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CASE REPORT

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Postpartum fevers, a rare presentation of secondary hemophagocytic lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease of excessive immune system activation. We report a case of HLH in a 20-year-old primigravid woman who presented with postpartum fevers. She was successfully treated with dexamethasone and anakinra, a deviation from the HLH-94 protocol, to preserve her ability to breastfeed.

KEYWORDS

anakinra, fever of unknown origin, hemophagocytic lymphohistiocytosis, postpartum fevers

1 | BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease of immune dysregulation that mimics many other conditions at presentation. Prompt diagnosis and treatment of pregnancy-related HLH is critical to reduce maternal-fetal morbidity and mortality. Current diagnostic criteria for HLH, as determined by the 2004 Histiocyte Society Study group, includes fever, organomegaly, bicytopenia or pancytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis on bone marrow biopsy, low/absent natural killer (NK) cell activity, elevated serum ferritin, and high soluble interleukin-2-receptor levels. Patients must meet at least five of the eight criteria for a clinical diagnosis of HLH.[1] HLH can be further categorized into two subtypes: (i) primary or familial HLH (linked to genetic defects) and (ii) secondary HLH, which is an acquired or sporadic form. Secondary HLH may be triggered by various infections, autoimmune diseases, rheumatologic disorders, hematologic malignancies, and immunodeficiencies.[1] Pregnancy-related HLH is exceedingly rare and only described in case studies.[2–4] An expert consensus panel of pediatricians, convened by the Histiocyte society in 1994, developed the current primary HLH treatment recommendations of dexamethasone and etoposide, commonly referred to as the HLH-94 protocol.[5] Treatment of secondary HLH is extrapolated from the HLH-94 protocol, though some clinicians opt for alternative immunomodulators to etoposide given its extensive toxicity profile.[6] Since HLH is a rare disease, safety and efficacy data on newer alternative therapies to the HLH-94 protocol often come from small, retrospective studies. We present a case of postpartum HLH successfully treated with dexamethasone and anakinra as an important contribution to fill the knowledge gap on secondary HLH diagnosis and management.

2 | CASE PRESENTATION

We report the case of a 20-year-old primigravid woman, previously healthy, who had a spontaneous vaginal

delivery of a healthy female infant at term. Her delivery was complicated by postpartum hemorrhage, attributed to retained placenta (requiring manual extraction), as well as fevers of unknown origin. She underwent a dilation and curettage (D&C) with pathology results concerning for endometritis and retained products of conception. Her cyclical high-grade fevers persisted despite 3 weeks of treatment with broad-spectrum antibiotics administered as follows: (i) ceftriaxone, metronidazole, and gentamycin; (ii) imipenem, vancomycin, and doxycycline; (iii) linezolid; (iv) ampicillin/sulbactam; (v) doxycycline, vancomycin, and meropenem. Although we considered drug fevers as part of the differential diagnosis, this was deemed less likely since her fevers persisted despite discontinuation of all antibiotics for several days. At 2 weeks postpartum, she developed acute kidney injury, elevated liver enzymes with hepatomegaly, thrombocytopenia, and anemia. An exploratory abdominal laparoscopy and repeat D&C were unrevealing. Her second D&C was complicated by intrauterine hemorrhage requiring emergent bilateral uterine artery embolization. She required a massive transfusion protocol of 6 units packed red blood cells (pRBCs), 3 units fresh frozen plasma, 4 units platelets, and 2 units cryoprecipitate. Her postoperative course was further complicated by transfusion-associated cardiogenic overload requiring intubation for airway protection. She received intravenous furosemide for diuresis and was successfully extubated a day later.

Her persistent fevers prompted a workup for HLH. Additional labs obtained on postpartum day 24 showed serum ferritin of >20,000 ng/mL (normal range 10–291 ng/mL) and triglycerides at 960 mg/dL (normal range 35–160 mg/dL). Since she had only received 6 units pRBCs, this degree of hyperferritinemia was not attributed to transfusion-related iron overload.[7] She underwent a bone marrow biopsy that demonstrated hemophagocytic histiocytes (Figure 1D). We initiated oral dexamethasone at 10 mg/m^2 daily on postpartum day 25, and she defervesced within 24 h. Additional send-out tests returned with soluble CD25 level elevated at 35,000 pg/mL (normal range 175.3–858.2 pg/mL) and decreased NK cell activity (NK 50:1 was 7.3%, normal value ≥7.8%); thus, she met all eight HLH diagnostic criteria. To minimize etoposide-related toxicity and support our patient's wishes to breastfeed her newborn, we substituted etoposide with anakinra an interleukin-1 (IL-1) inhibitor. We started the anakinra 200 mg subcutaneous injections twice daily on postpartum day 28 (3 days after dexamethasone initiation) due to medical insurance barriers. Her kidney injury and thrombocytopenia resolved within 3 and 6 days of starting dexamethasone, respectively. Her elevated liver enzymes, ferritin, and triglyceride levels gradually decreased, and she was safely discharged from the hospital 20 days after initiating HLH treatment. Under close observation with twice weekly labs and weekly symptoms assessment, we tapered her off dexamethasone and anakinra 1 month after her hospital discharge. Other than injection site pain, moon facies, insomnia, and arthralgias (all expected steroid-related side effects), she tolerated this regimen well.

3 | INVESTIGATIONS

Pathology from our patient's initial D&C was notable for severe acute-on-chronic inflammation and necrosis concerning for infection. A computed tomography scan of her

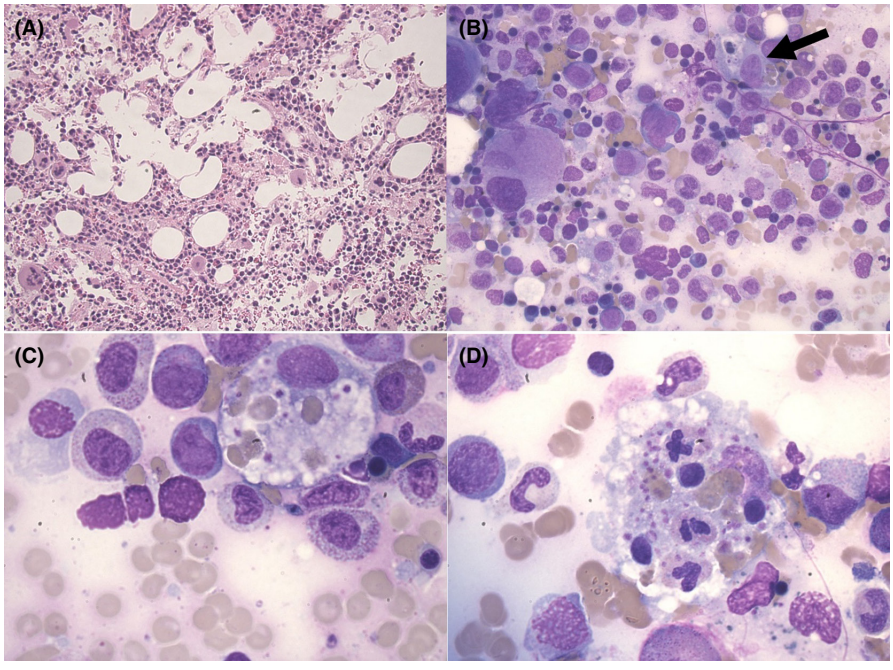

FIGURE 1 (A) Bone marrow trephine biopsy (H&E) shows trilineage hematopoiesis with complete maturation (200x magnification). (B) The corresponding aspirate smear (Wright–Giemsa stain) also shows trilineage hematopoiesis with a hemophagocytic histiocyte (indicated by the arrow) within the field. (C) At high power magnification (1000x), hemophagocytic histiocytes are seen engulfing mature red blood cells and cellular debris. (D) Rare hemophagocytic histiocytic forms demonstrate multiple hematopoietic cells within the cytoplasm, including mature red blood cells, lymphocytes and granulocytes.

abdomen and pelvis showed a heterogeneous and mildly enlarged uterus, no intra-abdominal abscess/fluid collection, and hepatomegaly with steatosis. She developed symptomatic anemia with a hemoglobin nadir of 6.7 g/dL (normal range 12–16 g/dL) and required red blood cell transfusions. Other laboratory derangements included thrombocytopenia with a platelet nadir of 63,000 platelets/mm^3 (normal range 130,000–400,000 platelets/mm^3), elevated liver enzymes with aspartate aminotransaminase 380 U/L (normal range 15–43 U/L), alanine aminotransferase 250 U/L (normal range 5–54 U/L), alkaline phosphatase 920 U/L (normal range 30–130 U/L), and hyperbilirubinemia with total bilirubin of 4.4 mg/dL (normal range 0.3–1.3 mg/dL). Results from her extensive infectious and autoimmune work up are summarized in Table 1.

She underwent repeat uterine D&C with pathology showing retained products of conception and chronic endometritis. A concurrent abdominal exploratory laparoscopy did not reveal any abscesses or hematomas that could explain her cyclical fevers. Given her negative broad infectious work up, a bone marrow biopsy was performed to evaluate for HLH. Examination of the bone marrow trephine biopsy (Figure 1A) and phenotyping studies by flow cytometry and immunohistochemical analyses (not shown), did not show any neoplastic infiltrate of hematopoietic or non-hematopoietic origin. The bone marrow aspirate (Figure 1B) showed trilineage hematopoiesis with complete maturation and mild erythroid hyperplasia (myeloid: erythroid ratio of approximately 1.6:1). Morphologic examination did not show any significant dyspoiesis or viral cytopathic effect, and blasts were not increased. As previously mentioned, hemophagocytic histiocytes were readily identified (Figures 1B–D), including a rare example of a histiocyte engulfing multiple hematopoietic cells (granulocytes, erythroid precursors, mature lymphocytes, and mature red blood cells) as shown in Figure 1D. Immunohistochemical studies for CMV and in-situ hybridization studies for EBV-encoded RNA (EBER) were negative (not shown).

TABLE 1 Summary of infectious and autoimmune laboratory studies.

	Tests	Results
Infectious	Blood cultures	No growth
	Uterine tissue cultures (bacterial, AFB, fungal)	No growth
	EBV viral load	1043 copies/mL (baseline)
		<750 copies/mL (repeated 2 weeks later)
		<750 copies/mL (repeated 6 weeks later)
	CMV Ab	Negative
	Leptospirosis Ab	Negative
	Q fever Ab IgG	Negative
	Brucella Ab	Negative
	Rocky Mountain spotted fever Ab	Negative
	Coccidioides IgG/IgM	Negative
	Herpes simplex virus 6	Negative
	Hepatitis A IgG	Reactive
	Hepatitis A IgM	Nonreactive
	Hepatitis B core Ab	Nonreactive
	Hepatitis B surface Ag	Nonreactive
	Hepatitis E IgG/IgM	Negative
	SARS-CoV-2 S1/S2 IgG	Positive
Autoimmune	ANA Ab	Negative
	dsDNA Ab, IgG	Negative
	Complement C3	180 mg/dL (normal range 92–210 mg/dL)
	Complement C4	51 mg/dL (normal range 18–56 mg/dL)

Abbreviations: Ab, antibody; AFB acid-fast bacilli; ANA, anti-nuclear antibody; CMV, cytomegalovirus; dsDNA, anti-double stranded deoxyribonucleic acid; EBV, Epstein–Barr virus; Ig Immunoglobulin; SARS-CoV-2 S1/S2 IgG, antibodies to severe acute respiratory syndrome coronavirus 2 spike proteins 1 and 2.

4 | DIFFERENTIAL DIAGNOSIS

Our broad differential diagnoses for postpartum fevers includes infectious, autoimmune, rheumatologic, and malignant etiologies. As previously discussed, our patient met all eight diagnostic HLH criteria. Given her young age and the rarity of postpartum HLH, we worked her up for primary HLH and other causes of secondary HLH. Genetic tests for HLH were negative including *SLAM-associated Protein* (*SAP*) mutations, associated with familial HLH. Her CD163 was also elevated at 9000 ng/mL (normal range 387–1785 ng/mL), which also supported a secondary HLH diagnosis.[8] A CD107a assay was also sent to detect defects in *STXBP2, MUNC,* and other genes involved in degranulation of NK cells; however, the results were not reportable as the sample lacked sufficient NK cells. Her elevated EBV load was concerning for Epstein–Barr viremia, a known cause of secondary HLH, but EBER in situ hybridization from her bone marrow was negative and repeat EBV load declined after initiating treatment with dexamethasone and anakinra. She was positive for severe acute respiratory syndrome coronavirus 2 spike proteins 1 and 2 antibodies (SARS-CoV-2 S1/S2 IgG), but this was attributed to a past infection since she denied any concurrent COVID-19 symptoms or previous vaccinations. Imaging studies did not reveal any lymphadenopathy or masses concerning for malignancy, and other causes of secondary HLH were deemed unlikely given her extensive negative infectious and autoimmune workup.

5 | TREATMENT

To preserve our patient's ability to breastfeed and to avoid etoposide-related toxicity in a young person, we substituted the etoposide in the HLH-94 regimen with anakinra. Limited retrospective data in pediatric and adult HLH cases showed anakinra and dexamethasone had good overall survival and low hospital-related mortality.[9–12] More importantly, anakinra is considered safe during breastfeeding.[13] We initiated her on oral dexamethasone 10 mg/m^2 daily, then added anakinra 200 mg subcutaneously (SQ) twice daily 3 days later. Her fever curve and laboratory derangements improved by day 4 of treatment, so anakinra was tapered by 100 mg every 3 days until she reached a dose of 100 mg SQ daily by the time of discharge. She was continued on anakinra 100 mg SQ daily for 1 week, decreased to anakinra 100 mg SQ every other day for 3 weeks, then discontinued. Dexamethasone was tapered starting on day 5 of treatment by 20% every 3 days until she reached a dose of dexamethasone 4 mg daily by the time of discharge. We switched her from dexamethasone to prednisone 20 mg daily, which was tapered off over 1 month. She was also placed on antimicrobial prophylaxis with trimethoprim/sulfamethoxazole, acyclovir, and posaconazole. Topical lidocaine and ice packs were applied to her abdominal wall prior to the anakinra administration to reduce injection site pain.

6 | OUTCOME AND FOLLOW-UP

Our patient was successfully discharged home on anakinra and dexamethasone with close outpatient hematology follow-up. She continued to show clinical improvement as demonstrated by downtrending liver enzymes and ferritin levels, along with uptrending hemoglobin levels. She was successfully tapered off dexamethasone/prednisone and anakinra 46 days after initiating treatment. All laboratory derangements normalized within 11 days of initiating dexamethasone and anakinra. Figure 2 shows the trend in her serum ferritin levels over the treatment course. She remains under close observation with routine hematology follow-up as an outpatient.

7 | DISCUSSION

Although postpartum HLH is rare, it should be included in the differential diagnosis for postpartum fevers, cytopenia(s), and elevated liver enzymes. The differential diagnoses should also include sepsis, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, hypertensive disorders, and acute fatty liver of pregnancy. Postpartum sepsis should be ruled out with a broad infectious work up including blood cultures and diagnostic D&C. HELLP syndrome typically resolves after delivery of the fetus, unlike HLH where symptoms persist or even worsen in the postpartum period. Serum ferritin levels greater than 500 ng/mL may differentiate HLH from other causes of postpartum fever, but iron overload from chronic RBC transfusions or hereditary hemochromatosis should be ruled out in the right clinical context. In pediatric patients, serum ferritin levels >10,000 ng/mL are >90% sensitive and specific for HLH. In adult patients, hyperferritinemia is less specific but should still raise suspicion for HLH.[14] A bone marrow biopsy study is helpful in cases where HLH is suspected; in addition to documenting the presence or absence of hemophagocytic histiocytes, it can help rule in or out underlying malignancy or viral infections. In our clinical case, the bone marrow biopsy confirmed her HLH diagnosis with the presence of hemophagocytic histiocytes, including a single histiocyte engulfing multiple hematopoietic cells. Of note, histologic findings of hemophagocytosis are not specific to HLH even when

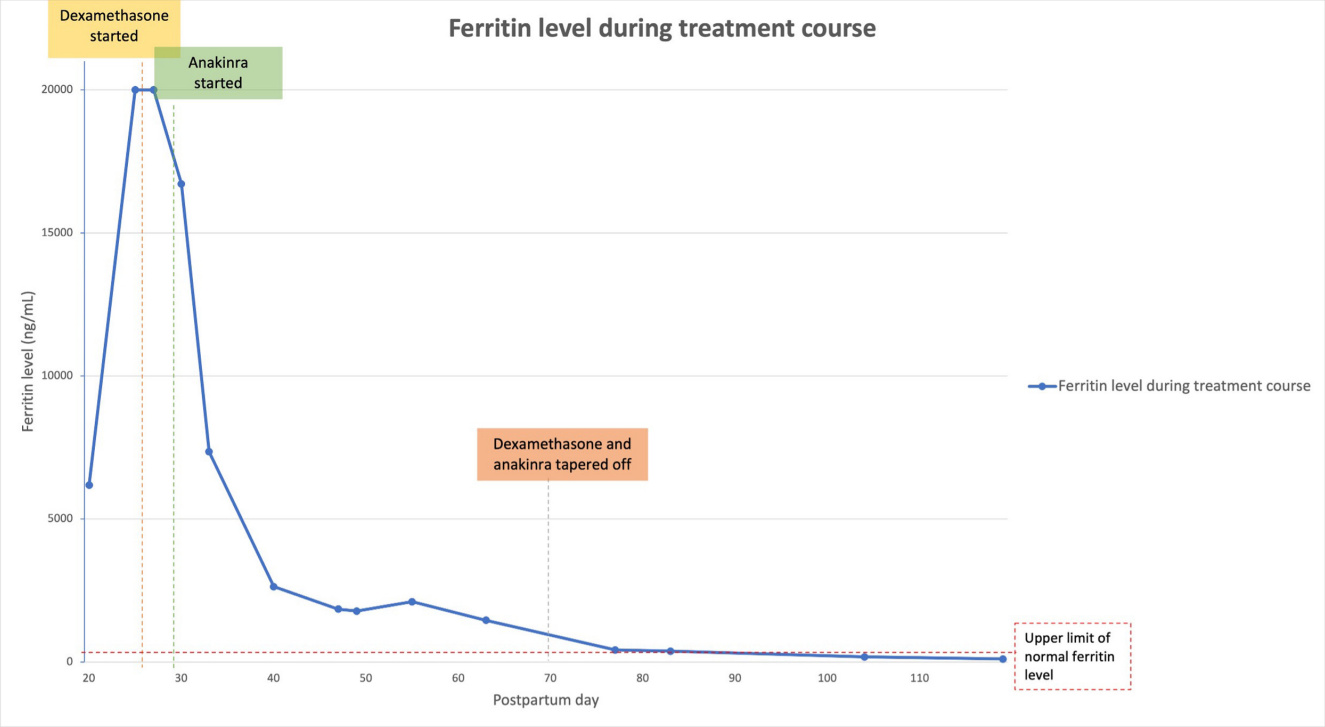

FIGURE 2 Ferritin level throughout treatment course.

present at high levels. A recent study showed that the presence of multiple nucleated cells within a single hemophagocyte, as highlighted in our case, was predictive of a diagnosis of HLH in patients who present with other signs or symptoms that are clinically concerning for HLH.[15]

Secondary HLH management involves treating the underlying cause, reducing cytokine secretion and production, and decreasing T-cell activation. Most patients with secondary HLH are treated with the HLH-94 protocol of dexamethasone and etoposide, with intrathecal methotrexate administered to those with central nervous system involvement. In a case series of postpartum HLH, six of the eight patients included in the study received the HLH-94 protocol. Although most of the women included in this case series recovered from their postpartum HLH, two of the six who received the HLH-94 protocol died from multiorgan failure after HLH relapse.[2] Anakinra is more commonly recommended in the treatment of secondary HLH triggered by an underlying rheumatologic condition, also known as macrophage-activating syndrome (MAS or MAS-HLH).[12] Anakinra is also increasingly used to treat HLH without a rheumatologic trigger. In another case report of pregnancy related HLH, the patient received anakinra, intravenous immunoglobulins (IVIG), and corticosteroids with good response.[16] Wohlfarth et al. analyzed eight HLH patients in the intensive care unit, who received anakinra with IVIG and/or corticosteroids. Of these, five were successfully discharged from the ICU to a step-down hospital unit, and four later discharged alive from the hospital, resulting in a 50% survival rate with the anakinra-based regimen.[9] Although our patient responded well to anakinra and dexamethasone, additional studies on the safety and efficacy of anakinra-based regimens in treating secondary HLH, including postpartum cases, are warranted.

AUTHOR CONTRIBUTIONS

Jacqueline Lee: Conceptualization; data curation; writing – original draft; writing – review and editing. **Brian Pham:** Writing – review and editing. **Zarir E Karanjawala:** Data curation; writing – original draft; writing – review and editing. **Oyebimpe Adesina:** Conceptualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare there are no conflicts of interest related to the publication of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request for the corresponding author. The data are not public available due to privacy or ethical restrictions.

CONSENT STATEMENT

Written informed consent was obtained directly from the patient regarding the publication of this case report and the photos used in this case report. The patient had the opportunity to review the manuscript prior to publication.

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