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Reviewer's code: 05382254

SPECIFIC COMMENTS TO AUTHORS

Postpartum hemophagocytosis is rare in clinical practice, and its diagnostic and therapeutic criteria have not been clearly unified, and the pathogenesis is not well understood. Based on their own clinical experience, the authors provide a literature review and targeted discussion of this disease, which is of certain guiding value for clinical practice. The authors have a clear thought process, a reasonable article structure, and are written according to World Journal of Clinical Cases guidelines with a standardized reference format. Disadvantages: First, it is suggested that the authors revise the sentence "Only 11 cases of postpartum HLH have been reported globally[3,5]", including the two tables in the article that relate to the relevant content. Because I used keywords "Postpartum" and "Hemophagocytic Lymphohistiocytosis" for incomplete search, only with the English publication of the article retrieved three additional. Second, there are several places where spaces are missing (of course, these mistakes are not excluded because of the download of the document). 1 Lee J, Pham B, Karanjawala ZE, Adesina O. Postpartum fevers, a rare presentation of secondary hemophagocytic lymphohistiocytosis. Clin Case Rep. 2023-03-01;11(3):e7070. PMID: 36941837 DOI: 10.1002/ccr3.7070 2 Ibarra Stone KA, Solis JG, Blanco-Lemus E, Malagón-Rangel J, Gordillo-Perez, G. Spotted Fever: An Undercover Cause of Hemophagocytic Lymphohistiocytosis in the Immediate Postpartum. CASE REP INFECT DIS. 2022-01-01;2022:3348393. PMID: 35273815 DOI: 10.1155/2022/3348393 3 B Rathna R, Dhali A, Varghese AK, H Balakrishnan C. Rare association of haemophagocytic lymphohistiocytosis (HLH) and antiphospholipid syndrome (APS) in postpartum period: a considerable overlap? BMJ Case Rep. 2022-02-02;15(2). PMID: 35110287 DOI: 10.1136/bcr-2021-247376

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Thank you for your feedback and the opportunity to revise our manuscript now entitled "Postpartum Hemophagocytic.

In the revised manuscript, we have carefully considered the reviewers' comments and suggestions. As instructed, we have attempted to succinctly explain all changes made in response to comments, by replying to each comment in a point-by-point fashion. We have highlighted revisions in the manuscript in yellow ("text"). The responses to the concerns raised by reviewers are below and are color coded: a) Comments from editors or reviewers are italicized ("*text*") and b) our responses are in blue ("text").

We trust that our revisions have successfully addressed all concerns and move this manuscript closer to publication. Thank you for your careful review again.

1.

First, it is suggested that the authors revise the sentence "Only 11 cases of postpartum HLH have been reported globally[3,5]", including the two tables in the article that relate to the relevant content. Because I used keywords "Postpartum" and "Hemophagocytic Lymphohistiocytosis" for

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incomplete search, only with the English publication of the article retrieved three additional

Response Thank you for this insightful comment. Accordingly, we performed a more thorough search for postpartum HLH cases. We found only 3 papers that the reviewer mentioned. Unfortunately, we could not check papers in languages other than English; however, we did our best to check all papers in English. We have added the three cases mentioned by the reviewer to Table 2.

Currently, only 11 cases of postpartum HLH have been reported in English literature.

Additionally, we reviewed the 11 reported cases of postpartum HLH, including eight patients in a case series (3) and three case reports (6-8). We compared the diagnostic criteria used in these cases, focusing on initial treatment and mortality, to help increase the awareness of this disease.

The first case series of patients with postpartum HLH was described by Song et al. in 2019 (3). Additionally, three more postpartum HLH cases reported in English were identified (6-8), and 11 patients were compared (Table 2). Table 2 shows the number of diagnostic criteria that each patient met, as well as initial treatments and patient outcomes. Nine patients survived

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Table 2. Number of diagnostic criteria met, treatments, and outcomes

Case no	Diagnostic criteria met	Primary therapy	Outcome
1	1,2,3,4,5,7,8	HLH-04	died
2	1,2,3,4,5,6,7	HLH-04	survived
3	1,3,4,5,7,8	HLH-04	survived
4	1,2,4,5,6,7,8	HLH-94	survived
5	1,2,4,5,6,7,8	HLH-94	survived
6	1,3,4,5,7	HLH-94	died
7	1,2,4,6,7,8	FD	survived
8	1,2,4,5,6,7,8	DEP	survived
9	1,2,3,4,5,6,7,8	HLH-94 with anakinra	survived
10	1,2,3,4,5,7	HLH-04	survived
11	1,2,3,4,7	Methylprednisolone	survived

FD, fludarabine + prednisolone; DEP: doxorubicin +etoposide + methylprednisolone

Diagnostic criteria met: 1. Fever; 2. Splenomegaly; 3. cytopenia affecting ≥ 2 of 3, 4; hypertriglyceridemia and/or hypofibrinogenemia; 5. hemophagocytosis in bone marrow or spleen or lymph nodes or liver; 6. Low or absent NK-cell activity; 7 Ferritin elevation; and 8. Elevated Soluble

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CD25

2.

Second, there are several places where spaces are missing (of course, these mistakes are not excluded because of the download of the document).

Response Thank you for this comment. The manuscript has once more undergone English proofreading (certificate attached), and the authors also rechecked the manuscript prior to resubmission.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially life-threatening condition that develops concurrently with various conditions, including infection, immunodeficiency syndrome, hematologic malignancy, autoimmune disease, and pregnancy [1-3]. Postpartum HLH is often overlooked due to its low incidence rate [4]; currently, only 11 cases have been reported in English literature [3, 5-8]. Therefore, patient symptoms may not prompt this disease to be considered in a differential

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diagnosis, which may delay accurate diagnosis and lead to adverse outcomes. To prevent this, awareness of this disease should be increased.

This case report aims to augment the existing body of medical evidence regarding postpartum HLH and enhance its awareness among healthcare professionals. Additionally, the 11 reported cases of postpartum HLH, including eight patients in a case series [3] and three case reports [6-8], have been reviewed in this report. We compared the diagnostic criteria used in these cases, focusing on initial treatment and mortality, to help increase the awareness of this disease.

DISCUSSION

The first case series of patients with postpartum HLH was described by Song et al. in 2019 [3]. In addition, three more cases reported in English were identified [6-8]. Eleven patients were compared in Table 2, which shows the number of diagnostic criteria met by each patient, as well as initial treatments and patient outcomes. Nine patients survived; however, the two patients who died met five or seven of the diagnostic criteria described in Table 1. The time from disease onset to diagnosis is not described for each patient. However, considering the rarity of the disease in the postpartum setting, the relationship between treatment regimen and survival described for the eight patients is important. In our case, although five of the diagnostic criteria were met, the prognosis was poor owing to diagnostic treatment delays. Based on the criteria reported by Song et al. [3], fever was reported in eleven patients, splenomegaly in nine, cytopenia in seven, hypertriglyceridemia and/or hypofibrinogenemia in eleven, hemophagocytosis in nine, low natural killer cell activity in six, ferritin level elevation in eleven, and soluble CD25 level elevation in seven. Where a differential diagnosis is required based on clinical symptoms and results, conducting a ferritin test is important after confirming cytopenia, hypertriglyceridemia, and/or hypofibrinogenemia. In addition, a bone marrow biopsy

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should be performed to confirm hemophagocytosis, as this provides clinicians with more information than other nonspecific symptoms and test results.

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SPECIFIC COMMENTS TO AUTHORS

Postpartum HLH is a very rare condition and deserves a publication. Making the diagnosis of HLH could be quite challenging due to the broad range of presenting symptoms and the lack of specificity. Hovewer, the reported case may not be HLH, as hemophagocytosis is neither specific nor sensitive for HLH. The patient had 4-day fever, then was afebrile? or, besides was bicytopenic with hyperferritinemia and hypertgiciceridemia. The diagnosis of HLH could be supported supported by splenomegaly, neurologic dysfunction, marked cytopenias (this patient had only mild thrombocytopenia), hypofibrinogenemia, low CRP, and characteristic cytokine profile. The dilemma about the diagnosis could be appropriately addressed.

Thank you for your feedback and the opportunity to revise our manuscript now entitled "Postpartum Hemophagocytic Lymphohistiocytosis : Insights from a Case Report and Literature Review".

In the revised manuscript, we have carefully considered the reviewers' comments and suggestions. As instructed, we have attempted to succinctly explain all changes made in response to comments, by replying to each comment in a point-by-point fashion. We have highlighted revisions in the manuscript in yellow ("text"). The responses to the concerns raised by reviewers are below and are color coded: a) Comments from editors or reviewers are italicized ("*text*") and b) our responses are in blue ("text").

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Response_ Thank you for these constructive comments. Indeed, there is always a diagnostic dilemma when attempting to diagnose HLH. Because the diagnosis of HLH is made according to set diagnostic criteria, a perfect diagnosis is difficult. However, when antibiotics were used, there was no particular reaction; hence, the possibility of an infection-related pathology seemed low. After the patient's death, the experts reached a consensus that HLH was the most possible by discussion. Therefore, we propose that the diagnosis for this case was HLH.

Because HLH diagnosis is made according to diagnostic criteria, accurate diagnosis of the disease remains difficult. In our study, we faced similar challenges. Although the diagnostic criteria for HLH were met, they were not differentiated from those for other diseases. However, no particular reaction was observed upon administration of antibiotics; therefore, the possibility of infection-related diagnosis seemed low. A final

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consensus on HLH diagnosis was reached when experts discussed the diagnosis after the patient's death.

DISCUSSION

HLH, a rare disease associated with uncontrolled inflammatory response [9], is characterized by dysregulated hyperinflammatory immune response resulting in histiocytic proliferation, significant bone marrow hemophagocytic activity, and massive release of inflammatory cytokines [1, 2]. The disease may be classified as primary or secondary [2, 10], with underlying causes of secondary HLH including infections, malignancies, and autoimmune diseases. Pregnancy-related HLH is a type of secondary HLH, with postpartum HLH being the less well-known subtype. To date, only a few cases of the latter have been reported [3, 5]. Yildiz et al. [5] described 21 cases of pregnancy-related HLH, only three of which were postpartum. Additionally, Song et al. [3] described a case series of eight patients with postpartum HLH. Despite the paucity of published information, understanding this disease is important to minimize diagnostic delays leading to poor patient prognoses.

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HLH is characterized by tissue cell proliferation, hyperinflammation, bone marrow hemophagocytic activity, and release of large amounts of inflammatory cytokines produced by lymphocytes. These characteristics are similar to those observed during pregnancy [4, 11-15]. However, unlike pregnancy-related HLH, postpartum HLH is characterized by disease onset after childbirth. Here, HLH may have been induced by an infection and the resultant inappropriate immune response where the pathophysiology of pregnancy/childbirth was similar to that of HLH. Since the pathogenic factors associated with pregnancy and childbirth have been eliminated, they cannot be part of the etiology of postpartum HLH. However, even after childbirth, the altered immune system may have been confounded by infection, leading to postpartum HLH [16].

Since no diagnostic criteria exist for postpartum HLH, pediatric HLH diagnostic criteria have been used (Table 1) [4, 17]. In this case, when the patient returned to the ED, the diagnostic criteria for HLH were not met, except fever and elevated ferritin levels. Cytopenia, hypertriglyceridemia, and bone marrow hemophagocytosis were not confirmed until after ICU admission. In clinical practice, all the tests necessary to meet the HLH diagnostic criteria cannot be conducted in the ED. Blood test results may not meet diagnostic criteria during the early stages of the disease, which are characterized by rapid disease progression. As in our case, if a postpartum patient visits the ED with fever, but the symptoms are nonspecific and ferritin levels are high, the patient should be advised to undergo a bone marrow biopsy under the outpatient setting.

The first case series of patients with postpartum HLH was described by Song et al. in 2019 [3]. In addition, three more cases reported in English were identified [6-8]. Eleven patients were compared in Table 2, which shows the number of diagnostic criteria met by each patient, as well as initial treatments and patient outcomes. Nine patients survived; however, the two patients who died met five or seven of the diagnostic criteria described in Table 1. The time from disease onset to diagnosis is not described for each

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Because HLH diagnosis is made according to diagnostic criteria, accurate diagnosis of the disease remains difficult. In our study, we faced similar challenges. Although the diagnostic criteria for HLH were met, they were not differentiated from those for other diseases. However, no particular reaction was observed upon administration of antibiotics; therefore, the possibility of infection-related diagnosis seemed low. A final consensus on HLH diagnosis was reached when experts discussed the diagnosis after the patient's death.

Currently, no standard therapeutic regimen exists for postpartum HLH treatment [4, 18]. Based on previous studies, the standard post-abortion HLH-94/04 treatment seems to be the most efficient and safe option [19]. In this regimen, etoposide and dexamethasone, with or without cyclosporine A, are used to treat active HLH. A recent review estimates the mortality rate for secondary HLH as approximately 41% [14]. Additionally, doxorubicin, etoposide, and high-dose methylprednisolone [20], as well as fludarabine with prednisolone, can be used to treat refractory HLH in adults [21].

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During the postpartum period, the effects of cytotoxic drugs on the fetus are negligible. However, the patient's general condition deteriorates markedly after childbirth, and use of high-dose steroids may increase risk of infection. In addition, most postpartum HLH cases are confused with sepsis, metabolic disorders, or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome (characterized by hemolytic anemia, elevated liver enzyme levels, and thrombocytopenia) [22, 23]. These factors delay postpartum HLH diagnosis, and may contribute to the high mortality rate.

Early diagnosis and prompt immunosuppressant administration are required to improve the prognoses of patients with postpartum HLH [24, 25]. However, complications may occur if a severe infection is mistaken for HLH and immunosuppressants are administered [26]. Nevertheless, it is necessary to consider treatment methods, including high-dose steroids, that improve prognosis. Unfortunately, the paucity of reported studies dealing with postpartum HLH prognosis makes determining the optimal treatment regimen challenging; therefore, more research is needed on methods to improve prognosis.