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Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in pregnancy managed with corticosteroids and Janus Kinase inhibition: a case report

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ABSTRACT:

— ***Background:*** Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by uncontrolled immune activation and multiorgan dysfunction. Epstein-Barr virus (EBV) is a common infectious trigger of secondary HLH. HLH during pregnancy is rare and poses significant diagnostic and therapeutic challenges owing to overlapping clinical features and limited treatment options.

— ***Case Report:*** We report the case of a primigravida at 26 weeks of gestation who presented with severe hyperinflammation, cytopenias, and hepatic dysfunction secondary to EBV-associated HLH. She was successfully managed with corticosteroids, which induced remission, followed by Tofacitinib as a steroid-sparing agent, resulting in sustained remission and a favorable maternal-fetal outcome.

— ***Conclusions:*** This case highlights the importance of individualized immunomodulatory therapy and pragmatic decision-making in resource-limited settings.

— ***Keywords:*** Hemophagocytic lymphohistiocytosis, Epstein-Barr virus, Pregnancy, JAK inhibitor, Hyperferritinemia.

— ***Abbreviations:*** AFLP, acute fatty liver of pregnancy; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; EBV, Epstein-Barr virus; HELLP, haemolysis, elevated liver enzymes, and low platelet count; HLH, hemophagocytic lymphohistiocytosis; IFN-γ, interferon-gamma; IL, interleukin; IU, international units; IV, intravenous; JAK, Janus kinase; LSCS, lower segment caesarean section; NK, natural killer; RA, rheumatoid arthritis; TMA, thrombotic microangiopathy; and TLC, total leucocyte count.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by uncontrolled activation of macrophages and cytotoxic T lymphocytes, resulting in a cytokine storm and progressive multiorgan dysfunction[1]. Secondary HLH is most commonly triggered by infections, particularly Epstein-Barr virus, as well as by malignancies and autoimmune disorders[1]. Pregnancy represents a unique immunological state marked by dynamic alterations in T-cell responses and cytokine balance, which may predispose susceptible individuals to immune dysregulation[2]. As a result, the diagnosis of HLH during pregnancy is particularly challenging because of substantial clinical overlap with sepsis, HELLP syndrome, acute viral hepatitis, and autoimmune flares. Therapeutic decision-making is further complicated by concerns regarding fetal safety and the limited evidence available to guide management.

In a recent systematic review of 104 cases of pregnancy-associated HLH, approximately half of pregnancies resulted in live births, while nearly 46% of antepartum cases were complicated by pregnancy loss. Preterm delivery was frequent, and adverse fetal outcomes were closely associated with disease severity and maternal stabilization, with uncontrolled HLH being linked to poor perinatal outcomes[3].

Here, we report a case of Epstein-Barr virus-associated HLH in pregnancy that was successfully managed with corticosteroids and Janus kinase inhibition.

CASE PRESENTATION

A 29-year-old primigravida at 25 weeks and 5 days of gestation was admitted (Day 0) with a five-day history of high-grade fever associated with chills, vomiting, jaundice, and generalized weakness. There was no history of bleeding, abdominal pain, or diarrhea. No history of rash, arthritis, photosensitivity, urogenital ulcers, or Raynaud's phenomenon.

She had symptoms suggestive of arthritis in 2018 and had received intermittent Ayurvedic medications (no past medical records available) and had been off all medications for 5 years. She was not receiving disease-modifying antirheumatic drugs. Initial evaluation at a local hospital revealed deranged liver enzymes and cervical lymphadenopathy, prompting referral to our tertiary care center.

Clinical Examination

On admission, the patient was febrile with a temperature of 101°F, tachycardic with a heart rate of 110 beats per minute, and tachypneic with a respiratory rate of 22 breaths per minute. Blood pressure was 110/70 mmHg, and oxygen saturation was 96% on room air.

Physical examination revealed icterus and pallor, along with a non-tender 2 × 2 cm right cervical lymph node. There was no pedal edema at presentation. Abdominal examination showed a soft, distended abdomen with a gravid uterus corresponding to gestational age. Neurological examination was normal. Obstetric evaluation confirmed a viable singleton pregnancy with appropriate growth.

Investigations

Initial laboratory investigations after admission revealed severe anemia with a hemoglobin level of 7.7 g/dL, thrombocytopenia with a platelet count of 92 × 10^3/μL, and leukocytosis with a total leukocyte count of 11.1 × 10^3/μL. Marked systemic inflammation was evident, with a serum ferritin level of 47,477 ng/mL and a C-reactive protein concentration of 174.5 mg/L. Liver function tests demonstrated significant hepatic involvement, with total bilirubin of 4.61 mg/dL, aspartate aminotransferase (AST) of 271 IU/L, and alanine aminotransferase (ALT) of 72.6 IU/L. Peripheral blood smear did not reveal schistocytes, and urine routine microscopy was unremarkable. During the subsequent hospital course, progressive worsening of hepatic dysfunction was observed, with peak total bilirubin reaching 5.93 mg/dL, AST 314 IU/L, and ALT 82 IU/L. Abdominal ultrasound revealed splenomegaly of 12.2 cm along the anteroposterior axis.

An extensive microbiological and serological evaluation for tropical and endemic infections was negative, including scrub typhus IgM, leptospira IgM, malaria by quantitative buffy coat, and Weil-Felix testing. Serological investigations for viral hepatitis, including hepatitis A and E IgM antibodies, hepatitis B surface antigen, and anti-hepatitis C virus antibodies, were non-reactive. Quantitative cytomegalovirus viral load testing was negative. Autoimmune workup, including antinuclear antibodies, anti-smooth muscle antibodies, anti-liver-kidney microsomal type 1 antibodies, and antibodies to liver soluble antigen, was also negative.

Virological testing demonstrated a markedly elevated Epstein-Barr virus viral load of 2.4 × 10^5 IU/mL by real time polymerase chain reaction (PCR) in whole blood with limit of detection of 681 IU/ml. EBV serology was not performed which made it difficult to differentiate between primary EBV infection versus reactivation. As the quantitative EBV DNA was already markedly elevated and management did not depend on serological phenotyping, this was not done, as EBV serology was not available at our center. Bone marrow aspiration revealed activated macrophages with evidence of hemophagocytosis, supporting the diagnosis of hemophagocytic lymphohistiocytosis. Ferritin was 47,477 ng/ml, triglycerides were 298 mg/dl, and fibrinogen was 168.2 mg/dl. These, with the presence of fever, cytopenia, and splenomegaly ful-

filled 6/8 HLH 2004 criteria. Soluble IL-2 receptor levels and NK cell activity were not available at our center and hence not assessed. Hscore was 258, which corresponded to more than 99% probability for hemophagocytic syndrome.

In view of cervical lymphadenopathy, she underwent ultrasound-guided-fine-needle aspiration of the cervical lymph node which showed reactive changes and was negative for malignant cells. GeneXpert on the same was negative. No evidence of lymphoproliferative disease was identified in the investigations performed.

Diagnosis

The clinical presentation of fever, cytopenias, and hepatic dysfunction in pregnancy warrants careful evaluation for several important differential diagnoses, including HELLP (Hemolysis, elevated liver enzymes, and low platelets) syndrome, acute fatty liver of pregnancy (AFLP), thrombotic microangiopathy (TMA), autoimmune hepatitis (AIH), and acute viral hepatitis.

HELLP syndrome was considered given the presence of thrombocytopenia and elevated liver enzymes. However, the absence of hypertension and proteinuria, lack of hemolysis on peripheral smear, markedly elevated ferritin levels, and the presence of persistent high-grade fever were not consistent with HELLP syndrome. Furthermore, progressive hyperferritinemia and hemophagocytosis on bone marrow examination favored HLH over HELLP syndrome.

Acute fatty liver of pregnancy was also considered because of jaundice and hepatic dysfunction. However, the patient did not demonstrate hypoglycemia, encephalopathy, severe coagulopathy, or hyperammonemia, which are characteristic features of acute fatty liver of pregnancy. Additionally, the degree of systemic inflammation and extreme ferritin elevation observed in this case are not typical of acute fatty liver of pregnancy.

Thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, was evaluated in view of anemia, thrombocytopenia, and elevated lactate dehydrogenase (> 1,000 U/L). However, the absence of schistocytes on peripheral smear, preserved renal function argued against a diagnosis of thrombotic microangiopathy.

Autoimmune hepatitis was considered because of transaminitis and hyperbilirubinemia. However, autoimmune serological markers, including antinuclear antibodies, anti-smooth muscle antibodies, anti-liver-kidney microsomal antibodies, and antibodies to liver soluble antigen, were negative. Moreover, the presence of systemic hyperinflammation, cytopenias, and hemophagocytosis was not compatible with isolated autoimmune hepatitis.

Acute viral hepatitis was excluded based on negative serological testing for hepatitis A, B, C, and E viruses, as well as a negative cytomegalovirus viral load. Although Epstein-Barr virus infection can cause hepatitis, isolated EBV hepatitis is typically associated with mild to moderate transaminase elevation and does not usually present with profound cytopenias, extreme hyperferritinemia, or hemophagocytosis. In this patient, the markedly elevated EBV viral load, together with fulfillment of HLH diagnostic criteria and bone marrow findings, supported a diagnosis of EBV-driven hyperinflammatory syndrome rather than uncomplicated EBV hepatitis.

Ayurvedic drug-induced liver injury was considered less likely as she had been off ayurvedic medications for 5 years prior to the current admission.

Taken together, the constellation of persistent fever, bicytopenia, extreme hyperferritinemia, hypertriglyceridemia, hepatic dysfunction, elevated EBV viral load, and hemophagocytosis on bone marrow examination was most consistent with Epstein-Barr virus-associated secondary hemophagocytic lymphohistiocytosis.

Management

The patient was managed by a multidisciplinary team comprising specialists in infectious diseases, rheumatology, and obstetrics. She received Inj Methylprednisolone 40 mg BD from Day 2 of hospital stay for 5 days. Following the commencement of corticosteroid therapy, the patient became afebrile within 48 hours, and inflammatory markers began to decline. She also received 1 unit blood transfusion on Day 2 of hospital stay. She was subsequently put on Tab Prednisolone 40 mg/ day from Day 7, tapered gradually off by Day 124.

Given the high risk of disease relapse and the potential complications associated with prolonged high-dose corticosteroid therapy, a steroid-sparing strategy was planned early in the treatment course. Calcineurin inhibitors and Janus kinase inhibitors were considered as adjunctive immunosuppressive agents. Although data regarding the safety of tofacitinib during pregnancy remain limited, its use in this patient was considered justified after careful evaluation of available alternatives. Calcineurin inhibitors, particularly cyclosporine, have been used in secondary HLH and in selected autoimmune conditions during pregnancy. However, several patient-specific and setting-specific factors limited their suitability in our case.

Cyclosporine exerts its immunosuppressive effects primarily through inhibition of T-cell activation and interleukin-2 production, which may further impair EBV-specific cytotoxic immune responses and potentially promote viral persistence[4]. In contrast, Janus kinase inhibition targets downstream cytokine signaling pathways, including interferon-γ and interleukin-mediated pathways central to HLH pathogenesis, without directly suppressing cytotoxic lymphocyte function to the same extent[5].

Furthermore, cyclosporine is associated with significant pharmacokinetic variability during pregnancy, necessitating frequent therapeutic drug monitoring to ensure efficacy and avoid toxicity[6]. In our setting, drug level estimation requires a turnaround time of approximately one week, which limits timely dose optimization and increases the risk of both disease flare and drug-related adverse effects. In addition, cyclosporine carries well-recognized risks of nephrotoxicity, hypertension, and electrolyte disturbances, which are of particular concern during pregnancy[6].

In contrast, tofacitinib does not require serum level monitoring, allows rapid dose adjustment based on clinical response, and provides predictable pharmacokinetics. This was particularly advantageous in our resource-limited setting, where access to timely drug monitoring is constrained. Moreover, emerging evidence supports the efficacy of JAK inhibition in refractory and secondary HLH by suppressing hypercytokinemia while permitting gradual steroid tapering[5,7].

Although robust pregnancy safety data for tofacitinib are lacking, available human reports have not demonstrated a consistent signal of major teratogenicity[8-10]. In this patient, the anticipated risks of prolonged high-dose corticosteroids and calcineurin inhibitor therapy were considered greater than the potential theoretical risks associated with short- to intermediate-term JAK inhibition. After multidisciplinary discussion and informed consent, tofacitinib was therefore selected as the most pragmatic steroid-sparing agent. Oral tofacitinib 5 mg twice daily was commenced on Day 8 (26 weeks + 6 days of gestation), reduced to 5 mg once daily on Day 40 (31 weeks + 3 days) and discontinued on Day 52 (33 weeks + 1 day). Total in utero exposure was therefore confined to the second and early third trimester, with no first-trimester exposure.

Clinical Course and Follow-Up

The patient showed progressive clinical improvement with resolution of fever, recovery of blood counts, normalization of liver enzymes, and marked decline in ferritin and CRP levels. EBV viral load became undetectable during follow-up. She was discharged on Day 11 of hospital stay with tapering doses of prednisolone and continued JAK inhibitor therapy. Serial laboratory trends and treatment milestones are summarized in Table 1. The clinical timeline has been summarized in Figure 1.

Oral tofacitinib 5 mg twice daily was commenced on Day 8 of admission. On Day 40, Tofacitinib dose was reduced from 5 mg twice daily to once daily. It was discontinued on Day 52. Corticosteroids were gradually tapered and stopped by Day 124. At approximately Day 105, corresponding to 40 weeks and 5 days of gestation, she underwent emergency lower segment cesarean section for fetal malposition. Perioperatively, she received stress-dose hydrocortisone at 200 mg/day, followed by gradual tapering. The postoperative period was uneventful. A healthy neonate with birth weight of 2.630 kg, with APGAR score of 9 at 1 minute and 9 at 5 minute was delivered. He did not require NICU care and there was no evidence of congenital abnormalities on screening.

Outcome

At final follow-up, the patient remained in sustained remission with normal inflammatory markers, stable liver function, improving hematological parameters, and no evidence of disease relapse. The infant showed normal growth and development and has completed 1 year of age at last follow-up with no history of infectious complications or congenital abnormalities. He continues to be under close follow-up for adverse outcomes that may arise in the future.

DISCUSSION

Epstein-Barr virus is the most frequent infectious trigger of secondary hemophagocytic lymphohistiocytosis and is associated with particularly aggressive disease due to uncontrolled proliferation of infected B cells and impaired cytotoxic T-cell surveillance[3]. In the present case, markedly elevated EBV viral load, extreme hyperferritinemia, and early hepatic involvement reflected a severe hyperinflammatory state with a high risk of rapid clinical deterioration.

The diagnosis of HLH in pregnancy remains challenging because of substantial clinical overlap with obstetric and infectious conditions. In our patient, the initial presentation with fever, jaundice, cytopenias, and transaminitis necessitated careful evaluation for HELLP syndrome, AFLP, TMA, AIH, and acute viral hepatitis. However, the absence of hypertension, hemolysis, hypoglycemia, and coagulopathy, together with progressive hyperferritinemia and hemophagocytosis on bone marrow examination, enabled early diagnostic clarification. Prompt recognition was critical in preventing progression to multiorgan failure, which has been consistently associated with poor maternal and fetal outcomes in pregnancy-associated HLH.

Our patient presented at 26 weeks of gestation, a period during which fetal viability is limited, and therapeutic options are constrained by concerns regarding teratogenicity. At this stage, termination of pregnancy as a therapeutic intervention was neither desirable nor ethically justifiable in the absence of refractory disease. Therefore, the primary management objective was to achieve rapid and sustained control of hyperinflammation while preserving fetal well-being.

Corticosteroids remain the cornerstone of initial HLH therapy and were effective in inducing early clinical remission in this patient, as evidenced by rapid defervescence, declining inflammatory mar-

Table 1. Serial hematological, inflammatory and virological parameters in relation to immunosuppressive therapy.

Day	Hb (g/dL)	TLC (×10³/µL)	Platelets (×10³/µL)	Ferritin (ng/mL)	CRP (mg/L)	Bilirubin (mg/dL)	EBV viral load (IU/mL)	Cortico-steroid	JAK inhibitor
D0	7.7	11.1	92	—	215.2	4.61	—	—	—
D1	7.8	8.9	87	47,477	174.5	5.19	2.4×10^5	—	—
D2	7.4	10.1	68	41,933	165.5	5.93	—	IV methylprednisolone 40 mg BD	—
D3	7.3	15.3	95	26,236	97.0	5.46	—	IV methylprednisolone 40 mg BD	—
D5	7.7	11.6	113	8,192	20.9	1.80	—	IV methylprednisolone 40 mg BD till Day 6.	—
D7	9.1	9.2	146	3,246	3.8	—	—	Oral prednisolone 40 mg OD	—
D8	9.4	7.8	172	—	2.3	—	Negative	Oral prednisolone 40 mg OD	Tab Tofacitinib 5 mg twice daily
D9	10.0	6.7	211	—	2.0	1.26	—	Oral prednisolone 30 mg OD till D11.	Continued twice daily
D11	—	—	—	882	1.0	1.12	Negative	Oral prednisolone 20 mg OD and taper by 5 mg per week.	Continued twice daily
D40	—	—	—	—	—	—	Negative	Oral prednisolone 5 mg OD	Tab Tofacitinib reduced to 5 mg once daily
D52	11.8	10.4	247	—	2.67	—	Negative	Oral prednisolone 5 mg alternate day continued	Stopped
D105	—	16.1	166	68.9	—	0.20	—	Stress-dose cover during pregnancy with Inj Hydrocrotisone 50mg IV q6h for 3 days and then changed over to oral prednisolone 5 mg alternate days	—
D124	13.6	7.0	294	—	—	—	—	Stopped	—

CRP, C-reactive protein; EBV, Epstein-Barr virus; Hb, hemoglobin; IU, international units; IV, intravenous; JAK, Janus kinase; TLC, total leucocyte count.
Em dash (—) indicates that the test was not performed or the agent was not administered on that day.
Ferritin fell from 47,477 ng/mL on D1 to 882 ng/mL by D11 and normalized (68.9 ng/mL) by D105; EBV DNA became undetectable by D8 and remained so throughout follow-up.

kers, and stabilization of hepatic function. However, EBV-associated HLH is characterized by a high risk of relapse and steroid dependence, particularly when viral replication persists[11]. Moreover, prolonged exposure to high-dose corticosteroids during pregnancy is associated with maternal complications, including gestational diabetes, hypertension, infections, osteoporosis, and adrenal suppression, as well as fetal risks such as growth restriction and preterm birth. In this context, reliance on corticosteroid monotherapy was considered suboptimal for long-term disease control.

The selection of an appropriate steroid-sparing agent in pregnancy is particularly challenging. Although calcineurin inhibitors such as cyclosporine have demonstrated efficacy in secondary HLH, their use in this patient was limited by several factors. Cyclosporine-mediated suppression of T-cell activation may further impair EBV-specific immune surveillance, potentially promoting viral persistence[4]. In addition, significant pharmacokinetic variability during pregnancy necessitates frequent therapeutic drug monitoring, which was not feasible in our setting[6]. The associated risks of nephrotoxicity, hypertension, and electrolyte disturbances were also of concern in a pregnant patient with evolving systemic illness[6].

In contrast, Janus kinase inhibition offers a targeted approach to suppressing cytokine-driven inflammation central to HLH pathogenesis. By inhibiting interferon-γ and interleukin-mediated signaling pathways, tofacitinib may attenuate hypercytokinemia, although its relative impact on cytotoxic lymphocyte function remains incompletely defined[12]. Furthermore, its predictable pharmacokinetics, lack of requirement for serum level monitoring, and ease of dose adjustment make JAK inhibition a pragmatic option in resource-limited settings. Remission occurred following corticosteroid therapy and was maintained during subsequent tofacitinib exposure and corticosteroid tapering, without disease reactivation. No maternal infectious complications were recorded

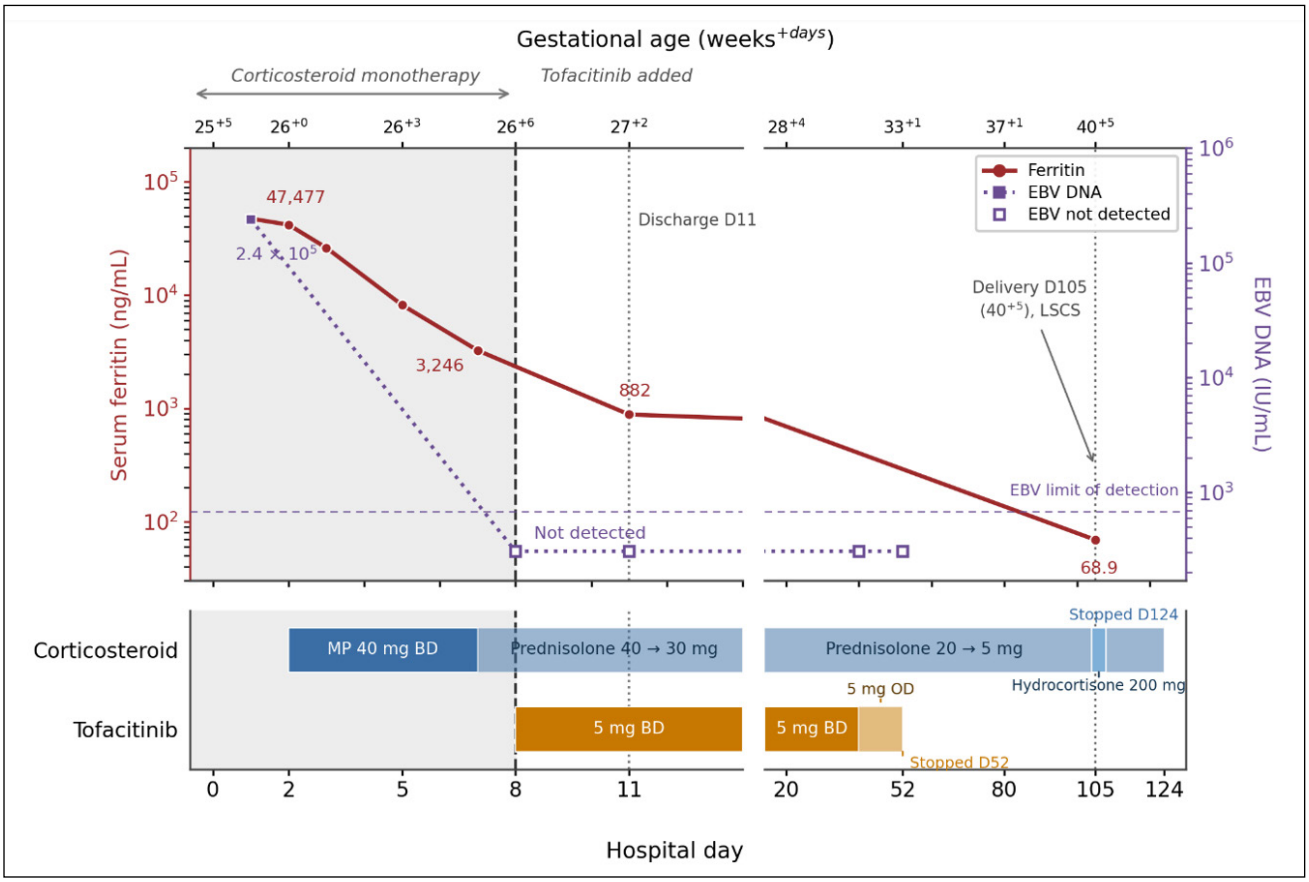

Figure 1. Clinical timeline graph. EBV, Epstein-Barr virus; MP, Methylprednisolone.

during follow-up. Whether tofacitinib contributed to the maintenance of remission cannot be determined from a single uncontrolled observation, and the possibility that corticosteroid therapy alone would have been sufficient cannot be excluded.

Several other strategies are used in severe or refractory EBV-associated HLH[13]. Etoposide-based protocols (HLH-94 and HLH-2004) remain the standard for progressive or refractory disease, and early etoposide has been associated with improved survival in EBV-driven HLH specifically[14]. Rituximab has been used as B-cell-directed therapy on the rationale that EBV resides within B lymphocytes and has been reported to reduce viral load in refractory cases[15]. None of these was required in our patient. She defervesced within 48 hours of intravenous methylprednisolone, ferritin fell from 47,477 ng/mL to 3,246 ng/mL by Day 7, C-reactive protein normalized, the platelet count recovered above 150 × 10^3/μL, bilirubin fell from a peak of 5.93 mg/dL, and EBV DNA was undetectable by Day 8. In the absence of refractory or progressive disease, escalation to cytotoxic chemotherapy or to biological agents with minimal pregnancy safety data could not have been justified, particularly at 26 weeks of gestation.

The favorable pregnancy outcome in this case reflects the importance of early disease control and coordinated multidisciplinary care. Previous systematic reviews have demonstrated that fetal survival in pregnancy-associated HLH is closely linked to maternal stabilization[3]. In our patient, rapid suppression of hyperinflammation prevented progression to shock, respiratory failure, or disseminated intravascular coagulation, thereby avoiding the need for preterm delivery or therapeutic termination. This allowed continuation of pregnancy to term and resulted in the delivery of a healthy neonate, though a single case report cannot establish fetal safety of Tofacitinib.

This case also highlights the importance of individualized decision-making in complex clinical scenarios. Although corticosteroid monotherapy induced initial remission, early introduction of a steroid-sparing agent was pursued to minimize cumulative steroid toxicity and reduce relapse risk. In retrospect, continuation of corticosteroids alone might have been feasible; however, this would have entailed prolonged high-dose exposure with uncertain long-term maternal and fetal consequences. The proactive adoption of JAK inhibition in this context represents a risk-balanced strategy tailored to disease biology, gestational age, and local healthcare constraints.

Finally, this report contributes to the limited literature on the use of JAK inhibitors in pregnancy-associated HLH. While long-term safety data remain scarce, our experience suggests that, in carefully selected patients and under close multidisciplinary

supervision, JAK inhibition may be considered as a steroid-sparing option, although a single case cannot demonstrate efficacy. Prospective studies and registry-based surveillance are needed to better define optimal treatment algorithms and long-term outcomes in this vulnerable population.

Limitations

This report describes a single case, limiting generalizability. Long-term maternal and neonatal outcomes following in utero exposure to JAK inhibitors require further evaluation.

CONCLUSIONS

Epstein-Barr virus-associated HLH in pregnancy is a rare but potentially fatal condition requiring prompt recognition and multidisciplinary management. Early initiation of immunomodulatory therapy is crucial to prevent irreversible organ dysfunction and adverse maternal-fetal outcomes. While corticosteroids remain the cornerstone of initial treatment and were effective in inducing early remission in our patient, prolonged high-dose therapy is associated with substantial maternal and fetal risks.

In this context, the early introduction of a steroid-sparing agent was aimed at minimizing cumulative steroid exposure and reducing the risk of relapse. Remission occurred following corticosteroid therapy and was maintained during subsequent tofacitinib exposure and corticosteroid tapering, without disease reactivation. Tofacitinib was tolerated without recorded adverse effects in our resource-limited setting, where therapeutic drug monitoring is challenging. This case suggests that JAK inhibitors may represent a pragmatic steroid-sparing option in selected patients with pregnancy-associated HLH, although larger studies are needed to establish their long-term safety and efficacy.

Ethics Approval:
As per the policy of the Kasturba Medical College Institutional Ethics Committee, formal ethics committee approval is not required for the publication of individual case reports.

Informed Consent:
Written informed consent was obtained from the patient prior to publication of this case report.

Conflict of Interest:
None.

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Authors' Contributions:
P.K.T. and N.G. drafted the original manuscript. A.S. was responsible for data collection and obtaining patient consent. M.V. and N.G. provided supervision. All authors were involved in patient management, reviewed and edited the manuscript, and approved the final version for publication.

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Data Availability:
The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

AI Disclosure:
ChatGPT was used for language editing and manuscript refinement. Claude AI was used to generate Figure 1.

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