QUIZ

A Nine Month Old Boy with Hemolytic Anemia

Shweta Patel[1], Jessica A. Hemminger[2], Samir B. Kahwash[3]

[1]Department of Pathology and Laboratory Medicine, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA
[2]Department of Pathology and Laboratory Medicine, Wexner Medical Center at the Ohio State University, Columbus, Ohio, USA
[3]Department of Pathology, Nationwide Children's Hospital, 700 Children's Drive, Columbus OH 43205, Ohio, USA.

Corresponding author: Dr. Samir B. Kahwashl Email: Samir.Kahwash@NationwideChildrens.org
Published: 15 July 2013
Ibnosina J Med BS 2013,5(4):223-226
Received: 01 May 2013
Accepted: 05 May 2013
This article is available from: http://www.ijmbs.org

Clinical History

The patient is a 9 month-old male with steroid-refractory chronic hemolytic anemia. Complete blood count (CBC) was significant for normochromic normocytic anemia (Hemoglobin=8.9 g/dL, RBC=3.42 million/mL, MCV= 76.3 fL). Peripheral blood and bone marrow aspirate smears revealed significant morphologic abnormalities, as demonstrated in Figures 1 and 2, respectively. Cytogenetic analysis demonstrated a normal male karyotype (46, XY), and fluorescence in situ hybridization (FISH) did not detect the presence of a myelodysplasia-related genetic abnormality (monosomy 5, 5q-, monosomy 7, or 7q-).

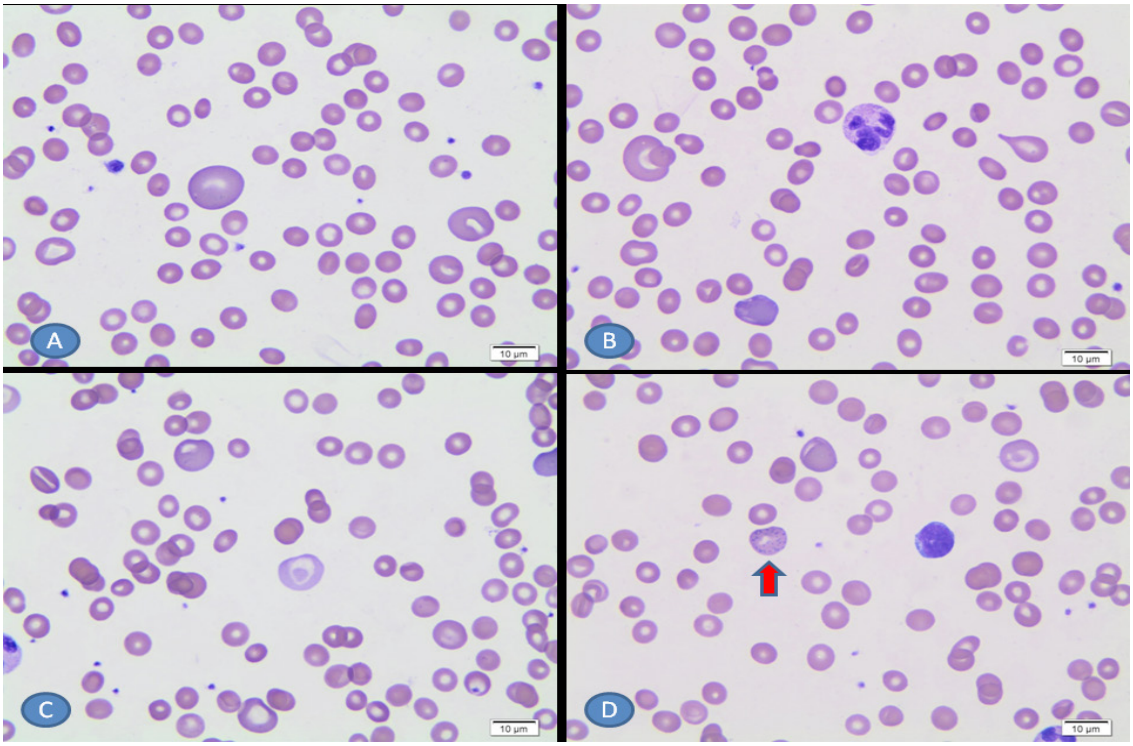

Figure 1. Macrocytic tear drop shaped and target-shaped red blood cells in stained peripheral blood smear (A, B, and C). Red blood cells with prominent basophilic stippling (Arrow) (D).

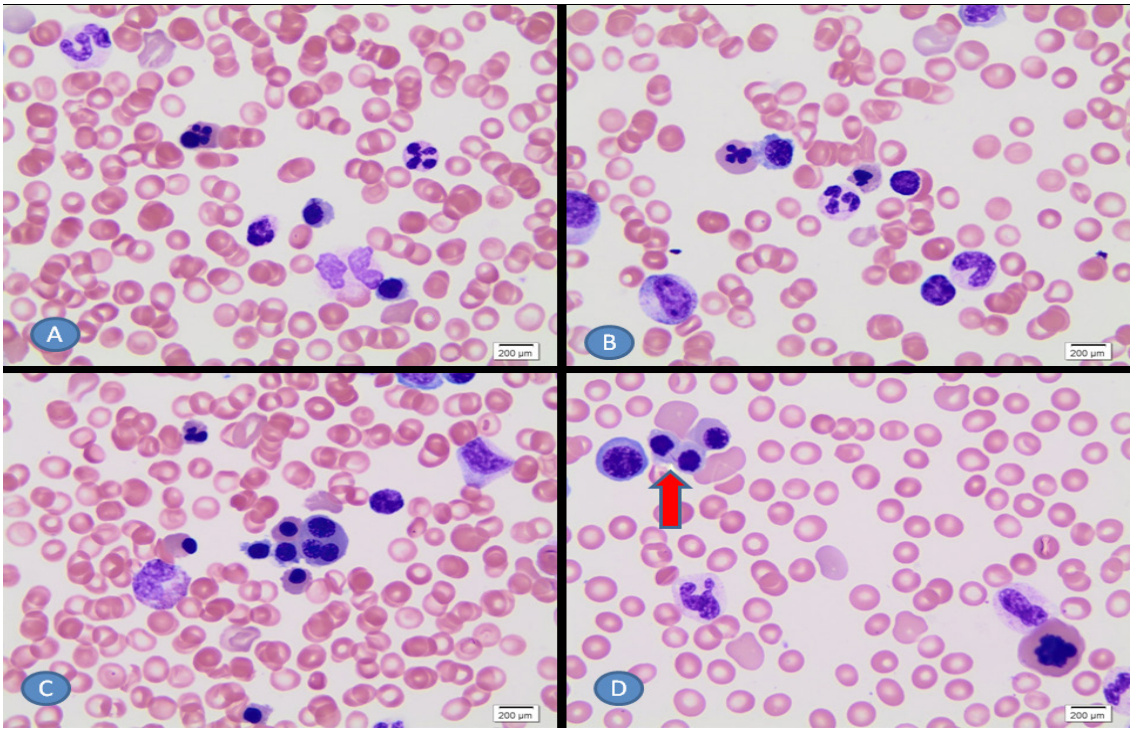

Figure 2. Bone marrow aspirate smear showing erythroid precursors with lobulated nuclei (A, B, and C). Evidence of Nuclear chromatin bridging (Arrow) (D).

Question: What is the most likely diagnosis?

Answer
Congenital dyserythropoietic anemia (CDA), type I.

Discussion
Congenital dyserythropoietic anemias (CDAs) represent a group of rare hereditary disorders characterized by dyserythropoiesis and associated ineffective erythropoiesis and shortened red blood cell lifespan. Of note, despite the striking dysplastic morphology involving erythroid precursors, the non-erythroid cell lineages appear morphologically normal. Traditionally, histomorphology, electromicroscopy, and certain serologic tests have been utilized to further subclassify CDAs into three major types: CDA I, II, and III (1). More recently, causal genetic aberrations have been identified in types I and II (2). The severity of anemia in CDA is variable among individuals, but the majority of patients has a mild to moderate anemia and are not transfusion-dependent. In general, CDA tends to be most symptomatic in infancy, during which transfusion therapy may be necessary. Additionally, given the high red blood cell turnover, CDA is frequently associated with splenomegaly, increased lactate dehydrogenase, hyperbilirubinemia, jaundice, bilirubin gallstones, and iron overload (1,2).

CDA type I is inherited in an autosomal recessive fashion and can be associated with various congenital abnormalities (1). The peripheral blood findings include a mild to severe anemia (mean hemoglobin of 9.2 g/dL) with 70% of cases having increased MCV. Red blood cell morphology is notable for macrocytes even in the setting of a normal MCV, teardrop cells, and basophilic stippling. The bone marrow usually demonstrates erythroid hyperplasia with megaloblastoid changes and dyserythropoiesis. The erythroid dysplasia includes markedly irregular nuclei, Howell-Jolly bodies, and binucleation in 3.5-7% of erythroid precursor cells. Of note, the binucleated erythroid cells may have unequal nuclear shape and size. One of the diagnostic features of CDA type I, though not entirely specific, is the presence of internuclear chromatin bridging, which usually involves less than 3% of erythroid precursors, necessitating careful morphologic evaluation (1,2). Another useful discriminatory finding in CDA type I is the detection by electron microscopy of a spongy, "Swiss-cheese" appearance in the heterochromatin of the erythroid precursor cells, which is a result of cytoplasmic invaginations into the nuclear membrane (1). More recently, mutations in the gene *CDAN1*, which is located at 15q15.1-15.3 and encodes codanin-1, have been implicated in most cases of CDA type I (1,2).

CDA type II, also known as hereditary erythroblastic multinuclearity with a positive acidified serum lysis test (HEMPAS), is the most common type of CDA (1,3). Similar to CDA type I, type II demonstrates autosomal recessive inheritance. The peripheral blood findings include a mild to moderate anemia (hemoglobin between 8 to 11 g/dL) with a normal MCV and occasional circulating erythroblast. The red blood cells show moderate to marked anisopoikilocytosis with teardrop cells and spherocytes as well as basophilic stippling. The bone marrow demonstrates normoblastic or megaloblastoid erythroid predominance and dyserythropoiesis notable for frequent (10-35%) binucleation of late erythroblasts. In contrast to the binucleated erythroid precursors in CDA type I, the nuclei in type II are equal in shape and size. Lipid-laden macrophages and pseudo-Gaucher cells are also frequently noted in the bone marrow. By electron microscopy the erythroid precursors in CDA type II have a discontinuous double membrane, referred to as a peripheral cistern, which runs parallel to the cell membrane. Another diagnostic characteristic of CDA type II is a positive acidified serum lysis test (Ham test) using ABO-compatible normal sera, which is likely secondary to a naturally occurring IgM antibody that recognizes an antigen present on CDA type II cells. In contrast to paroxysmal nocturnal hemoglobinuria (PNH), the acidified serum lysis test with autologous serum is negative as is the sucrose lysis test. Recently, mutations in the gene *SEC23B*, which is located at 20p11.23-20p12.1 and encodes the SEC23B component of the coat protein (COP) II complex, has been implicated in the vast majority of CDA type II cases (2,3).

CDA type III is the rarest type of CDA and both familial and sporadic forms have been described (1,2). Of note, the familial cases show autosomal dominant inheritance. The red blood cells demonstrate moderate to marked anisopoikilocytosis, including macrocytosis, as well as basophilic stippling. The bone marrow shows megaloblastoid erythroid hyperplasia and dyserythropoiesis notable for giant mononucleate and multinucleate erythroid precursor cells. The multinucleated cells, which can contain up to 12 nuclei that vary in size and shape, represent 10-40% of the erythroid precursors. The ultrastructural findings seen in CDA type III erythroid precursor cells are non-specific and include long intranuclear clefts, karyorrhexis, nuclear membrane abnormalities, and large autophagic vacuoles (1). The responsible gene has been mapped to 15q21-q25,

but has yet to be identified (4).

Acknowledgments
The authors thank Maria Nunez for her help in preparing this manuscript.

References

1. Wickramasinghe SN, Wood WG. Advances in the understanding of the congenital dyserythropoietic anaemias. *Br J Haematol* 2005;131(4):431-46.
2. Iolascon A, Russo R, Delaunay J. Congenital dyserythropoietic anemias. *Curr Opin Hematol* 2011;18(3):146-51.
3. Punzo F, Bertoli-Avella AM, Scianguetta S, Della Ragione F, Casale M, Ronzoni L, et al. Congenital Dyserythropoietic Anemia Type II: molecular analysis and expression of the *SEC23B* Gene. *Orphanet J Rare Dis* 2011;30;6:89.
4. Lind L, Sandstrom H, Wahlin A, Eriksson M, Nilsson-Sojka B, Sikstrom C, et al. Localization of the gene for congenital dyserythropoietic anemia type III, CDAN3, to chromosome 15q21-q25. *Hum Mol Genet* 1995;4:109-12.