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Dengue Fever with Hemolysis: Unmasking Beta-Thalassemia

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Abstract

Intravascular hemolysis is a rare but known complication of Dengue infection. Following is the description of a patient who presented with features of intravascular hemolysis with other sequelae of Dengue infection. Clinical stigmata of chronic iron overload led to a search for the aetiology of chronic hemolysis, which resulted in a diagnosis of non-transfusion-dependent beta-thalassemia.

Keywords: Secondary Iron Overload; Intravascular Hemolysis; Medicine in Resource Limited Areas; Complications of Dengue Fever; B-Thalassemia

Abbreviations: EDS: Expanded Dengue Syndrome, DHF: Dengue Hemorrhagic Fever, DF: Dengue Fever, DSS: Dengue Shock Syndrome, AIH: Acute Intravascular Hemolysis, G6PD: Glucose-6-Phosphate Dehydrogenase

Introduction

Expanded Dengue Syndrome (EDS) is a novel term coined by the World Health Organization (WHO) to include manifestations of Dengue infection that do not fit into the categories of Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS) **[1]**. Hemolysis is a rare complication in EDS with an unclear pathogenesis. Both immune and non-immune hemolytic anemia have been reported in the literature to be associated with EDS **[2-4]**.

This young gentleman had never contracted adequate medical care due to socio-economic limitations. At presentation, the clinical resemblance was with EDS with intravascular hemolysis. However, upon historical and ancillary investigations, beta-chain hemoglobinopathy was detected.

Case Presentation

A 23-year-old gentleman, presented with fever for 6 days with yellowish discolouration of sclera and cola coloured urine for 2 days. He had associated symptoms of upper abdominal pain, nausea, and generalised weakness. Urine output was normal. The patient had been admitted 3 years back with similar complaints and was treated for dengue infection. Medical records of the previous hospital stay were not available with him. He had not been diagnosed with any medical condition in the past. Family history was not significant. On examination, the patient was febrile, pale, and

icteric. Vitals at presentation were as follows: BP-114/74 mmHg, PR-132/min, RR-26/min, SpO2-98%. Brown deposits were present around the corneal limbus along with brownish discoloration of skin (especially forehead and ankles). Grade 3 digital clubbing was noted **Figure 1**). He had a palpable spleen 3 cm below he left costal margin and an early systolic murmur in the tricuspid area. No abnormality was detected on neurological examination.

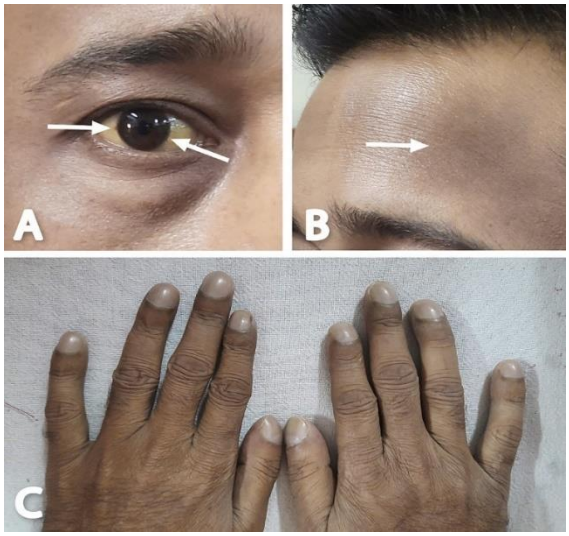

Figure 1: Patient images depicting A: Icterus and limbic iron deposits (arrows), B: Brownish discoloration of forehead skin, C: Grade 3 digital clubbing.

Routine investigation results are summarised in **Table 1**.

Investigation	Result	Reference Range
Hb	6.2 gm/dL	13.0-16.0 gm/dL
Platelets	34 x 10^9/L	150-410 x 10^9/L
MCV	62 fL	83-101 fL
RDW	13 %	11.6-14.0 %
TLC	4.12 x 10^9/L	4.0-10.0 x 10^9/L
DLC	84/14/1/1	40-80/20-40/2-10/1-6
Biirubin (Total)	5.0 mg/dL	0.2-1.0 mg/dL
Biirubin (Conj.)	1.1 mg/dL	<0.25 mg/dL
AST	241 IU/L	5-40 mg/dL
ALT	659 IU/L	5-35 mg/dL
Albumin	2.5 gm/dL	3.8-5.5 mg/dL
Dengue NS1 Antigen	Positive	Negative
FBS	101 mg/dL	60-110 mg/dL
PPBS	172 mg/dL	90-140 mg/dL

Table 1: Laboratory investigation results at presentation

Peripheral blood film: Microcytes, tear drop cells, target cells and giant platelets were seen. Schistocytes and Malarial parasite were absent **(Figure 2A)**. Rapid diagnostic test for Malaria was also negative. Coagulation profile was normal. 2D transthoracic echocardiogram was suggestive of mild mitral regurgitation with normal cardiac chambers. USG Abdomen: Liver size 16.5 cm, Spleen size: 14 cm, Portal vein normal, no ascites **(Figure 2B, 2C)**.

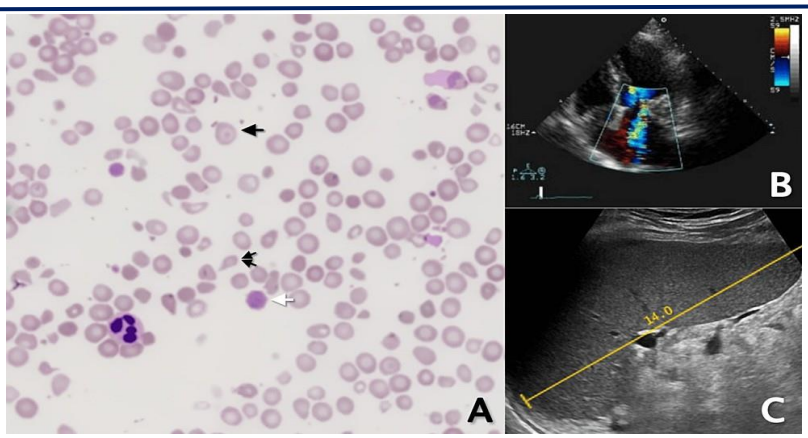

Figure 2: A: Peripheral blood film showing target cells (black arrow), giant platelets (white arrow), teardrop cell (double arrows), B: 2D echo showing MR jet, C: USG abdomen showing splenomegaly.

Hemolytic workup revealed non-immune Acute Intravascular Hemolysis (AIH) with elevated urine and plasma hemoglobin concentrations, and negative Coombs' test. Glucose-6-phosphate dehydrogenase (G6PD) levels and Hemoglobin electrophoresis were performed due to evidence of chronic hemolysis and iron overload (cutaneous and corneal deposits, Impaired blood sugar levels, abnormal cardiovascular examination). The results were the following **(Table 2)**.

Investigation	Result	Reference Range
Urine RBCs	Nil	0-2/HPF
Urine Hb	164 mg/dL	0-10 mg/dL
Plasma Hb	48 mg/dL	10-20 mg/dL
G6PD levels	14 IU/gm	8.6-18.6 IU/gm
Direct/Indirect Coombs' Test	Negative	Negative
HbA	62.4%	>95%
HbA_2	32.4%	<4%
HbF	5.2%	<2%

Table 2: Results of hemolytic workup

Profile correlated with non-transfusion dependent beta-thalassemia (formerly beta-thalassemia intermedia). The patient was managed with IV crystalloids, antipyretics, and transfusion of 2 units of packed Red Cells (pRBC). Urine color cleared spontaneously on Day 2 of admission and all lab parameters normalised by Day 5. The patient was subsequently discharged with an Hb level of 8.6 gm/dL and was then lost to follow-up.

Discussion

Infection by any of the four dengue serotypes may be asymptomatic or lead to classic dengue fever (DF) or more severe forms of the disease, DHF and DSS. Other manifestations of Dengue infection are classified as EDS. The patient was managed as per the WHO guidelines for treatment of Dengue infection **[1]**.

The patient had an otherwise uneventful dengue infection. Notable abnormalities were thrombocytopenia and hepatitis. Pre-existing hemoglobinopathy (which is primarily responsible for extravascular hemolysis) could have acted as a substrate for precipitation of intravascular hemolysis or AIH could have been solely attributable to dengue infection.

Existing case reports on hemolysis in dengue describe non-immune AIH more commonly than Coombs' positive AIH. The syndrome is self-limiting, and patients have been successfully managed with crystalloids and forced diuresis. Ruling out other common causes of AIH is paramount before labelling it as a manifestation of EDS **[2-4]**.

Other causes for hemolysis with hemoglobinuria such as autoimmune hemolytic anaemia, falciparum malaria, microangiopathic hemolytic anaemia, incompatible blood transfusions, G6PD deficiency, and ingestion of aniline dyes or other poisons were excluded by a combination of history, examination, and laboratory investigations.

Literature on Dengue in Thalassemia patients is also sparse. The common verdict is that anaemia rather than haemoconcentration is to be expected. Markedly increased AST levels compared to ALT, and severe dengue, especially severe liver involvement, is common **[5,6]**.

The patient was a daily-wage labourer, an immigrant and originally hailed from a tribal area. It has been observed amongst some non-tribal and tribal communities, that the prevalence of beta-thalassemia carriers is much higher (5.3-17.0%) than the projected national average of 3-4% **[7]**.

He had a history of poor exercise tolerance compared to his peers but never considered seeking medical care for the same. This healthcare contact provided a unique opportunity to detect a chronic illness which when adequately managed can significantly improve the patient's quality of life. His previous alleged admission 3 years ago for a similar history might have uncovered the existence of thalassemia but medical records from that time were not available with the patient. Similar events may unfold again in the future unless the records are preserved.

Conclusion

This case report highlights some important medical lessons: emphasis on history and examination in resource-limited settings, pattern recognition, limited healthcare reach to underprivileged classes, and benefits of individualising management rather than managing as a part of a cohort, especially during high burden epidemics as most of the cases of dengue infection are concentrated around a few months of the year. Fall in hemoglobin in dengue infection should alert the physician towards the possibilities of mucosal bleed and hemolysis. Similarly, thalassemia patients with dengue present with anaemia rather than hemoconcentration. Thus, in diagnosed cases of thalassemia, these atypical manifestations should point towards suspicion for dengue. Hemolysis in dengue may require even more liberal crystalloid infusions to prevent nephropathy along with monitoring for fluid overload as 3rd space losses due to capillary leak is a common phenomenon.

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