especially in high disease burden countries.

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An Unusual Case of Auto-Immune Hemolytic Anemia

Autoimmune hemolytic anemia in association with insect bites is a rare presentation, but delay in diagnosis can cause significant morbidity and mortality. Here, we report a case of Coombs positive hemolytic anemia after a wasp bite.

A 12-year-old male without significant past medical history was transferred to our hospital by his primary care physician with persistent fatigue, bilateral lower extremity pain, and history of undocumented fever. His laboratory work-up was remarkable for hemolytic anemia with hemoglobin of 4.5 g/dL, reticulocyte count of 6.4%, elevated indirect bilirubin of 9.2 mg/dL, and lactate dehydrogenase (LDH) of 1702 U/L. His serum creatinine kinase was also elevated at 1927 U/L.

Upon arrival to our hospital, he was febrile (102.9ºF) and had tachycardia. On physical exam, he was icteric and noted to have 1×2 cm and 1×3 cm eschars with surrounding induration on left side of his abdomen. Direct anti-globulin test (DAT) was positive with anti-IgG reagent (3+). He was admitted to the pediatric intensive care unit (PICU) with a cinical diagnosis of auto-immune hemolytic anemia (AIHA) due to insect bite. Mother gave a history of seeing wasps in the house on the day of bite and per the toxicologists, the rash was consistent with a *hymenoptera* bite.

Upon admission, he was given blood transfusion and started on methylprednisolone. He was also started on empiric vancomycin and cephalosporin, which were discontinued 48 hours later after negative blood cultures. During his course in the ICU, he continued to require blood transfusion with ongoing drop in hemoglobin. After three days of steroids, hemolysis stopped and his hemoglobin stabilized at 8.9 g/dL. Creatinine kinase, LDH, and reticulocyte count also decreased. He was discharged home after two days on a steroid taper with recommendations for outpatient follow up. Infection was ruled out on the basis of negative cultures. No other known exposure to a new medicine was elicited. The rash being localized, specific history to a topical agent was asked but was negative. Moreover, DAT positive for IgG reagent in the presence of history of exposure to wasp in the house was suggestive of warm auto-immune hemolytic anemia (AIHA).

AIHA is defined as the destruction of circulating red blood cells (RBCs) in the setting of anti-RBC autoantibodies that optimally react at 37°C [1]. About 50% of the warm AIHA cases are called primary because no specific etiology can be found, whereas the rest are recognized as secondary to lympho-proliferative syndromes, malignant diseases, rheumatologic diseases, especially systemic lupus erythematosus, infections (mostly viral), drugs, or a previous transfusion or trans-plantation. Laboratory work-up of the patient was not suggestive of any of these secondary causes.

This presentation caused by insect bite is a rare clinical entity. The exact mechanism of this type of hemolytic anemia is unclear. However, it has been proposed that the toxin from the insect bite alters the red blood cell membrane structure making it more vulnerable to complement-mediated lysis [1]. Medical management primarily consists of supportive treatment. General consensus for first line pharmacologic treatment is glucocorticoids. It is believed that steroids not only decrease antibody production, but also suppress the effect of tissue macrophage phagocytosis and direct effect on auto-antibody red blood cell affinity [2,3].

Such presentations of AIHA due to insect bites can pose a diagnostic challenge and can potentially be fatal. This case demonstrates the importance of a high level of suspicion to allow for timely recognition and intervention [2,4].

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Hereditary Non-Spherocytic Hemolytic Anemia (HNSHA): Four Children with Rare Hereditary Red Cell Enzymopathies

Hereditary red blood cell (RBC) enzymopathies, a group of non-immune, non-spherocytic hemolytic anemias, occur due to a defect in the genes encoding red cell enzymes. Glucose-6-phosphate-dehydrogenase (G6PD) deficiency and pyruvate kinase (PK) deficiency are the commonly reported red cell enzymopathies. Herein, we describe four children with rare red cell enzymopathies [1].

An 11-month-old girl child, the product of consanguineous marriage, presented with pallor, splenomegaly, and cardiac failure. Investigations were suggestive of hemolytic anemia (**Table I)**. Direct Coombs test (DCT), hemoglobin electrophoresis, osmotic fragility test (OFT), isopropanol stability tests for unstable hemoglobins, HbH preparation, and G6PD assay were non-contributory. She had a history of neonatal hyperbilirubinemia needing exchange transfusion followed by a history of blood transfusion at 3 and 6 months of age. Next-generation sequencing (NGS) detected a homozygous missense variation in exon 12 of the *glucose-6-phosphate-isomerase (GPI)* gene.

An 11-year-old boy born to a consanguineous marriage presented with severe pallor, and splenomegaly. Laboratory workups were suggestive of Coombs negative hemolytic anemia (**Table I**). He had a history of neonatal hyperbilirubinemia warranting an exchange transfusion, followed by global developmental delay with sensory neural hearing loss (neurological sequelae of bilirubin encephalopathy). He also had a history of blood transfusion in infancy. A homozygous missense variant in exon 6 of the GPI gene was detected by NGS, which has also been previously reported to cause neurologic impairment and HNSHA [2].

A 9-year-old boy, product of consanguineous marriage, presented with severe pallor and splenomegaly. He had a history of exchange transfusion for hyperbilirubinemia in the neonatal period and also needed repeated blood transfusions for anemia. Laboratory workup (**Table I**) did not reveal a cause for hemolysis. NGS detected a homozygous nonsense variation in exon 4 of the *AK1* (adenylate kinase*)* gene, previously reported to cause hemolytic anemia [3].

A 9-month-old girl, product of consanguineous marriage, presented with severe pallor and splenomegaly. She had neonatal hyperbilirubinemia and required exchange transfusion. Her elder sibling had a history of neonatal exchange transfusion; he died at 1.5 years of age due to severe anemia with jaundice. Investigations were suggestive of Coombs negative hemolysis (**Table I**). A homozygous missense variant in exon 4 of the PKLR (pyruvate kinase L/R) gene was detected by NGS, which can lead to HNSHA.

Table I Clinical Profile and Laboratory Work-up of the Children With Red Cell Enzymopathies

Characteristics	*Case 1*	*Case 2*	*Case 3*	*Case 4*
Age at presentation	11 mo	11 y	9 y	9 mo
Clinical features[a]	-	Developmental delay	-	-
Transfusion history	Once in 3 mo	During acute febrile illness	During acute febrile illness	Once in 3 mo
Consanguinity	3rd degree	3rd degree	3rd degree	2nd degree
Hb (g/dL), MCV (fL), Reticulocyte count (%), Indirect bilirubin (mg/dL)	2.1, 120, 39%, 3	5.2, 112, 11%, 4.5	6, 92, 7%, 3.9	5, 89, 12%, 3.5
Peripheral smear	Macrocytes, bite cells, polychromasia	Macrocytes, polychromasia	Polychromasia, elliptocytes	Polychromasia
Heinz body preparation	Positive	Negative	Negative	Negative

[a]Pallor, icterus and splenomegaly was present in all children. Other investigations (DCT: direct Coombs test, OFT: osmotic fragility test, HPLC: high performance liquid chromatography, HBH preparation (for alpha thalassemia), Isopropanol stability test (for unstable hemoglobinopathies), G6PD:Glucose 6 phosphate Dehydrogenase) were normal for all children. HB: hemoglobin, MCV: mean corpuscular volume. Bone marrow examination showed erythroid hyperplasia in all children.