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Case Report

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A Rare Presentation of Hemophagocytic Lymphohistiocytosis Secondary to Dengue Infection in a Sickle Cell Carrier with Concurrent Hyperhemolysis Syndrome

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ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a rare but life-threatening hyperinflammatory syndrome that can be triggered by infections, malignancies, and other immune dysregulations. This report discusses the case of a 27-year-old male with sickle cell disease with Beta thalassemia (heterozygous state) who presented with generalized fatigue, weakness, and fever and subsequently developed hemolysis following blood transfusions. A positive IgM dengue test and immunohematology findings, including negative alloantibody screening and negative Direct and Indirect agglutination tests, guided the diagnosis of HLH secondary to dengue infection, with hyperhemolysis syndrome considered a secondary differential. Early recognition of HLH and prompt use of corticosteroids can significantly improve outcomes in complex sickle cell cases with concurrent viral infections.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but aggressive and potentially life-threatening syndrome caused by a hyperinflammatory response leading to organ damage [1,2]. It is characterized by fevers, cytopenias, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia and hemophagocytosis by activated macrophages. HLH can either be primary (inherited) or secondary. Primary HLH generally presents in infancy and is associated with mutations that affect cytotoxic T-cell or inflammasome function [3,4]. Secondary HLH is thought to be more common and to be due to infection, hematologic malignancy, autoimmune disorders or drugs [1]. It has a high mortality rate if not promptly diagnosed and treated. This report highlights a rare case of HLH triggered by dengue infection in a patient with sickle cell trait, complicated by hyperhemolysis syndrome. HLH is a fatal syndrome that requires a timely diagnosis to initiate life-saving therapy [5].

Case Presentation

A 27-year-old male with known Sickle-beta thalassemia (heterozygous) was admitted with complaints of generalized fatigue, weakness, and fever persisting for one week. He had a history of blood transfusion one month ago. The patient reports receiving monthly blood transfusion due to low hemoglobin levels and was

not on hydroxyurea therapy.

Upon admission, blood tests showed a hemolytic picture with symptomatic anemia requiring blood transfusion. Leucoreduced blood transfused in ICU under careful monitoring. Post-transfusion hemoglobin level was transfused levels suddenly dropped below pre-transfusion complication and his sickle cell carrier status.

Initially, hyperhemolysis syndrome was suspected owing to the patient's sickle cell carrier status and severe post-transfusion anemia. However, immunohematology evaluation was unremarkable, with negative alloantibody screening, Direct agglutination tests (DAT), and Indirect agglutination tests (IAT), making classical transfusion reactions less likely. The subsequent detection of dengue IgM positivity provided a viral trigger, heightening the suspicion for secondary HLH.

The laboratory profile supports this diagnosis: profound anemia (Hb 5 g/dl) with reticulocytosis, thrombocytopenia (nadir 64,000/mm³), and fluctuating leukocyte counts fulfil cytopenia criteria. Hyperferritinemia (>4800 ng/ml), hypertriglyceridemia (404 mg/dl), markedly elevated LDH (>4500 U/L), and raised inflammatory markers (CRP, procalcitonin) indicate an exaggerated inflammatory response. Indirect hyperbilirubinemia with transaminitis (AST up to 377 U/L) reflects ongoing hemolysis and hepatic involvement. Clinically, hepatosplenomegaly was evident, and bone marrow biopsy excluded malignancy while remaining compatible with an inflammatory marrow process.

HLH-2004 Criterion (6)	Patient Finding	Status
Fever	Documented during illness	□ Present
Cytopenias (≥2 lineages)	Hemoglobin 5 g/dl, Platelets 64,000/mm³	□ Present
Hyperferritinemia (>500 ng/ml)	4879 ng/ml	□ Present
Hypertriglyceridemia (>265 mg/dl)	404 mg/dl	□ Present
Hepatosplenomegaly	On clinical examination	□ Present
Elevated LDH / hepatitis (supportive)	LDH >4500 U/L, AST 377 U/L, ALT 96 U/L	□ Supportive
Bone marrow	No malignancy, inflammatory marrow	□ Supportive
NK cell activity / soluble IL-2R	Not available	⍰ Not done

The patient was started on high-dose corticosteroids following HLH treatment guidelines. Alongside this, he received blood transfusions under close supervision to manage his severe anemia, with careful attention to fluid balance in view of the underlying dengue infection. His platelet counts, liver function, and inflammatory markers were monitored regularly, and with this combined approach he showed steady improvement, both clinically and hematologically.

DISCUSSION

Hemophagocytic Lymphohistiocytosis (HLH) is a syndrome of extreme immune activation that results in multi-organ dysfunction, often triggered by infections such as Epstein-Barr virus, cytomegalovirus, and dengue. The patient's clinical presentation of fever, splenomegaly, and a positive dengue test aligns with HLH, especially in the context of sickle cell trait, which may have predisposed him to an exaggerated immune response. In sickle cell carriers, HLH is rare but can develop secondary to infections. The role of dengue in triggering HLH has been documented, as its infection can cause cytokine storms and immune dysregulation—key factors in HLH pathophysiology. Hyperhemolysis syndrome, a rare but severe complication following transfusion in sickle cell patients, involves hemolysis of both transfused and native red cells. This syndrome can mimic HLH symptoms, including hemolysis and post-transfusion anemia, but usually presents with reticulocytopenia, which was not specified here. However, the patient's immunohematology results—absence of alloantibodies, negative DAT, and ICT—are consistent with hyperhemolysis, supporting its consideration as a secondary differential diagnosis.

CONCLUSION

This case highlights the diagnostic challenges in treating a sickle cell carrier presenting symptoms that overlapped between hemophagocytic lymphohistiocytosis (HLH) and hyperhemolysis syndrome. Although HLH, triggered by a dengue infection, was identified as the primary diagnosis, hyperhemolysis syndrome remained a significant possibility, especially given its connection to sickle cell conditions and complications from blood transfusions. The case emphasizes the importance of a collaborative, multidisciplinary approach in managing patients with hemoglobin disorders and viral infections, ensuring that treatment is both accurate and effective.

CLINICAL IMPLICATIONS:

This case serves as a reminder for clinicians to consider both HLH and hyperhemolysis syndrome in patients with hemoglobinopathies who develop hemolysis post-transfusion, especially in endemic regions for infections like dengue. Early recognition and differentiation of these syndromes are crucial for managing and preventing severe outcomes.

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Conflicts of interest

There are no conflicts of interest.

Figure 1: Post Transfusion Sample Showing Hemolysis

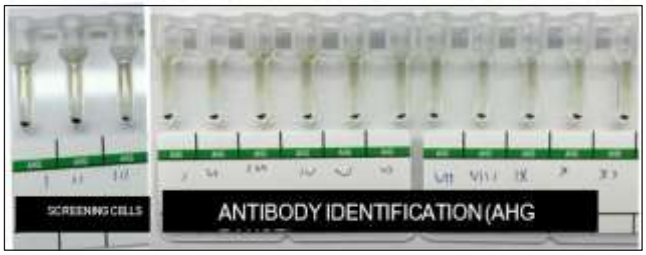

Figure 2: Antibody Screening and Identification DCT

PARAMATER/DATE	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10
HB A %	32.8	24.4		47.6			49.1			
HB A2 %	3.7	3.9		3.6			3.8			
HB F %	23	32.8		30.9			17.6			
HB S %	40	37.9		31.4			32.9			
ESR (mm/hr)	42	75		91				59		
RETICULOCYTE COUNT	4%									
CREATININE (mg/dl)	1.13		0.86				0.65	0.67		
SODIUM (mmol/L)	137		139				140	139		
POTASSIUM (mmol/L)	4.31		3.71				3.81	3.84		
CHLORIDE (mmol/L)	103.1		105.6				105.8	104		
BICARBONATE (mmol/L)	19.4		21.7				19.8	23		
MAGNESIUM (mg/dl)	2.04									
CALCIUM (mg/dl)	8.5									
PHOSPHORUS (mg/dl)	3.8									
FERRITIN (ng/ml)	[illegible]			4879						
LDH (U/L)	4532			3038						
TB (mg/dl)	10.5		7.07			6.8		3.5		
DB (mg/dl)	7.76		5.7			5.23		2.76		
IB (mg/dl)	2.72		1.3			1.4		0.82		
TP (g/dl)	5.8		5			6		5.8		
ALBUMIN (g/dl)	3.3		2.90			3.2		3.2		
AST (U/L)	377		194			60		54		
ALT (U/L)	60		52			39		36		
ALP (U/L)	359		227			204		190		
IRON (ugm/dl)	97.3									
UIBC (µg/dl)	145									
URIC ACID (mg/dl)	5.6									
UREA (mg/dl)	50		27				16	15		
HCV	NON REACTIVE									
HBV	NON REACTIVE									
CRP (mg/dl)	137									
PRO-CALCITONIN (ng/ml)	1.68									
SICKLE CELL TEST		POSITIVE								
PBS		Haemolytic anaemia Sickle cell Thalassemia trait								
HB (gm/dl)	7	5.8	5	6		7.11	7	7.3	8.23	9.6
PCV %	21.8	17.9	16.3	19.1		22.4	22.4	24.5	25.4	31.8
WBC	3900	12840	14300	8820		5730	8550	5360	5320	6210
PLATELET	135000	101000	83000	64000		95000	127000	167000	168000	214000
ANA		NEGATIVE								
HEPATITIS A			NEGATIVE							
HEPATITIS B IG M			NEGATIVE							
AMYLASE (U/L)			94							
GGT (U/L)			79							
LIPASE (U/L)			97.1							
TRIGLYCERIDES (mg/dl)			404							
Anti HCV IgG Report			NON REACTIVE							
FIBRINOGEN (mg/dl)			446.7							
PROTHROMBIN (Sec)				9.4						
APTT (Sec)				27.7						
DENGUE IGM ELISA					POSITIVE					

Figure 3: Investigation chart

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