Educational Case: Anemia in a Neonate

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, diagnostic medicine, hematology, anemia, CBC interpretation, peripheral smear evaluation, hyperbilirubinemia, acquired anemia

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Primary Objective
Objective H4.3: Peripheral Smear Evaluation in Anemia. Discuss the RBC and white blood cell morphology on a peripheral smear to develop a differential diagnosis for a patient with anemia.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic H: Hematology; Learning Goal 4: Diagnosis of the Anemic Patient

Secondary Objective
Objective H4.1: Causes and Diagnosis of Anemia. Describe the primary causes of anemia, compare and contrast the clinical features and mechanisms of each, and discuss the different testing strategies for normocytic, macrocytic, and microcytic anemia.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic H: Hematology; Learning Goal 4: Diagnosis of the Anemic Patient

Objective HRC1.5 Anemias of Red-Cell Destruction. Explain the mechanisms by which anemia is produced on the basis of shortened red cell survival, distinguishing between intrinsic and extrinsic causes of red cell destruction.

Competency 2: Organ System Pathology; Topic HRC: Hematopathology—Red Cell Disorders; Learning Goal 1: Anemia

Patient Presentation
A female newborn infant is delivered along with her twin via planned uncomplicated Cesarean section to a 31-year-old G2P1 female at 37 weeks and 0 days gestation. The mother has an O positive blood type and negative antibody screen with one previous parity and live birth. The father is known to have glucose-6-phosphate dehydrogenase (G6PD) deficiency. The infant receives Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. She weighs 2335 g (fifth percentile—small for gestational age) and measures 47 cm in length. The other twin is larger. A non-fused bilobed placenta is delivered complete and intact with grossly diagnostically–dichorionic morphology later confirmed on histology. A physical examination is within normal limits. She has an unremarkable first 12 hours of life with good latch during breastfeeding and normal vital signs, with an adequate number of stools and wet diapers. An

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indirect bilirubin drawn at 12 hours of life is elevated and prompts additional workup with a complete blood count (CBC), reticulocyte count, and umbilical cord blood typing.

**Diagnostic Findings, Part I**

A CBC and peripheral smear are performed and presented in Table 1 and Figures 1 to 4, respectively.\(^2\)\(^-\)\(^4\)

### Table 1. Complete Blood Count.

| Peripheral blood component | Patient laboratory values | Reference ranges |
|----------------------------|----------------------------|------------------|
| WBC (\(\times 10^3/\mu\text{L}\)) | 13.2 | 9.0-30.0 (\(\times 10^3/\mu\text{L}\))* |
| RBC (\(\times 10^3/\mu\text{L}\)) | 2.44↓ | 3.90-5.90 (\(\times 10^3/\mu\text{L}\))* |
| Hemoglobin (g/dL) | 10.1↓ | 13.4-19.9 (g/dL)* |
| Hematocrit (%) | 29.8↓ | 42.0-65.0 (%)* |
| MCV (fL) | 122.1 | 88.0-123.0 (fL)* |
| RDW | 24.5↑ | 16.65 ± 1.81* |
| Reticulocytes (%) | 19↑ | 1-3 (%)* |
| RBC morphology | Spherocytes, polychromatophils, and nucleated RBCs increased | Rare polychromatophils and nucleated RBCs* |

Abbreviations: MCV, mean corpuscular volume; RBC, red blood cells; RDW, red cell distribution width; WBC, white blood cell.

* These reference ranges are specific to newborn infants up to 1 month old and delivered at full term.\(^2\)\(^-\)\(^3\)

**Figure 1.** Reticulocytes (A) demonstrate ribosomal RNA throughout the cytoplasm while Heinz bodies (B) demonstrate clumped denatured hemoglobin contiguous with the cell membrane (supravital stain, \(\times 1000\) magnification, original image used with written permission from the publisher, previously published in Rodak’s Hematology: Clinical Principles and Applications, 5th Ed, Clark KS, Hippel TG, Chapter 14: Manual, semiautomated, and point-of-care testing in hematology, Figure 14-11, Copyright Elsevier. 2015.)\(^4\)

**Figure 2.** Spherocytes are small, rounded mature red blood cells with no central pallor (arrow) (\(\times 1000\) magnification).

**Questions/Discussion Points, Part I**

**What Is the Immediate Clinical Concern in This Patient?**

The urgent concern being investigated is potential hemolytic disease as a source of excess bilirubin—a normal product of red blood cell (RBC) destruction that can be neurotoxic in newborns whose liver function cannot effectively compensate. Phototherapy and feeding supplementation with formula are started immediately in order to optimize the newborn’s ability to excrete excess bilirubin in the urine and stool. Phototherapy uses a specific frequency of blue light (450-490 nm) that converts the difficult to excrete trans-bilirubin to more easily excretable cis-bilirubin. Formula supplementation ensures adequate hydration and increases urine and stool output, thus increasing the rate of bilirubin excretion. Although the initial treatment for elevated indirect bilirubin is straightforward and...
effective in a number of underlying etiologies, it is important to further investigate to guide ongoing management. This case allows for a discussion of the unique differential diagnosis of anemia in newborns and the algorithmic approach to its workup based on these considerations (Figure 5).5

What Can Be Learned From the CBC?

This patient’s low hemoglobin and hematocrit establish an anemia—a quantitative deficit in RBCs. Anemias can be divided into 3 categories based on size of the RBCs: macrocytic, normocytic, or microcytic, each with their specific differential diagnoses. The mean corpuscular volume (MCV) given in a CBC is a helpful tool to quickly screen for abnormally large or small RBCs. In this case, the MCV is normal for the age of the patient, but the red cell distribution width (RDW) is significantly elevated.5,3 When RDW is elevated, the MCV must interpreted with caution because, like in this case, although the average red cell size is normal, there is wide variation from cell to cell. Mean corpuscular volume in the case of wide variation in cell size may indicate a masked microcytic or macrocytic process or both. There are a range of cell sizes present in this specimen without one dominant cell type or size that best represents the findings. So in this instance, classifying the anemia based on cell size is not helpful.

Two helpful components of the CBC are the RBC and reticulocyte counts. The low RBC count shows that the overall number of red cells is less than normal. However, the reticulocyte count is elevated. A reticulocyte (Figure 1) is an anucleate red blood which has successfully completed the maturation stages that occur in the bone marrow and lost its nucleus in the process, but is naive to the peripheral circulation. Reticulocytes are distinguishable from mature RBCs by a supravital stain which will highlight the residual ribosomal RNA that remains in the cells for hours to days after they leave the bone marrow.4

A reticulocyte count is essentially analogous to the rate of mature red cell production from the bone marrow because they are always the newest cells in the circulation. Anemias can be hyperproliferative or hypoproliferative based on a high or low reticulocyte count. Several types of anemia are secondary to impaired ability of the bone marrow to produce an adequate quantity and/or quality of RBC including iron deficiency anemia, aplastic anemia, and Diamond-Blackfan anemia to name a few. This patient displays no issue with red cell production given her high reticulocyte count, so these etiologies can be ruled out. Increased production, as is evidenced in this case, is often a normal bone marrow response low RBC counts or hypoxia secondary to RBC loss or destruction.

What Does the Peripheral Smear Reveal?

When CBC counts are not conclusive, peripheral smear review can give a more accurate picture of the morphologic changes in the red cells (Figure 6). This patient’s peripheral smear has several RBC morphologies with abnormal size and shape, called poikilocytes. There are very small round RBCs without central pallor called spherocytes (Figure 2). Spherocytes form when a portion of an RBC membrane is removed by macrophages in the spleen. Their cell membranes reapproximate despite the loss of a small portion of membrane and cytoplasm, forming a smaller spherical cell which returns to the circulation. Some of the other morphologies present in this patient’s specimen are medium-sized cells with central pallor (mature RBCs) and large cells with a bluish hue and no central pallor (polychromatophils; Figure 3). Polychromatophils are immature RBCs, which comprise a subset of reticulocytes. The only way to tell which polychromatophils are reticulocytes is the supravital stain. Nucleated RBCs are also present (Figure 3). These cells are very immature RBC precursors, usually only found in the bone marrow, sometimes present in very small
proportions in a normal newborn. Finally, there are immature red cells with Howell-Jolly bodies (dot-like peripheral condensation of retained nuclear material) which can be seen in conditions where there is a bone marrow response to red cell destruction (Figure 4).

**What Broad Etiologies Should Be Considered in the Differential Diagnosis?**

**Blood loss.** Etiologies caused by blood loss relevant to this case include trauma, chronic fetomaternal hemorrhage, and twin-twin transfusion syndrome. History of blood loss from chronic fetomaternal hemorrhage or trauma is not mentioned and unlikely from delivery in an uncomplicated full-term Cesarean section. Twin-twin transfusion syndrome, in which blood is preferentially shunted to one twin resulting in intrauterine growth restriction of the other twin, is important to consider in multiple gestation pregnancies, especially when there is a weight discrepancy between siblings. However, in this case, the placenta showed non-fused diamniotic–dichorionic morphology, meaning the twins did not share placental circulation, eliminating the possibility of twin-twin transfusion syndrome. The fact that only one of the twins is anemic in this diamniotic/dichorionic twin gestation is interesting; the cause of the anemia is less likely to be related to the shared pregnancy environment (as both twins would be affected) and more likely to be a genetic difference that predisposes one of the infants. Blood loss is not a plausible explanation in this case.

**Hemolysis.** Red blood cell destruction in hemolysis occurs either within the blood vessels themselves (intravascular) or in other tissues such as the spleen where abnormal RBCs are sequestered (extravascular), and can be differentiated based on morphology. The primary poikilocyte in intravascular hemolysis is a
schistocyte. Schistocytes are red cells with irregularly shaped membranes exhibiting at least 2 points and no central pallor (Figure 7). Microangiopathic hemolytic anemias, which demonstrate schistocytes, are limited to disseminated intravascular coagulation (DIC) in a newborn; while other causes are much more common in adults. Although DIC must be considered if hemolysis is a concern, this patient’s peripheral smear does not demonstrate schistocytes; thus DIC is ruled out. In extravascular hemolysis, the primary poikilocyte is the spherocyte, which is demonstrated in this case. It forms when red cells are sequestered and partially engulfed by macrophages in the spleen. The differential diagnosis for extravascular hemolysis includes genetic structural and functional defects predisposing red cells to sequestration, immune-mediated processes, and the physiologic stress of thermal injury. Based on the patient’s history of delivery via an uncomplicated Cesarean section with an unremarkable first 12 hours of life, the possibility of extravascular hemolysis from thermal injury is an unlikely explanation. Genetic structural and functional defects in red cell production include hereditary spherocytosis, G6PD deficiency, and pyruvate kinase deficiency.

Now That Extravascular Hemolysis Is Established as the Etiology, What Is the Differential Diagnosis?

Structural defects in RBC production. Hereditary spherocytosis is a congenital hemolytic anemia that results from abnormal spectrin and ankyrin molecules which are responsible for maintaining RBCs’ disc-like shape, characteristic central pallor, and membrane plasticity. The abnormalities in hereditary spherocytosis increase the likelihood of sequestration, and subsequent hemolysis, in the spleen. Splenectomy, the mainstay of treatment for this disorder, resolves the hemolysis; but the RBCs are still structurally abnormal. Hereditary spherocytosis is relatively common in those of Northern European ancestry occurring in 1/2000 in that population.6

Functional defects in RBC production. G6PD deficiency is a relatively common X-linked recessive genetic disorder affecting RBCs’ resistance to oxidative stress. G6PD deficiency is present in 10% to 15% of African American and Mediterranean populations. The glucose-6-phosphate dehydrogenase enzyme’s byproducts of carbohydrate metabolism are protective against reactive oxygen species. In the absence of these byproducts, the red cells are more likely to be sequestered and destroyed by the spleen. The primary poikilocyte in G6PD is a bite cell (Figure 8): a red cell that has a concave defect in the membrane resembling a “bite” secondary to removal of Heinz bodies (Figure 1) by the spleen. Heinz bodies are denatured hemoglobin that precipitates during oxidative stress. Heinz bodies are not visible on a standard peripheral smear but, like reticulocyte ribosomal RNA, require a supravital stain for visualization. Intravascular hemolysis with schistocytes is also possible in G6PD deficiency but is not always present. Manifestations of the disease are often mild but can result in symptomatic anemia and jaundice at times of increased oxidative stress such as infections, dietary, or pharmacologic triggers. Surprisingly, of the small number of severe cases of hyperbilirubinemia with kernicterus reported in the United States (125 neonates from 1992-2004), G6PD deficiency is implicated in 1 in 5 cases.7 Although G6PD deficiency is common, little is known about its role in neonatal hemolytic anemia in the United States. It is diagnosed by measuring the level of the glucose-6-phosphate dehydrogenase in plasma. Reticulocytes naturally have a higher concentration of this enzyme in their cytoplasm. Because of this, ordering the test should be avoided in acute hemolytic episodes, where reticulocytes may be elevated, due to the increased likelihood of false-negative results. No known cure exists, and the diagnosis is often managed with preventative and supportive measures.8

Figure 7. Schistocyte—a mature red blood cell with at least 2 sharp points and no central pallor (arrow; ×1000 magnification).

Figure 8. A bite cell is the primary poikilocyte in G6PD deficiency and is a mature red blood cell that has a concave defect in the cell membrane resembling a “bite” (arrow; ×1000 magnification). G6PD indicates glucose-6-phosphate dehydrogenase deficiency.
Another congenital disorder that makes red cells more vulnerable to destruction is pyruvate kinase deficiency. It is an autosomal recessive loss of function mutation in the PKLR gene which encodes the pyruvate kinase enzyme. The enzyme is crucial in the generation of the energy molecule adenosine triphosphate (ATP) during glycolysis, interfering with the ability of the red cell to metabolize glucose - its primary source of energy. Red blood cells affected by this shortage of ATP are prematurely sequestered in the spleen and hemolyzed. Manifestations of the disease range from mild to severe. It is rare, only occurring in 1 in 20,000 Americans of European descent, with a higher prevalence in the Amish population of Pennsylvania.

Immune-mediated extravascular hemolysis. This immune-mediated hemolytic anemias broadly include autoimmune hemolytic anemia, acute and delayed hemolytic transfusion reactions, and hemolytic disease of the newborn and fetus (HDNF). A newborn’s immature immune system is incapable of forming a significant number of antibodies to any antigen. Furthermore, there was no history of blood transfusion; so the first 2 possibilities can be ruled out. Hemolytic disease of the newborn and fetus is caused by maternal antigen binding to fetal or newborn RBC surface antigens, usually to ABO or Rh(D) blood group antigens. Rarely other blood group antigens are the culprit. The antibodies from mother can either be transferred to the fetal circulation during trauma or hemorrhage in utero or via passive transmission through the placental circulation.

What Are the Most Likely Diagnoses and Why?
Statistically, HDNF is the most likely diagnosis. It is estimated that up to 15% of live births have ABO incompatibility with the potential for development of HDNF. However, only a small fraction of these cases develop clinically significant sequelae with only 3% presenting clinically and less than 0.1% requiring advanced treatment such as exchange transfusion. This may be due to the fact that when maternal immunization to ABO blood groups occur, it is often accomplished by IgM antibodies which do not cross the placenta. Therefore, the chances of maternal antibodies reaching the fetal circulation in significant numbers is low. Hemolytic disease of the newborn and fetus can also be caused by Rh(D) incompatibility but is now rare due to the use of anti-Rh(D) immune globulin. Anti-Rh(D) immune globulin is a prophylactic treatment given to Rh(D) negative gravid women to prevent immunization against the Rh(D) RBC cell surface antigen. The treatment essentially neutralizes the immunogenicity of any exposure to Rh(D) antigen during pregnancy by binding to the antigen itself when it enters the circulation, before host immune cells are sensitized to it. It was developed to prevent the tragic and often fatal consequences of maternal immunization to the antigen when exposed to their Rh(D) positive fetus’s blood. Immunization to the Rh(D) antigen is often accomplished by IgG antibodies which can be passively transmitted from the maternal circulation to the fetal circulation through the placenta, causing immune-mediated hemolysis in the fetus.

Less is known about the frequency of clinically significant hemolysis in newborns from other genetic etiologies such as hereditary spherocytosis, G6PD deficiency, and pyruvate kinase deficiency. This patient already has an immediate family member with known G6PD deficiency, making this a plausible diagnosis in addition to HDNF. However, being an X-linked recessive disease, it would be rare in a female born to a father with G6PD deficiency because it would require inheritance of an affected X chromosome from the mother as well. Other congenital hemolytic anemias are less likely in this patient.

What Further Laboratory Tests Are Indicated?
A simple way to differentiate HDNF from the other causes discussed here is by its immune-mediated etiology—coating of the fetal RBCs by maternal antibodies. Hemolytic disease of the newborn and fetus is the only disease under consideration; so the DAT will cross-link with the existing antibodies attached to the RBC surface antigens and form a strong agglutination reaction— which can be seen in the test tube as clumps of red cells that do not mix back into the serum when gently agitated. If the RBCs are free of antibodies on their surface, the antiglobulin antibodies won’t bind, and the red cells will remain individually suspended in serum. Umbilical cord blood typing is also useful to determine whether ABO or Rh(D) incompatibility between mother and newborn is present. Although cord blood typing can be inaccurate due to maternal contamination, it is preferred over a blood draw when an anemia is already present.

Diagnostic Findings, Part II
An ABO + Rh blood type and DAT is performed on the cord blood and presented in Table 2.

Questions/Discussion Points, Part II
How Does This Laboratory Result Limit the Differential Diagnosis Above?
A positive DAT supports the diagnosis of HDNF. As mentioned above, there is a possibility of contamination with maternal blood, which can cause a false-positive DAT. An ABO and Rh(D) blood type is helpful to correlate with the DAT result to determine whether ABO incompatibility is present. In the case of this patient, there is clear incompatibility (mother: O positive, newborn: B positive); so it is likely that the DAT is truly positive due to maternal antibodies binding to the B antigen on the infant’s RBCs.
Does This Change the Most Likely Diagnosis?

The most likely diagnosis is HDNF, both statistically and based on the laboratory results from Table 2. If the patient had hereditary spherocytosis, G6PD deficiency, or pyruvate kinase deficiency, the DAT would be negative. Since there is family history of G6PD deficiency and there is still a small possibility that this is concomitantly present, it would be helpful to test the patient to make sure that the hemolysis seen is not multifactorial from both HDNF and G6PD deficiency. However, the laboratory findings cannot be explained by G6PD deficiency alone. Furthermore, as mentioned above, it would not be practical to test this patient for G6PD in the acute setting due to the elevated reticulocyte count. Testing for G6PD should be performed later on a routine basis as an outpatient.

What Are the Two Most Common Causes of Hemolytic Disease of the Newborn and Fetus?

**Rh(D) incompatibility.** Primigravid pregnant women with Rh(D) negative blood type carrying a fetus with Rh(D) positive blood type may form IgG alloantibodies to fetal RBCs that can passively transfer to the fetal circulation through the placenta. Any minor sensitizing event during pregnancy such as hemorrhage, trauma, miscarriage, or even amniocentesis can cause maternal alloimmunization, transfer of maternal antibodies to the fetal circulation, and resultant fetal immune-mediated hemolytic anemia in utero. In severe cases, hydrops fetalis and intranuclear fetal demise may result. In addition, in untreated cases, the almost certain sensitization that occurs during delivery of an Rh(D) positive infant in a primigravid woman will result in alloimmunization to Rh(D) positive fetal RBCs in any future pregnancies, making the risk of intrauterine complications more likely with subsequent pregnancies.

**ABO incompatibility.** Pregnant women with fetal ABO blood type incompatibility may have low levels of preexisting antibodies to ABO blood group antigens which, during a sensitizing event such as hemorrhage or trauma, often develop increased number of IgM antibodies to the ABO antigens. Unlike with anti-Rh(D) IgG antibodies, the IgM antibodies of ABO incompatibility cannot passively cross the placenta, decreasing the likelihood of intrauterine complications. Furthermore, blood group A and B antigens on fetal RBCs are not fully developed before birth, so sensitization to fetal blood may not result in effective alloimmunization.

How and Why Do They Differ in Presentation?

**Rh(D) incompatibility.** Historically, Rh(D) incompatibility was a significant cause of newborn and fetal morbidity and mortality with 50% of HDNF cases caused by Rh(D) incompatibility proving fatal in the first half of the 20th century. With the advent of prophylactic anti-Rh(D) immune globulin—administered antenatally and postnatally, the incidence of maternal alloimmunization to the Rh(D) antigen in primigravid women decreased to 1 in 2500 women, significantly decreasing both the morbidity and mortality associated with this issue to a rarity.10,11
**ABO incompatibility.** Although the frequency of ABO incompatibility in all corner pregnancies is approximately 15%, the clinical impact of this issue is rarer with less than 1/5 of incompatible cases resulting in clinically significant disease, and most are mild. An even smaller fraction of those who manifest clinically significant disease are severe enough to require treatment such as transfusion or plasma exchange. Mortality from ABO incompatibility is rare.\(^1\)

**How Do They Differ in Approach to Prevention and Treatment?**

**Rh(D) incompatibility.** Rh(D) incompatibility is aggressively treated with preventative measures. It is standard of care for any pregnant woman with Rh(D) negative blood to prophylactically receive anti-Rh(D) immunoglobulin antenatally, postnatally, and in response to any known sensitization event during pregnancy.

**ABO incompatibility.** There is no preventative treatment for ABO incompatibility. Individual hospital policies differ on whether cord blood is automatically tested for ABO/Rh(D) and DAT in blood group O mothers versus only tested if clinically indicated (neonatal hyperbilirubinemia or symptomatic anemia). Generally, infants affected by HDNF secondary to ABO incompatibility are treated for hyperbilirubinemia with phototherapy and formula supplementation. However, if bilirubin remains elevated despite treatment or anemia is symptomatic, blood transfusion or plasma exchange may be considered.

**Teaching Points**

- Intravascular and extravascular causes of hemolytic anemia can be differentiated on peripheral smear by evaluating for the predominance of schistocytes versus spherocytes
- Presence of increased spherocytes in the absence of schistocytes on a peripheral smear has a differential diagnosis including structural, functional, and immune-mediated causes of extravascular hemolysis.
- The differential diagnosis for hemolytic anemia in a fetus or newborn is markedly different than the differential diagnosis in a child or adult due to specific considerations in this population:
  - Potential for maternal alloimmunization to fetal RBC surface antigens
  - Quiescent newborn immune response to foreign RBCs due to immature immunity
  - First presentation of congenital anemias
- Direct antiglobulin testing is used to detect antibodies bound to RBCs which can come from:
  - Alloimmunization: Antibodies directed against a foreign antigen such as a blood transfusion (IgG and IgM), passive transmission of maternal antibodies through the placenta (IgG only), or mixing of maternal blood with fetal blood during hemorrhage or trauma (IgG and IgM)
  - Autoimmunization: Antibodies made by the patient’s own immune system (does not occur in newborns)
- Rh(D) incompatibility has a higher risk of morbidity and mortality because the involved IgG antibodies passively cross the placenta, while ABO incompatibility is usually IgM-mediated and requires an event where maternal blood contaminates the fetal circulation (ie, hemorrhage or trauma)
- The most common cause of hemolytic anemia in a newborn is due to maternal–fetal ABO incompatibility.
- Although G6PD deficiency is common in African American and Mediterranean populations (prevalence 10%), little is known about its role in neonatal hemolytic anemia.

**Authors’ Note**

The views expressed in this educational case report are those of the author(s) and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or US Government.

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