FROM FEVER TO RESOLUTION: SUCCESSFUL MANAGEMENT OF SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS WITH DEXAMETHASONE MONOTHERAPY IN A RESOURCELIMITED SETTING – A CASE REPORT

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare, lifethreatening hyperinflammatory syndrome characterized by uncontrolled immune activation, leading to cytokine storm, multiorgan dysfunction, and high mortality if untreated. Secondary HLH in adults is often triggered by infections, malignancies, or autoimmune conditions, presenting with nonspecific symptoms such as persistent fever, cytopenias, and organomegaly, which pose significant diagnostic challenges in resource limited settings. This case report describes a 35yearold male from Panchkhal, Nepal, who presented with prolonged high grade fever initially misdiagnosed as enteric fever and later complicated by hospital acquired pneumonia. Despite broad spectrum antibiotics, symptoms persisted, prompting transfer to Dhulikhel Hospital. Clinical examination revealed splenomegaly, bicytopenia, and respiratory distress requiring intensive care and mechanical ventilation. Laboratory findings included marked hyperferritinemia, hypertriglyceridemia, and evidence of hemophagocytosis on bone marrow aspiration, fulfilling ⩾5 HLH2004 diagnostic criteria, supporting a diagnosis of secondary HLH likely infection triggered.

Standard treatment per HLH2004 protocol involves dexamethasone and etoposide, with cyclosporine in select cases. However, due to financial constraints and limited availability of etoposide in this resource limited setting, dexamethasone monotherapy was initiated (10 mg/m^2/day initially, tapered over weeks). The patient showed rapid clinical improvement: fever resolved within days, cytopenias corrected, and organ function normalized. He was extubated, weaned off support, and discharged after full recovery without relapse on followup.

This case highlights the diagnostic hurdles of HLH in low resource environments, where advanced tests (e.g., soluble CD25, NK cell activity, genetic profiling) are unavailable. It also demonstrates that dexamethasone monotherapy can achieve complete remission in select adult secondary HLH cases, particularly infection associated forms, avoiding the toxicity and cost of etoposide. In regions like Nepal, where HLH remains underreported and mortality high due to delayed diagnosis, this approach may offer a feasible alternative, warranting further prospective studies to validate efficacy and identify predictors of response.

Keywords: Hemophagocytic lymphohistiocytosis, Secondary HLH, Dexamethasone monotherapy, Resource limited setting

ОТ ЛИХОРАДКИ ДО ВЫЗДОРОВЛЕНИЯ: УСПЕШНОЕ ЛЕЧЕНИЕ ВТОРИЧНОГО ГЕМОФАГОЦИТАРНОГО ЛИМФОГИСТИОЦИТОЗА МОНОТЕРАПИЕЙ ДЕКСАМЕТАЗОНОМ В УСЛОВИЯХ ОГРАНИЧЕННЫХ РЕСУРСОВ – КЛИНИЧЕСКИЙ СЛУЧАЙ

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Аннотация
Гемофагоцитарный лимфогистиоцитоз (ГЛГ) — это редкий, угрожающий жизни гипервоспалительный синдром, характеризующийся неконтролируемой активацией иммунной системы, приводящей к цитокиновому шторму, полиорганной дисфункции и высокой смертности при отсутствии лечения. Вторичный ГЛГ у взрослых часто провоцируется инфекциями, злокачественными новообразованиями или аутоиммунными заболеваниями, проявляясь неспецифическими симптомами, такими как стойкая лихорадка, цитопения и органомегалия, что создает значительные диагностические трудности в условиях ограниченных ресурсов. В данном случае описывается 35-летний мужчина из Панчхала, Непал, у которого наблюдалась длительная высокая температура, первоначально ошибочно диагностированная как брюшной тиф, а позже осложненная внутрибольничной пневмонией. Несмотря на применение антибиотиков широкого спектра действия, симптомы сохранялись, что привело к переводу в больницу Дхуликхель. Клиническое обследование выявило спленомегалию, бицитопению и дыхательную недостаточность, потребовавшую интенсивной терапии и искусственной вентиляции легких. Результаты лабораторных исследований включали выраженную гиперферритинемию, гипертриглицеридемию и признаки гемофагоцитоза при аспирации костного мозга, что соответствовало ⩾5 диагностическим критериям HLH2004 и подтверждало диагноз вторичного гемофагоцитарного лимфогистиоцитоза, вероятно, спровоцированного инфекцией.

Стандартное лечение по протоколу HLH2004 включает дексаметазон и этопозид, а в отдельных случаях — циклоспорин. Однако из-за финансовых ограничений и ограниченной доступности этопозида в условиях ограниченных ресурсов была начата монотерапия дексаметазоном (10 мг/м^2/день первоначально, с постепенным снижением дозы в течение нескольких недель). У пациента наблюдалось быстрое клиническое улучшение: лихорадка прошла в течение нескольких дней, цитопения скорректирована, функция органов нормализовалась. Он был экстубирован, отключен от аппарата искусственной вентиляции легких и выписан после полного выздоровления без рецидива при последующем наблюдении.

Стандартное лечение по протоколу HLH2004 включает дексаметазон и этопозид, а также циклоспорин в отдельных случаях. Данный случай подчеркивает диагностические трудности гемофагоцитарного лимфогистиоцитоза (ГЛГ) в условиях ограниченных ресурсов, где недоступны современные методы диагностики (например, определение

растворимого CD25, активности NK-клеток, генетическое профилирование). Он также демонстрирует, что монотерапия дексаметазоном может привести к полной ремиссии у отдельных пациентов с вторичным ГЛГ, особенно при инфекционных формах, избегая токсичности и высокой стоимости этопозида. В таких регионах, как Непал, где ГЛГ остается недостаточно изученным заболеванием, а смертность высока из-за задержки диагностики, этот подход может предложить приемлемую альтернативу, требующую дальнейших проспективных исследований для подтверждения эффективности и выявления предикторов ответа.

Ключевые слова: Гемофагоцитарный лимфогистиоцитоз, Вторичный ГЛГ, Монотерапия дексаметазоном, Условия ограниченных ресурсов

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome driven by excessive activation of macrophages and Tlymphocytes, resulting in a cytokine storm, tissue damage, and multiorgan failure [1,2]. Classified as primary (genetic, predominantly pediatric) or secondary (acquired, triggered by infections, malignancies, or autoimmune diseases), adultonset HLH is increasingly recognized but remains underdiagnosed due to its nonspecific presentation mimicking sepsis or malignancy [3,4].

The incidence of HLH is low globally, estimated at 1–10 cases per million in adults, with higher rates in Asia due to endemic infections like EpsteinBarr virus (EBV), dengue, and scrub typhus [5]. In Nepal, HLH is exceptionally rare and challenging to manage in resource limited settings. Limited published data indicate only sporadic cases, often infection associated, with diagnostic delays contributing to mortality exceeding 50% in untreated or late diagnosed adults [6,7].

Diagnosis relies on the HLH2004 criteria, requiring ⩾5 of 8 features: fever, splenomegaly, cytopenias (⩾2 lineages), hypertriglyceridemia/hypofibrinogenemia, hemophagocytosis, hyperferritinemia, low NKcell activity, and elevated soluble CD25 [8]. Recent validations and minor refinements (HLH2024) maintain high accuracy in adults, emphasizing clinical and accessible laboratory markers [9,10].

Standard treatment, based on HLH94 and HLH2004 protocols, combines dexamethasone, etoposide, and cyclosporine, achieving survival rates >50% in pediatric cohorts but lower (20–40%) in adults due to underlying triggers and comorbidities [11]. Etoposide targets hyperactivated lymphocytes, but its myelotoxicity, cost, and availability limit use in low and middleincome countries (LMICs) [12]. Emerging evidence suggests that in infection triggered secondary HLH, treating the underlying cause with corticosteroids alone may suffice, avoiding chemotherapy related risks [13,14].

This case is reported to illustrate the diagnostic and therapeutic challenges of adult secondary HLH in Nepal, where advanced diagnostics and etoposide are often inaccessible. It provides insight into the potential efficacy of dexamethasone monotherapy, offering a pragmatic approach for LMICs and contributing to the sparse literature on nonetoposide regimens in adults.

Case Presentation

A 35yearold previously healthy male from Panchkhal, Nepal, presented in midMarch 2025 (Nepali date 2082/03/13) to a local hospital with 6 days of continuous highgrade fever (Tmax 103°F) associated with chills, rigors, and multiple episodes of vomiting. He was diagnosed with enteric fever based on positive typhoid IgM and treated with intravenous antibiotics for 7 days. Fever persisted, leading to referral.

On March 19, 2025 (2082/03/19), he was admitted to a private ICU in Kathmandu. Initial therapy included piperacillintazobactam and doxycycline. He developed hospitalacquired pneumonia with dry cough, excessive sweating, and chest pain. Antibiotics were escalated to meropenem and levofloxacin. Fever briefly subsided for 4 days but recurred (Tmax 104°F) with persistent leukocytosis. Respiratory panel PCR was negative. Bone marrow biopsy was planned but the patient was discharged against medical advice.

From March 30 to April 1, 2025 (2082/03/30–04/01), at home, fever continued with progressive lethargy, decreased responsiveness, and abdominal fullness.

On April 1, 2025 (2082/04/01), he presented to Dhulikhel Hospital emergency with dyspnea, restlessness, excessive sweating, and altered sensorium. Vital signs: febrile (39.5°C), tachypneic (respiratory rate 38/min), hypotensive (90/60 mmHg), tachycardic (128/min), SpO2 82% on room air. Examination: ill looking, pale, mild bilateral pedal edema, bilateral diffuse crepitations, distended nontender abdomen with splenomegaly (>2 cm below costal margin), GCS 13/15 (E4V3M6), bilateral plantar downgoing.

He was admitted to the Adult Intensive Care Unit (AICU) and intubated the next morning for respiratory failure.

• *Table 1. Key Laboratory Findings*

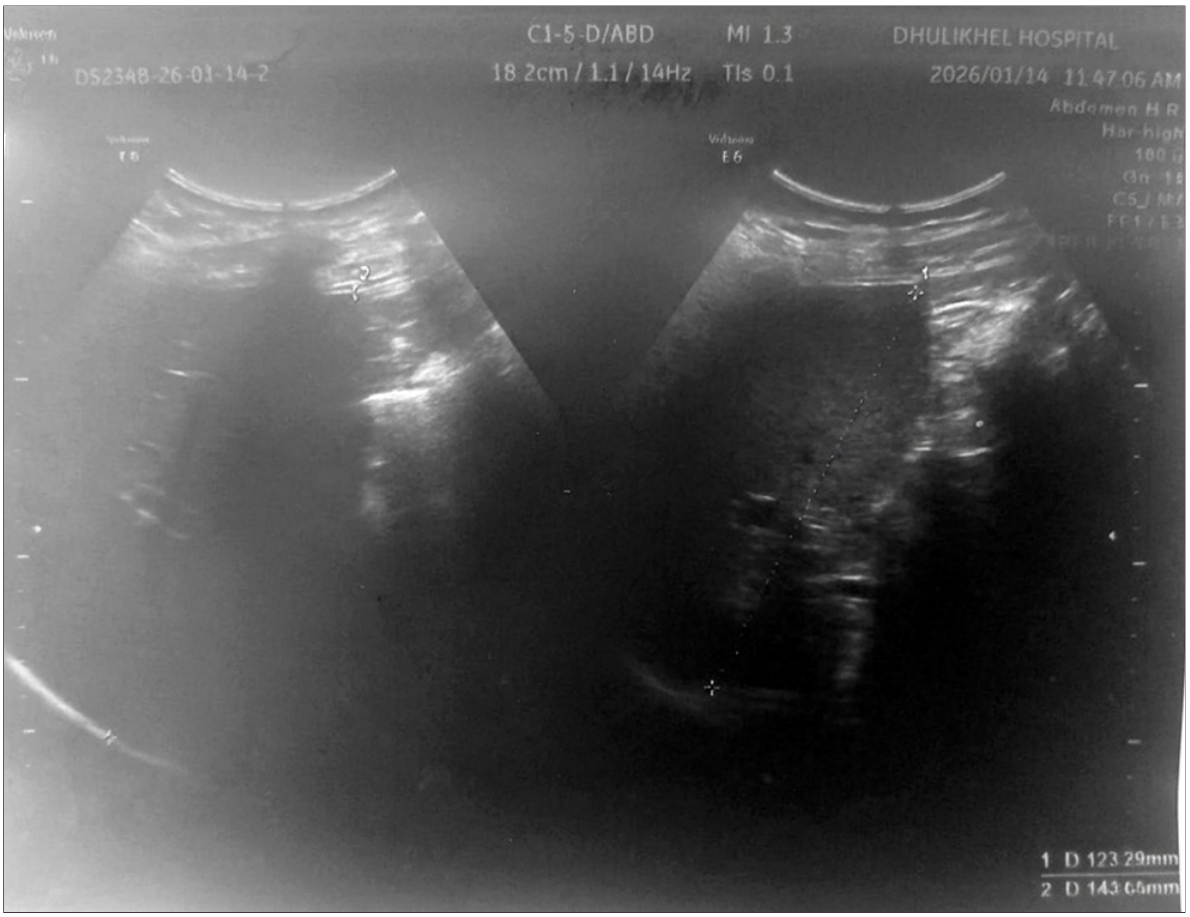
Parameter	Admission Value	Reference Range	Day +7 (PostDexamethasone)
Hemoglobin (g/dL)	8.2	13–17	11.5
Platelets (×10^9/L)	68	150–450	212
WBC (×10^9/L)	18.4 (neutrophilia)	4–11	9.2
Ferritin (µg/L)	>10,000	30–400	1,850
Triglycerides (mmol/L)	3.8	<1.7	2.1
Fibrinogen (g/L)	1.2	2–4	3.1
ALT/AST (U/L)	185/220	<40	62/78
Bilirubin (mg/dL)	2.8	<1.2	1.1

Infectious workup (blood/urine/CSF cultures, viral PCRs including EBV/CMV, malaria, dengue, scrub typhus serology) was negative except prior typhoid IgM (likely falsepositive). Bone marrow aspiration showed hypercellular marrow with prominent hemophagocytosis: activated macrophages engulfing erythrocytes, leukocytes, and platelets (Figure 1).

The patient met 6/8 HLH2004 criteria: persistent fever ⩾38.5°C, splenomegaly, bicytopenias (anemia, thrombocytopenia), hypertriglyceridemia, hyperferritinemia, hemophagocytosis.

Supportive care included broad spectrum antibiotics (meropenem, vancomycin), transfusions, and ventilation. On hospital day 3 (April 4, 2025), dexamethasone was initiated (10 mg/m² IV daily). Fever defervescence occurred within 48 hours, sensorium improved, and extubation was possible on day 5. Cytopenias resolved progressively (table 2).

• *Figure 1. Bone marrow aspiration*



• *Table 2: Trend of hemoglobin, platelets, and ferritin showing rapid normalization postdexamethasone*

Parameter	Admission Value	Day 7 Post-Dexamethasone	Reference Range
Hemoglobin (g/dL)	8	11	13-17
Platelets (10^9/L)	68	212	150-450
WBC (10^9/L)	18	9	4-11
Ferritin (x10 µg/L)	100	18	30-400
Triglycerides (mmol/L)	4	2	<1.7
Fibrinogen (g/L)	1	3	2-4
ALT (U/L)	185	62	<40
AST (U/L)	220	78	<40
Bilirubin (mg/dL)	3	1	<1.2

Dexamethasone was tapered over 8 weeks. No etoposide was used due to cost and availability. The patient was discharged after 3 weeks in stable condition. Followup at 3 months showed complete resolution without relapse.

Discussion

Hemophagocytic lymphohistiocytosis was first described in 1939 as histiocytic medullary reticulosis, with familial forms recognized in the 1950s and infection associated variants in the 1970s [15]. In adults, secondary HLH predominates, with infections (EBV, CMV, bacterial) accounting for ~50% of triggers, followed by malignancies (28%) and autoimmune diseases (12%) [3,16].

In Nepal, HLH remains exceedingly rare, with limited reports highlighting infection triggered cases (e.g., scrub typhus, histoplasmosis, sarcoidosis associated) [6,17,18]. National data are scarce, but sporadic publications (5–10 cases in PubMed since 2010) underscore diagnostic delays due to overlapping sepsis presentations and limited access to specialized tests [7].

Our patient fulfilled HLH2004 criteria without advanced markers (soluble CD25, NK activity), aligning with validated approaches in resource limited settings where clinical/laboratory features suffice [9,10]. Negative extensive infectious workup suggests possible resolved bacterial trigger (prior pneumonia/enteric suspicion) or occult viral etiology.

Standard therapy emphasizes early immunosuppression. HLH2004 protocol survival benefits derive from etoposide's lymphocyte depletion, reducing 5year mortality from >90% to ~60% in pediatrics, though adult outcomes remain poorer (20–40%) [11,19]. However, etoposide's toxicity and cost restrict use in LMICs [12].

Comparative analysis reveals parallels with infection triggered adult HLH cases managed without etoposide. A 2024 Nepalese case of scrub typhus associated HLH responded to doxycycline plus corticosteroids alone [20]. Similarly, dengue associated HLH series report remission with steroids/IVIG without chemotherapy [21]. In scrub typhus endemic areas, immunomodulation with dexamethasone (without etoposide) achieved survival in >70% when combined with antibiotics [13,22].

Validation in our case: Rapid defervescence, cytopenia correction, and ferritin decline postdexamethasone mirror these reports, suggesting infection triggered secondary HLH may represent a milder spectrum responsive to steroid mediated cytokine suppression without cytotoxic therapy. Early intervention (day 3 of AICU) likely prevented progression, unlike delayed cases with >50% mortality [16,23]. Absence of malignancy/autoimmune trigger and negative advanced screening support transient infectious etiology.

Limitations include lack of genetic testing (ruling out underlying primary HLH) and soluble CD25/NK assays. Longterm followup is needed to exclude relapse. Nonetheless, complete remission without etoposide validates corticosteroid monotherapy as feasible in select adult secondary HLH, particularly LMICs, reducing treatment burden and toxicity.

This case contributes to emerging evidence favoring tailored approaches: triggerdirected therapy plus steroids for infection associated HLH versus full protocol for refractory/ malignancy associated forms [14,24].

Conclusion

Secondary HLH in adults presents formidable challenges in resourcelimited settings like Nepal, where diagnostic delays and treatment barriers contribute to high mortality. This

case demonstrates successful management with dexamethasone monotherapy in likely infectiontriggered HLH, achieving rapid remission without etoposide. It validates emerging evidence that select patients—particularly with infectious triggers and early intervention—may not require cytotoxic chemotherapy, offering a costeffective, less toxic alternative for LMICs. Prospective studies are needed to define predictors of steroid responsiveness and optimize protocols, potentially improving outcomes in underserved regions.

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