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A Rare Presentation of Acute Hemolytic Anemia in a Newborn Infant – Case Report

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1. Abstract

Hereditary Elliptocytosis (HE) is a heterogeneous group of inherited Red Blood Cell (RBC) disorders characterized by the presence of elongated, oval, or elliptically shaped RBCs on the peripheral blood smear. Hemolytic anemia in these disorders ranges from absent to life-threatening .Transient hemolytic anemia has been reported in neonates with some of the more severe HE syndromes.

We will present a newborn with acute hemolysis anemia that experienced recurrent hemolysis with strong positive family history of Anemia and one mortality because of hydrops fetalis due to severe hemolysis.

2. Hereditary Elliptocytosis

Hereditary elliptocytosis (HE; also called hereditary ovalocytosis) is a heterogeneous group of inherited red blood cell (RBC) disorders in which genetic alterations that affect spectrin, protein 4.1, band 3, or (rarely) glycophorin C cause circulating RBCs to become elliptical (Figure 1); this shape-change occurs in the peripheral circulation fter repeated cycles of deformation and failure of elastic recoil [1] (Figure 2). In some cases, HE can also cause other RBC morphologies (ovalocytosis (Figure 3), Pyropoikilocytosis, and chronic hemolytic anemia) and/or hemolysis, which can range from mild to life-threatening [2].

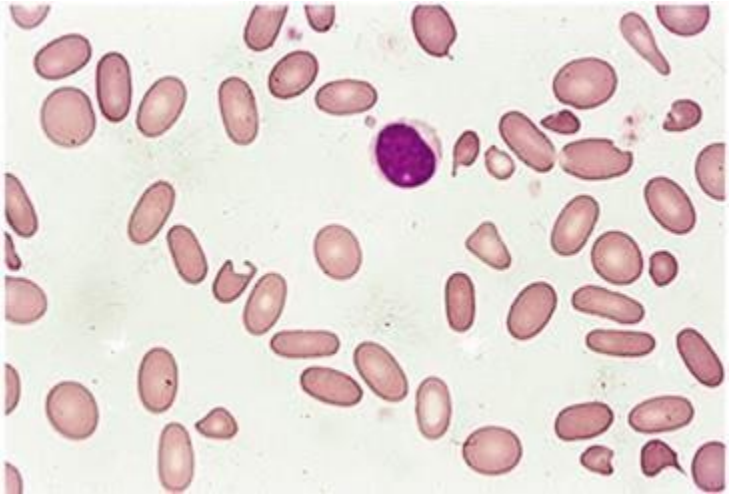

Figure 1: Blood smear shows Elliptical cells

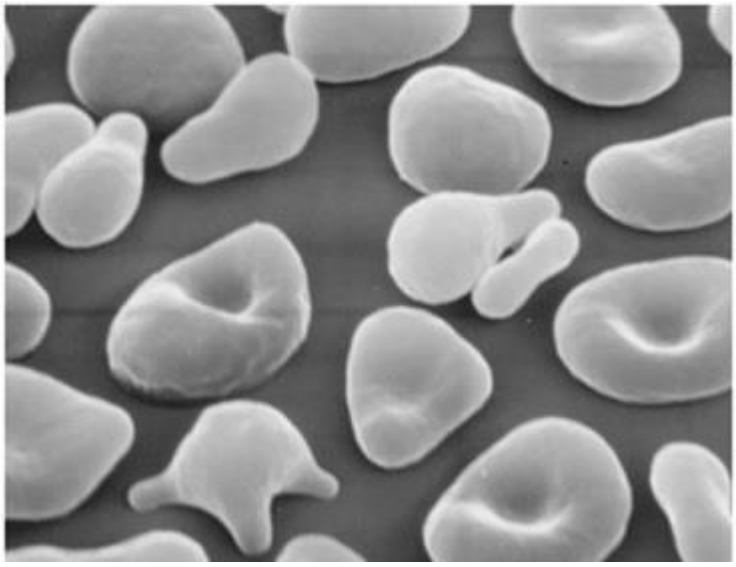

Figure 2: Difference between normal RBC and Elliptical RBC on Electronic Microscope

The prevalence of HE is estimated at approximately 1 in 2000 to 1 in 4000 (0.05 to 0.025 percent) worldwide; it is most common in individuals of African, Mediterranean, or Southeast Asian descent, paralleling the distribution of malaria [3].

The clinical presentation of HE is highly variable, which is partly, but not completely, genotype-dependent. Subtypes of HE include common HE, Hereditary Pyropoikilocytosis (HPP), Southeast Asian Ovalocytosis (SAO), and spherocytic elliptocytosis [3]. The major clinical differences in these syndromes are in the RBC morphology and severity of hemolysis.

HE may be suspected in an individual with unexplained hemolytic anemia or a family member of an affected individual, or it may be an incidental finding. All individuals with suspected HE should have a Complete Blood Count (CBC) with differential and RBC indices, as well as review of the peripheral blood smear by an individual familiar with RBC morphology. Testing for hemolysis is appropriate if >15 percent elliptocytes or other characteristic HE morphologies are present or if the patient has anemia.

We consider the diagnosis of an HE syndrome (HE, SAO, or HPP) to be confirmed in an individual who has ovalocytes or elliptocytes on the peripheral blood smear without another explanation [3, 4]. Specialized testing (eg, testing for iron deficiency and/or thalassemia, analysis of RBC proteins, ektacytometry, genetic testing) is not required for diagnosis but may be helpful in challenging cases or those with implications for family testing, preconception counseling, or prenatal testing.

The differential diagnosis of HE includes other inherited RBC disorders such as thalassemia, hereditary stomatocytosis, and hereditary spherocytosis , as well as acquired conditions that produce similar-appearing RBC morphologies (eg, iron deficiency, myelofibrosis, myelodysplasia) .

Most cases of HE are asymptomatic and require no specific therapy or follow-up care. It is especially helpful to explain the diagnosis to the patient and document it in the medical record. Individuals with hemolysis are given regular folic acid (eg, 1 mg daily). Occasional transfusions are used for some cases with intermittent hemolysis, and chronic transfusions may be used for those with severe chronic hemolysis. Splenectomy is reserved for selected transfusion-dependent individuals. Individuals considering splenectomy should be evaluated by clinicians with expertise in inherited RBC disorders and the procedure should have appropriate prophylaxis and education to address the increased risks of infection and thromboembolic disease [5-7].

Transient hemolytic anemia with more striking morphologic abnormalities (schistocytes, fragments, budding forms, and microcytes) has been reported in neonates with some of the more severe HE syndromes [8, 9]. These changes have been hypothesized to occur as a consequence of the high concentrations of fetal hemoglobin (HbF) in neonatal RBCs. HbF does not bind 2,3-diphosphoglycerate (DPG), and, as a result, large amounts of free 2, 3-DPG are available to interact with and destabilize the RBC cytoskeleton [9, 10]. Excess 2, 3-DPG does not appear to have a discernible effect on RBC shape or survival in infants without HE. However, in RBCs with a weakened cytoskeleton, 2,3-DPG is thought to decrease mechanical stability, producing poikilocytosis and hemolytic anemia. As HbF levels decline over the first few months of life, the contribution of 2,3-DPG to the hemolytic process wanes, hemolysis disappears, and poikilocytes are replaced by the elliptocytes that are characteristic of common HE. Transient hemolysis and/or anemia may also be precipitated by intercurrent illnesses or infections in older children and adults [11].

Here, we present a newborn with acute hemolysis anemia who experienced recurrent hemolysis with strong positive family history of anemia and one mortality because of hydrops fetalis due to severe hemolysis. His course further highlights the delaying of diagnosis and requesting many unnecessary investigations and treatment. This case presentation supports the need to request pe-

ripheral blood smear with every CBC in every new born baby especially if there is hyperbilirubinemia and high retics counts.

Nine days old infant (baby girl) full term, Normal vaginal delivery with uncomplicated prenatal course.The post natal course was complicated by indirect Hyperbilirubinemia treated with Phototherapy from day 2 till day 9. Paediatric Hematology was consulted for Normocytic Normochromic Anemia with Hyperbilirubinemia. Her Physical examination was unremarkable except yellowish color in the sclera and skin.

At this moment her lab's tests Hg 9.9 g/dL MCV 90 MCH 31 MCHC 34 WBC 10K PLT 460K T BIL 267 umol/L D Bil 17 umol/L No ABO or RH incompatibility Retic count 2.8% DCT Negative < repeated more than one time > and G6Pd 20.

She has positive family history of hydrops fetalis (her sister 12 years ago) and there is No positive family history of SCD, thalassemia, or G6Pd but according to her parents they have two sisters diagnosed with IDA and had received many courses of Iron (13 Y and 16 Y) without improvement both of them have Same history during infancy time and their Hg dropped to around 7 g/dl. She has two other sibling with normal Haemoglobin (6 year old boy and 4 year old girl).

Paediatric Haematologist asked to do blood smear for her, sisters and parents. but the patient was discharged and given appointment in the pediatric hematology clinic after 2 days .

First visit to PHO clinic (refereed from Neonatology clinic with CBC – Retics) after 2 days: Hg 8.8 g/dL T Bil 240 umol/L Retics 2.7 % The PLAN: to do Blood smear for her and both sisters and Parents and Hg electrophoresis (family decided to do the blood tests after 2 days)

She came to the ER next day and was admitted for extensive phototherapy blood tests showed a drop in Hg 7.5 g/dL and T Bil 333 umol/L Hg electrophoresis FA , Hg Bart's and Hg H negative , and Osmotic Fragility test was normal .

Blood smear showed severe pyropoikilocytosis with hemolysis (Figure 4 and 5)

• Blood smear for both sisters: elliptocytosis > 50 % Hg 9.8 g/dL MCV 72 MCH 23 Retic 1.9 (Figure 6)

• Blood smear for her father showed elliptocytosis >50 % Hg 11 g/dL MCV 70 MCH 23 Retic 1.3% and for her Mother was Normal.

Also her two other siblings had normal Hg and blood smear.

Hereditary family tree shows type of inheritance (Figure 7).

Whole exon sequencing showes mutation in the SPTA1 gene (Figure 8).

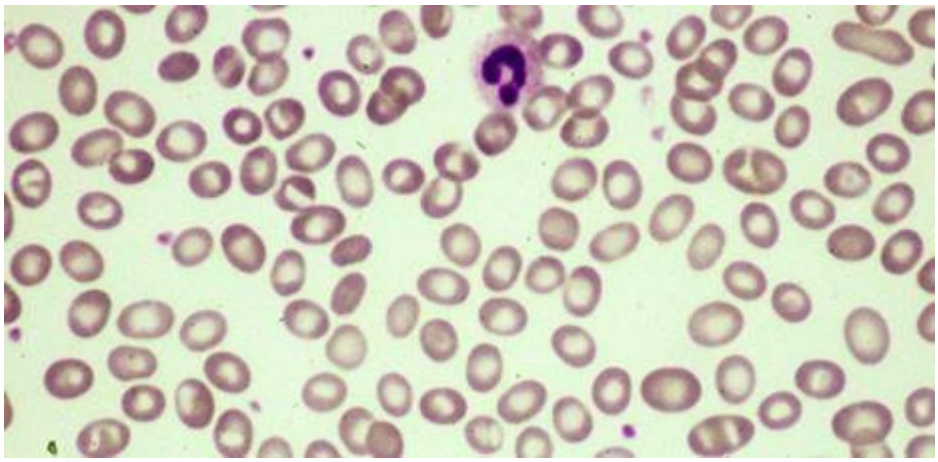

Figure 3: Blood smear shows ovalocytosis

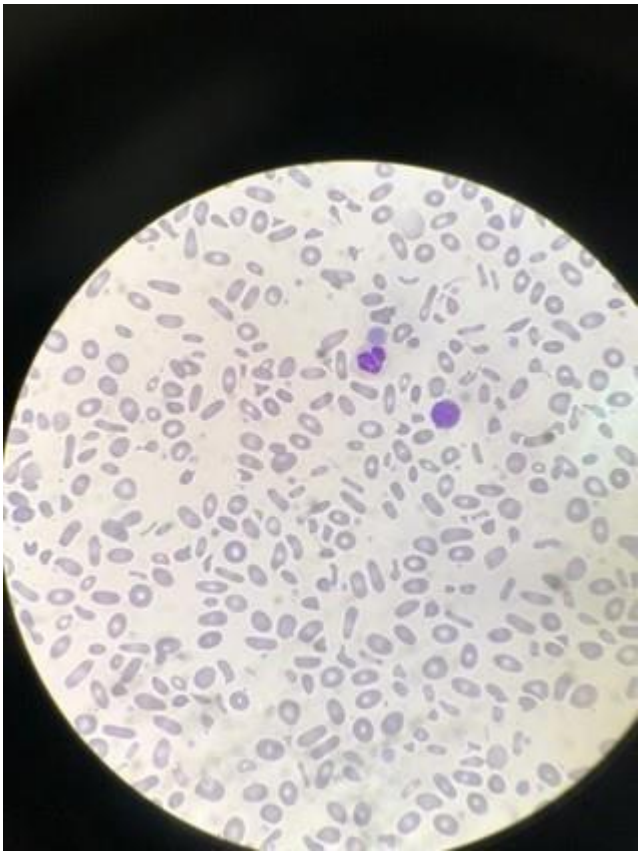

Figure 4: Blood film shows sever pyropoikilocytosis.

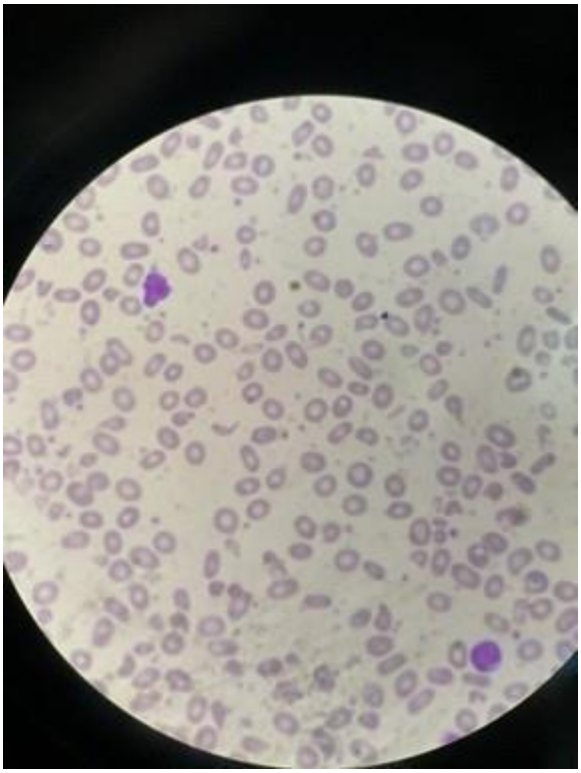

Figure 5: Blood film shows sever pyropoikilocytosis.

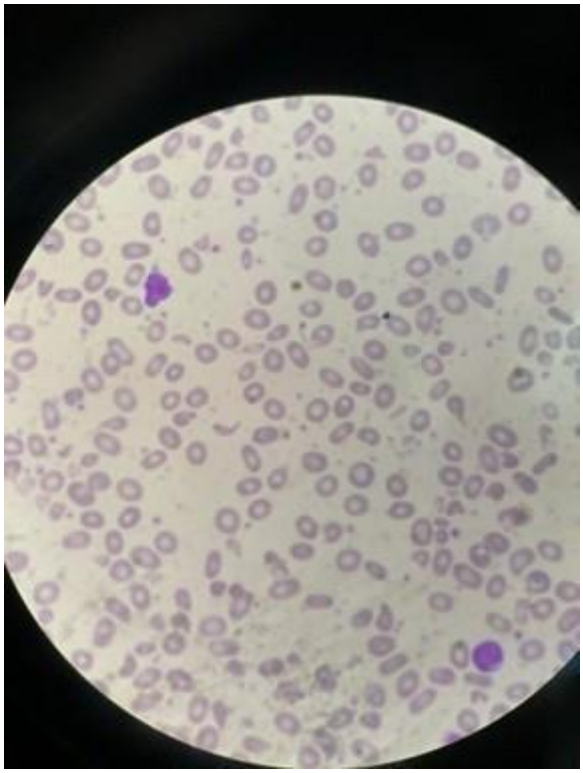

Figure 6: Blood film shows Hereditary Elliptocytosis.

Figure 7: Hereditary family tree shows type of inheritance

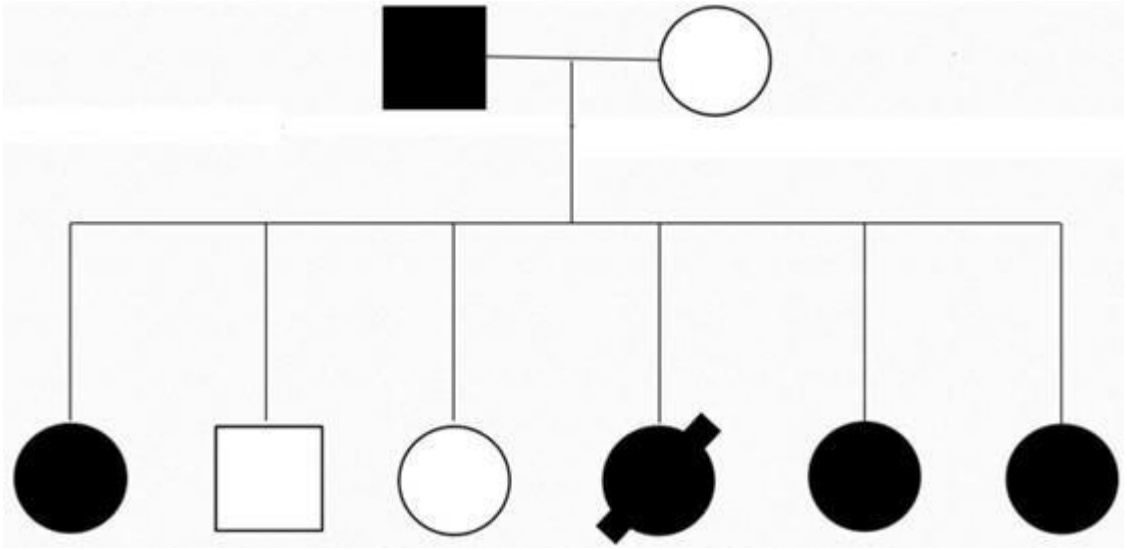

Figure 8: Whole exon sequencing showes mutation in the SPTA1 gene

Gene (Isoform)	Phenotype MIM Number (Mode of Inheritance)	Variant	Zygosity	MAF gnomAD [%]	Classification
SPTA1 (NM_003126.4)	130600 (AD)	c.460_462dup p.(Leu155dup) chr1:158651385	het.	0.0084	Pathogenic

Interpretation: The performed analysis identified the heterozygous variant c.460_462dup p.(Leu155dup) in the *SPTA1* gene (OMIM: *182860). This duplication of three base pairs leads to a duplication of the amino acid Leucine, which is shown to affect protein self-dimerization (PMID: 3922449). The variant has already been described in the literature in patients with elliptocytosis (PMID: 2567189, 30393954, 31589614, 33074480, 8857939) and it is classified as pathogenic/likely pathogenic in ClinVar database. The variant is found in 0.0084 % of the overall population (10x heterozygous, 0x homozygous; gnomAD v2.1.1 controls). **Considering the available information, the variant is classified as pathogenic.**

Pathogenic variants in the *SPTA1* gene are causative for autosomal dominant elliptocytosis 2 (EL2; OMIM: #130600). This disorder is characterized by manifestations ranging from mild to severe transfusion-dependent hemolytic anemia, as well as jaundice, splenomegaly and gallstones. Hydrops fetalis may be seen in rare cases. Less than 10% of the patients manifest with the severe variant of hereditary pyropoikilocytosis. However, many of patients remain asymptomatic (ORPHA: 288).

In summary, considering the supportive phenotype of the patient as well as the provided family history, it is very likely that the heterozygous pathogenic variant in the *SPTA1* gene is in a causal relationship to the clinical phenotype of Elin Khaled Al Abood. We recommend segregation analysis of the identified variant in the parents to evaluate a possible *de novo* occurrence, and in the affected siblings of the index. Targeted molecular genetic testing and, if indicated, prenatal analysis can be offered to family members of the patient.

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