regardless of the precipitating cause. Due to the potential teratogenicity of chemotherapy (etoposide), it is better to use steroids as first line therapy and IVIG or cyclosporine in steroids-resistant cases. This can avoid premature delivery and allow fetal delivery in better condition.

Only 20 cases of HLH during pregnancy are described in the literature and on Table 1, we present all the characteristics of these patients (3—22). Mean gestational age seems to be 20 weeks. Fever, hyperferritinemia and cytopenia are present in almost all patients. Acute hepatitis has been described in 8 cases (40%). Liver biopsy was made in 2 cases but no sign of HLH was observed. We describe here the first case of HLH proven on liver biopsy in pregnant patient. HLH can occur before delivery (17/20, 85%) or in post-partum (3/20, 15%) and it has been described once in the context of HIV. To our knowledge, this is the second case of HLH during pregnancy in a HIV patient. Death occurred in 3 cases (15%) a possible lower rate than the usual mortality rate of HLH without pregnancy (50%) [2]. Thus, the prognosis seems to be better if there is no treatment delay but this need to be confirmed in larger studies.

The pathophysiology of pregnancy-related HLH is not fully understood. Although most of the cases are in complete remission after pregnancy, suggesting a strong association between pregnancy and HLH [19], we have to keep in mind that the disease can present in the post-partum period or worsen after pregnancy as in our patient. The delivery alone is not sufficient to cure the patient. In the future, case control studies are needed to better identify potential risk factors for HLH secondary to pregnancy.

Conclusion

HLH should be suspected during pregnancy when the patient persists with fever, cytopenia and hepatitis. Other obstetrical emergencies must be excluded like infections, HELLP syndrome and acute fatty liver of pregnancy. We present an original case with HLH proven on liver biopsy, which has never been described before. Secondary cause of HLH must be ruled out and treatment should be given rapidly to reduce mortality rate. Initiating treatment before the end of pregnancy is critical to the survival of both mother and fetus.

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Authors contributions

Dr Halil Yildiz and Geraldine Dahlqvist contributed equally to the writing of this paper. All the authors contributed to the management and the diagnosis of the patient.

Disclosure of interest

The authors declare that they have no competing interest.

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