QUIZ

Rosette-like Structures in the Bone Marrow of a Child Treated for Neuroblastoma: The Story of "Red" Cells in a "Green" Machine!

Basil M. Kahwash[1], Wei Chen[2], Samir B. Kahwash[3]

[1]University of Toledo College of Medicine, Toledo, Ohio, 43606, USA
[2]Department of Pathology, the Ohio State University Wexner Medical center, Columbus, Ohio 43210, USA
[3]Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus OH 43205, USA

Corresponding author: Dr. Samir B. Kahwash Email: samir.kahwash@nationwidechildrens.org
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Quiz:
These photomicrographs (Figure 1) represent microscopic findings from the bone marrow aspirate of a 3 year-old child, who is status post-chemotherapy treatment for neuroblastoma.

What is your diagnosis?

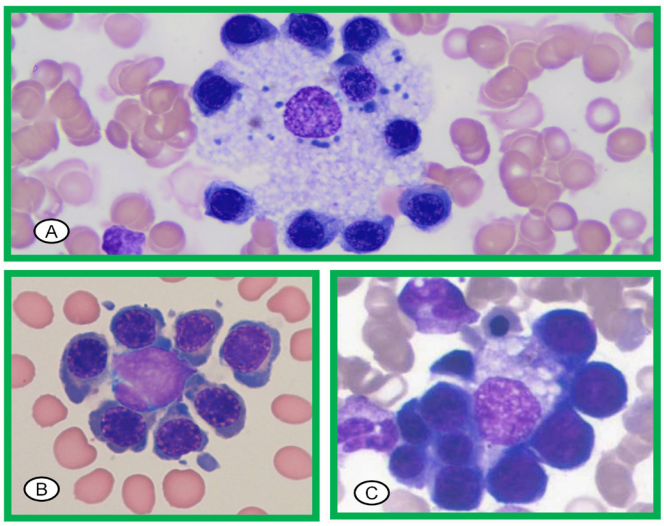

Figure 1. Bone marrow aspirate

Answer

These cell groups represent early erythroid precursors arranged to receive iron from hemosiderin-laden macrophages (HLM). They are often referred to by the term "suckling" erythroid precursors, and the providing HML cells are called "nurse cells" (see Figure 2). This phenomenon is usually seen in regenerating bone marrows, particularly in the pediatric population.

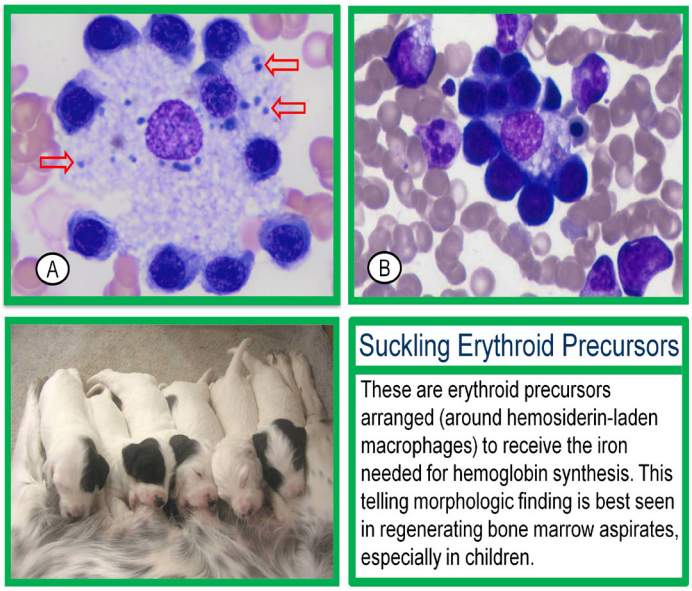

Figure 2. Bone marrow "suckling" erythroid precursor cells around "nurse cells" . Note the hemosiderin deposits in the cytoplasm of a nurse cell in A (arrows).

Discussion

The uptake, utilization and recycling of iron by the human body is an elaborate, highly efficient and conservation-oriented process. As illustrated in figure 3, the majority of the iron in circulation is absorbed from dietary sources in the duodenum by the enterocytes of the intestinal lining epithelium. The iron is then exported from enterocytes into the blood stream by a transporter protein called ferroportin. Once in circulation, serum iron couples with transferrin to form the iron-transferrin complex, which can then bind to the transferrin receptor expressed on the surface of most cells. Upon being engulfed by various cells, iron is released from transferrin into the cytoplasm. The intracellular iron is either stored as ferritin or hemosiderin (a degradation product of ferritin), or utilized in the synthesis of hemoglobin, myoglobin, cytochromes and other enzymes.

Excess iron is primarily stored in the form of ferritin in the liver (inside hepatocytes and Kupffer cells), heart (inside cardiac myocytes) and other tissues. Under normal conditions, most iron in the human body is present in red blood cell hemoglobin (66% of total body iron), and myoglobin (13%), ferritin and hemosiderin (13%), the transport protein transferrin (less than 1%), and other cells (5%) (1). A small but steady amount of iron is also lost daily in sweat and shedding of cells in the skin, the mucosa of the gastrointestinal tract and menstrual blood of women during reproductive years. Excessive loss of iron without adequate intake results in microcytic hypochromic anemia of iron deficiency. The latter is the most prevalent type of anemia worldwide.

Iron reserves are located in the bone marrow where iron (in the form of ferritin and hemosiderin) is stored in specialized macrophages, termed "nurse cells". Ultrastructure examination by electron microscopy suggested that the central reticular nurse cell can impart ferritin to surrounding erythroblasts by a process known as rhopheocytosis (micropinocytosis) (2). The electron dense ferritin molecules appeared to be released by the nurse cell, subsequently adhere to the surface of the erythroblasts and eventually enter the erythroblasts through invagination of the cell membrane. Once inside the erythroblasts, the intracellular ferritin is utilized to make hemoglobin. A morphologic manifestation of this phenomenon is a "rosette" like arrangements of erythroid cell precursors around a central hemosiderin laden "nurse cell" (Figure 2). This is best seen in the regenerating bone marrow, especially in children and young adults.

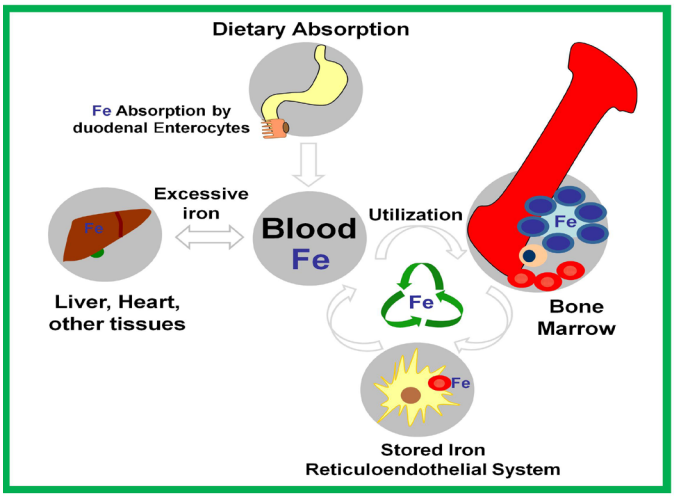

Figure 3. Human iron metabolism cycle and recycle

Mature red blood cells are filled with copious amounts of iron-containing hemoglobin. When the red blood cells reach their average life span of 120 days (3), they are destroyed and degraded by the reticuloendothelial system in the spleen and liver (4). During degradation of heme to bilirubin, iron is released and recycled to make new crops of red blood cells in the bone marrow, and the cycle continues. When it comes to conservation of the precious iron, it appears that the human body is the ultimate and most efficient "green machine"!

The differential diagnoses for suckling erythroid precursors in bone marrow aspirate include metastatic neuroblastoma and hemophagocytic lymphohistiocytosis. Metastatic neuroblastoma may show tumor cells arranged in a rosette (Figure 4B), resembling circular arrangement of erythroid precursors (Figure 4A). However, unlike erythroid precursors, neuroblastoma cells have high nuclear/cytoplasmic ratio, irregular nuclear contour (Figure 4B, arrow), and are arranged around central fibrillary neurophil, not a central cell. In hemophagocytic lymphohistiocytosis (Figure 4C), activated phagocytic histiocytes engulf red blood cells, white blood cells, and platelets (5). As a result, cells at variable stages of degradation and cellular debris are randomly distributed within the cytoplasm of histiocytes- in contrast to the orderly arrangement of intact suckling erythroid precursors around a central nurse cell.

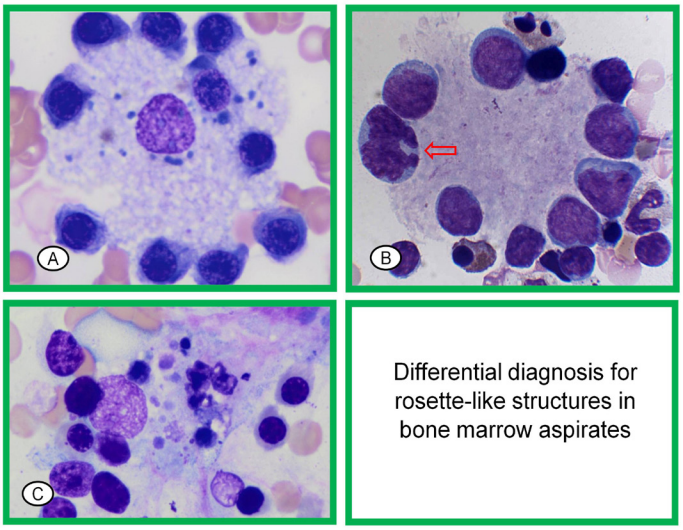

Figure 4. Suckling erythroid precursors and mimickers in bone marrow aspirates (A) Suckling erythroid precursors around a "nurse cell" (B) metastatic neuroblastoma cells forming a "rosette" around a neurofibrillary center: note the irregular nuclear contour of individual neuroblastoma cells (arrow); (C) hemophagocytic histiocyte with ingested erythroid precursors and cellular debris from a case of Hemophagocytic Lymphohistiocytosis (HLH).

Acknowledgments

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