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Nucleated RBCs—Significance in the Peripheral Blood Film

ABSTRACT *Nucleated RBCs (NRBCs) are immature RBCs not normally seen in the peripheral blood beyond the neonatal period. Their appearance in peripheral blood of children and adults signifies bone marrow damage or stress and potentially serious underlying disease. The presence of numerous NRBCs increases the WBC count in automated hematology analyzers. Most analyzers generate suspect flags to help identify abnormal cells, and the samples involved should be reviewed manually. Unfortunately, analyzers may not detect low levels of NRBCs. We recommend correcting the WBC count with even 1 NRBC/100 WBCs and reporting "occasional NRBC seen." This alerts clinicians of the significance of unexplained normoblastemia.*

Nucleated RBCs, (NRBCs) are in the peripheral blood of normal infants up to the fifth day of life.[1] At birth, 3 to 10 NRBCs per 100 WBCs are present (Fig 1).[1,2] Premature birth[3] and fetal hypoxia can cause this number to increase.[4] Beyond the neonatal period, the presence of NRBCs in the peripheral blood is usually associated with malignant neoplasms, bone marrow diseases, and other serious disorders.[1,5,6]

The bone marrow has a special architecture whose disruption leads to predictable changes. Normal mature bone marrow cells are deformable, so they can squeeze through small "portholes" in the endothelium to enter the peripheral circulation.[7] Normoblasts and immature granulocytes, however, are less deformable and rarely enter the circulation (Fig 2). Their presence in the peripheral blood means that the bone marrow barrier has been disrupted or that extramedullary hematopoiesis has been activated.

This article discusses the conditions associated with NRBCs in peripheral blood and explains why it is important to report their presence.

Mechanisms Associated With Normoblastemia

The mechanisms associated with normoblastemia are not completely understood but may be classified as shown in the Table.[8-19] Although it is useful to try to attribute the condition to a single process, it is important to understand that multiple interrelated mechanisms are often involved.

Hyposplenism and Asplenia

Hyposplenism reflects the developmental immaturity of the reticuloendothelial system and is the reported cause of physiologic normoblastemia of neonates.[5,15] Because normoblasts that escape from the marrow are normally cleared by the spleen, their presence in the peripheral blood suggests a hyposplenic state.[10] In patients with myeloproliferative disorders, cellular overload may incapacitate splenic function.[3] The same phenomenon develops in patients with sickle cell disease in which abnormal RBCs glut the splenic machinery. Moreover, marrow stress and release of too many normoblasts can overwhelm the ability of a normal spleen to clear them from circulation. This occurs with hypoxia, hemolytic anemia, anemia under treatment, megaloblastic anemia, ineffective erythropoiesis, collagen vascular diseases, malignant neoplasms, and chemotherapy treatment.[5,10]

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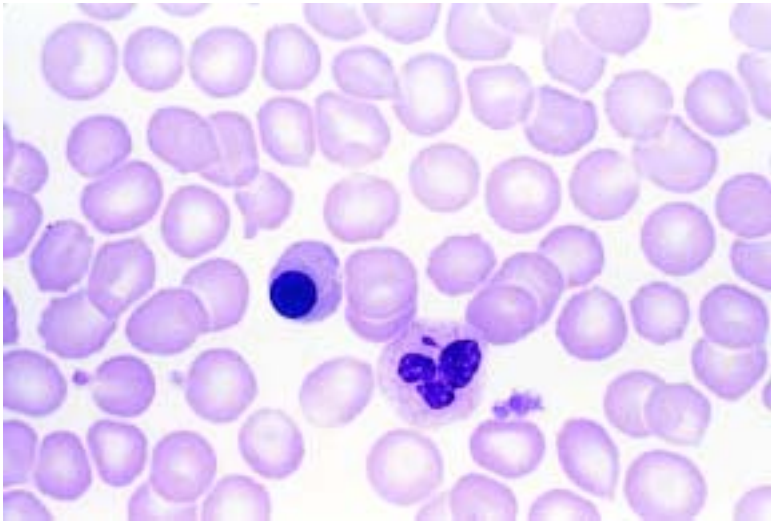

Fig 1. Wright-stained peripheral blood smear from a normal newborn showing polychromasia, a nucleated RBC, and a neutrophil. Cells are crowded together due to the high RBC count (× 1,000). From Maedel L, Sommer S. *Blood Cell Morphology: Morphologic Changes in Erythrocytes, 4*. Chicago, IL: ASCP Press; 1993: Fig 4-31.

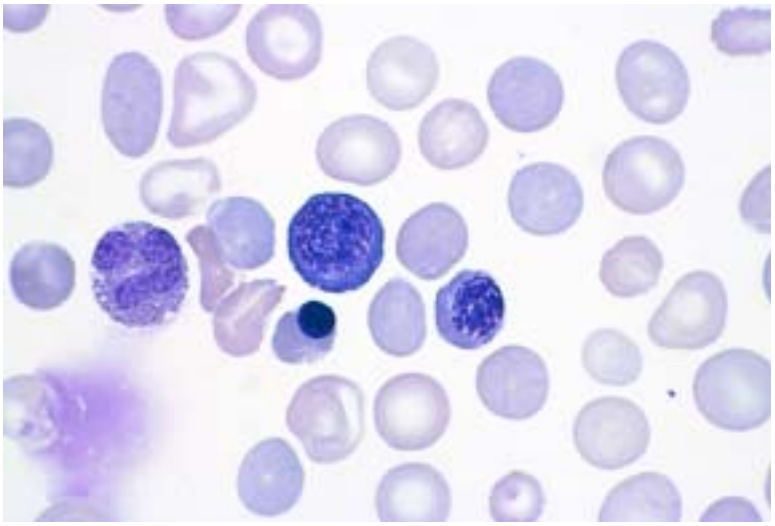

Fig 2. Wright-stained bone marrow smear showing stages of erythroid maturation: basophilic normoblast, polychromatophilic normoblast, orthochomic normoblast. An eosinophil is also shown (× 1,000). From Maedel L, Sommer S. *Blood Cell Morphology: Normal Cells of the Bone Marrow, 2.* Chicago, IL: ASCP Press; 1993: Fig 2-05.

The most useful and sensitive indicator of splenic function, however, is the presence of Howell-Jolly bodies (RBC inclusions) in the peripheral blood film (Fig 3).[10-11] The presence of normoblasts, although useful, may be nonspecific. Acanthocytes, target cells, stippled cells, and fragments are also nonspecific findings.[10]

Anemia and Compensatory Erythropoiesis

In all types of severe anemia—hemolytic, nutritional, or anemia of blood loss—normoblastemia is caused by hypoxic erythropoietin-induced compensatory erythropoiesis.[11] The reduced oxygen-carrying capacity of anemic blood causes tissue hypoxia,[20] the main stimulus for RBC production. When hypoxia occurs, the kidneys produce erythropoietin which, when increased markedly, results in intense marrow erythropoietic activity.

Whether marrow erythropoiesis is effective or ineffective depends on the underlying cause of the anemia. With effective erythropoiesis, the resulting accelerated compensatory activity produces prominent reticulocytosis, polychromasia, immature granulocytes (at times), and occasional NRBCs in the peripheral blood. Which and how many of these cells or conditions are present depends on the severity of the anemia and marrow response. If the marrow response is exaggerated, NRBCs are plentiful with many "stress" reticulocytes, causing pseudomacrocytosis. When erythropoiesis is ineffective, NRBCs may be prematurely released into the peripheral blood without reticulocytosis. Dysplastic RBC changes may occur, as shown by the appearance of macro-ovalocytes and teardrop cells in the peripheral blood.

Hypoxia

Any condition that reduces the quantity of oxygen transported to the tissues causes an increase in the rate of RBC production. Although normoblastemia occurs in response to hypoxia in both anemia and cardiopulmonary disorders, the cause of hypoxia differs in these conditions. In anemia, hypoxia results when the reduced hemoglobin concentration causes a corresponding decline in the oxygen-carrying capacity of the blood. Cardiopulmonary hypoxia, however, may involve several mechanisms, including failure of the blood to absorb oxygen from the lungs, inadequate ventilation of alveoli, or right-to-left intrapulmonary shunting of the blood. Impaired cardiovascular circulation leading to an inadequate supply of oxygenated blood to the tissues may also cause hypoxia.[21,22] Because some patients with cardiopulmonary disorders have pulmonary emboli or coronary thrombosis complications, the presence of normoblasts in these disorders may indicate unfavorable prognosis.[23,24]

The hemoglobin concentration also differs in these hypoxic situations. In cardiopulmonary hypoxia, the hemoglobin level is either high or within the reference interval, whereas in anemic

Mechanisms and Conditions Associated With Normoblastemia[8-19]	
Hyposplenism, asplenia	Sickle cell anemia[8]
	Newborn (physiologic)[1,6]
	Splenectomy[3,9]
	Essential thrombocytosis[10]
	Hemolytic anemia[10]
	Malaria[10]
Anemia, compensatory erythropoiesis	Severe anemia (any cause)[11]
	Hemolytic anemia[8]
	Iron deficiency anemia[8]
	Megaloblastic anemia[8]
	Hemorrhage[5,12]
	Anemia under treatment[8]
	Microangiopathic hemolytic anemia[8]
	Thalassemia major[8]
Hypoxia	Severe pulmonary disease[5,13]
	Congestive cardiac failure[5,13]
	Cyanotic heart disease[5,13]
Marrow replacement, invasion	Preleukemia[13]
	Leukemia[8,13]
	Lymphoma[13]
	Neuroblastoma[13]
	Myelodysplasia[8]
	Myelofibrosis[8,13]
	Plasma cell myeloma[8]
	Myeloproliferative disorder[8,13]
	Gaucher and other storage disease[14]
	Granuloma (ie, tuberculosis)[13]
	Collagen vascular disease[5,13]
	Fungal infection[14]
	Histiocytosis[14]
	Tumor cell presence[8,13]
	Sarcoidosis[14]
	Osteopetrosis[13]
Extramedullary hematopoiesis	Myelophthisis[13,15]
	Osteopetrosis[13]
	Myeloid metaplasia[13]
	Myelofibrosis[8]
	Chronic hemolytic anemia[15]
	Polycythemia vera[13]
	Leukemia[15]
Other	Uremia[16]
	Sepsis[17]
	Liver disease[18]
	Diabetic ketoacidosis[18]
	Inflammatory bowel disease[18]
	Renal transplant[18]
	Thermal injury[19]
	Chemotherapy[5]

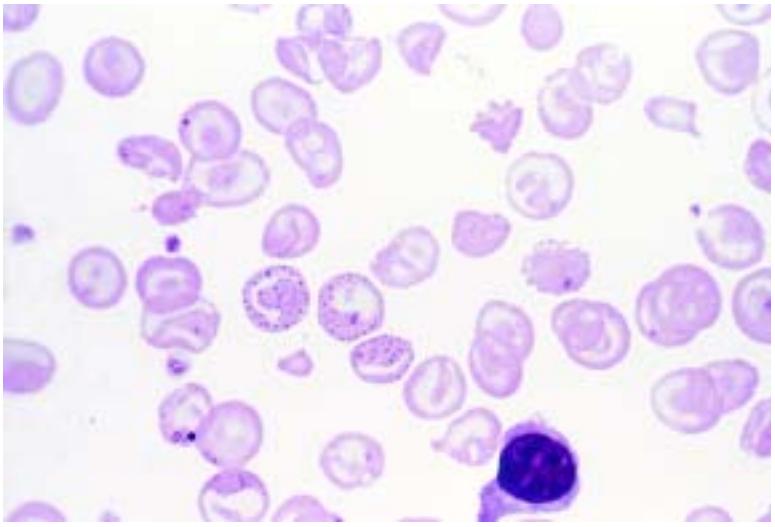

Fig 3. Wright-stained peripheral blood smear showing basophilic stippling, Howell-Jolly bodies, and a nucleated RBC (× 1,000). From Maedel L, Sommer S. *Blood Cell Morphology: Morphologic Changes in Erythrocytes, 4*. Chicago, IL: ASCP Press; 1993: Fig 4-81.

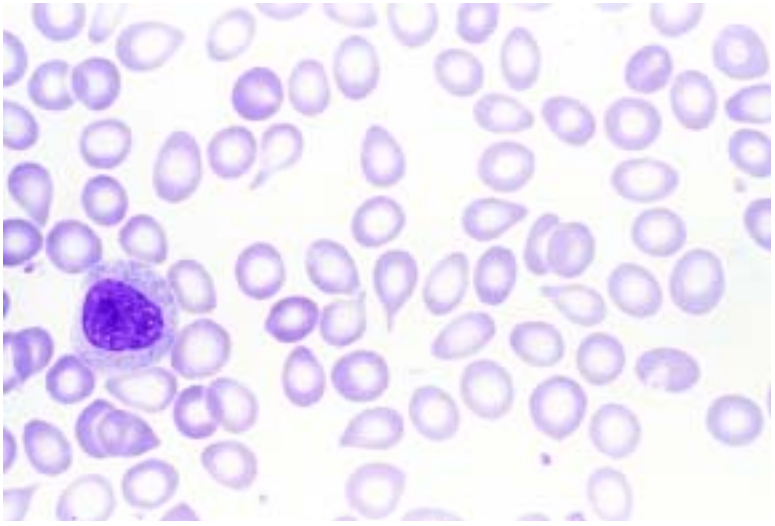

Fig 4. Wright-stained peripheral blood smear from a patient with myelofibrosis showing many teardrop RBCs and a myelocyte (× 1,000). From Maedel L, Sommer S. *Blood Cell Morphology: Chronic Hematopoietic Malignancies, 6*. Chicago, IL: ASCP Press; 1993: Fig 6-18.

hypoxia, it is much lower.[21,24] The rate of RBC production, however, is not controlled by hemoglobin concentration; it appears to vary with the ability of the cells to transport oxygen to the tissues in response to a demand. Thus, if the oxygen supply is less than the tissues demand, more RBCs are produced, which, in turn, results in a higher hemoglobin level until the supply of oxygen meets the demand. In cases of transient increases in oxygen demand (a hypoxic stimulus), normoblastemia, if present, disappears with relief of the hypoxia.[24]

Accordingly, a hypoxic stimulus should be suspected whenever normoblastemia is accompanied by a normal to high hemoglobin level and mild to moderate polychromasia.

Bone Marrow Replacement and Invasion

Marrow replacement can occur in association with a primary hematologic disease such as leukemia, myeloma, or lymphoma. It can also be the result of secondary insult by invading tumor cells, the presence of sarcoidosis, or infectious agents such as mycobacteria and fungi. Both primary and secondary reactions can produce marrow fibrosis (myelofibrosis), which changes the normal marrow microarchitecture. This disruption may break down the marrow-blood barrier, causing untimely and disorderly release of NRBCs and progenitor cells into the circulation (Fig 4).[14,25] Similarly, extensive marrow infiltration and replacement may cause mechanical "crowding out" of normal hematopoietic cells, leading to their escape into the peripheral blood and lodgment in other organs such as the spleen, liver, and lymph nodes. This process may contribute to extramedullary hematopoiesis.

The initial peripheral blood picture may present unexplained normoblastemia, mild macrocytosis, giant platelets, myelocytes, thrombocytopenia, and, possibly, leukopenia with or without teardrop cells or blast cells.

Extramedullary Hematopoiesis

Recognized clinically as splenomegaly or hepatomegaly, extramedullary hematopoiesis appears to be caused by anemia, marrow replacement associated with acute leukemia, or other nonhematopoietic infiltrative processes (myelophthisis).[15] Presumably, hematopoietic stem cells are displaced from the marrow into the spleen or liver where they proliferate to cause hepatomegaly and splenomegaly. Splenomegaly also occurs when the marrow has been dispossessed by fibrosis. Because the spleen does not retain immature cells as efficiently as normal marrow, it may release NRBCs,

immature granulocytes, megathrombocytes, and occasional blast cells into the peripheral blood, resulting in leukoerythroblastosis or the coexistence of myeloid precursors and NRBCs in the peripheral blood.[17] Teardrop cells may be present. A leukoerythroblastic reaction may also be seen without marrow infiltration in normal newborns as well as in patients with thalassemia major with severe hemolytic crisis, hemorrhage, postsplenectomy, septicemia,[26] and therapy with granulocyte colony-stimulating factor (G-CSF).[27,28]

In addition, when bone marrow reserve is unable to meet the demand for accelerated erythropoiesis (as in chronic hemolytic anemia or longstanding anemia), blood cells may form in tissues other than the bone marrow.[15] This extramedullary hematopoiesis represents a reversion of the involved tissues to their fetal blood-forming function, although this compensatory activity may also occur in myelophthisic anemia with fibrosis. Thus, differentiating between chronic hemolytic anemia and myelophthisic anemia with fibrosis is difficult without the patient's clinical history.

Leukoerythroblastosis is evident in peripheral blood films, and teardrop cells may or may not be present. Teardrop cells are not usually seen in leukoerythroblastic reactions associated with hemorrhage, infection, or G-CSF therapy. They can be found in severe iron deficiency anemia,[29] thalassemia, megaloblastic anemia, hemolytic anemia, leukemia, myelofibrosis, and drug-induced Heinz body formation.[26] Teardrop cells may reflect dyspoiesis and thus are not specific for a single condition. Although the exact mechanism of teardrop cell formation is unclear, the formation of these cells from inclusion-containing RBCs is well documented. As cells with large rigid inclusions try to pass through the small splenic sinus openings, parts with large inclusions get pinched, causing the cells to stretch with irreversible loss of their shape. The result is teardrop cells.[30] Moreover, teardrop cell formation represents the cells' tortuous circulation through deformed marrow sinuses and diseased splenic cords.[26] The presence of teardrop cells in the peripheral blood is thus significant and should alert morphologists to search for occasional NRBCs, megathrombocytes, stippled cells, immature granulocytes, or blast cells that would constitute conclusive evidence of myeloid metaplasia or leukoerythroblastosis.[26]

Other Mechanisms

Why normoblastemia occurs with these disorders remains enigmatic. Although the marrow-blood barrier appears to break down, the cause of the breakdown is unknown.[13] Most of the disorders involve complex conditions that cause systemic diseases and influence bone marrow response.[17] These diseases include uremia, sepsis, liver disease, and thermal injury.[18,19]

Role of the Laboratory

Laboratory professionals play an important role in detecting NRBCs when they review CBC and WBC differential results obtained by automated hematology analyzers. Most analyzers generate suspect flags, (eg, WBC*R, NRBC, Review Slide, Blasts) to help identify abnormal WBCs, and samples with flags should be microscopically examined. Although most instruments have >80% specificity for NRBC flags, they cannot consistently detect <5% NRBCs.[31,32] The number of NRBCs in a 100- or 200-WBC differential count is reported as the number of NRBCs per 100 WBCs. In addition, the corrected WBC count is reported. It is also good practice to manually scan all blood films of new patients (without a diagnosis) for abnormalities that may not have been flagged.

To Correct or Not To Correct the WBC Count

Recognizing NRBCs is important not only because their presence affects the WBC count, but also because only a few NRBCs can have ominous implications in some patients. We therefore recommend that WBC counts with even 1 NRBC/100 WBCs be corrected and reported. This

alerts clinicians of the significance of unexplained normoblastemia. The correction can be made with a simple formula:

Corrected WBC count, $\times 10^9$/L = WBC count, $\times 10^9$/L $\div$ (1 + [NRBC/100 WBCs])

For example, if the WBC count is 6.0×10^9/L and the NRBC count is 50/100 WBCs, the corrected WBC count
$= 6.0 \times 10^9$/L $\div$ (1 + [50/100])
$= 6.0 \times 10^9$/L $\div$ (1 + 0.5)
$= 4.0 \times 10^9$/L

Computerized laboratory systems do these calculations automatically. Recent advances in hematology analyzers and their widespread use will alleviate manually correcting WBC counts.[33,34]

As the example shows, a sample with an NRBC count of 50/100 WBC and a WBC count of 6.0×10^9/L yields a corrected WBC count of 4.0×10^9/L—a difference that may be statistically but not clinically significant. Therefore, setting a threshold of more than 4 or 5 NRBCs/100 WBCs before correcting the WBC count does not make clinical sense. In addition, many authors[26,35-37] advocate different correction formulae and cutoff values. We recommend correcting the WBC count with even 1 NRBC/100 WBCs and reporting "occasional NRBC seen" with <1 NRBC/100 WBCs.

Comments

Although the appearance of NRBCs in blood does not in itself provide a diagnosis of disease, it may give invaluable clues to the presence of a serious condition. Homeostatically, NRBCs in blood represent a compensatory response to an excessive demand on the blood-forming organs (marrow stress) such as in severe anemia or hypoxia. Clinically, NRBCs may represent marrow fibrosis, marrow replacement by leukemic cells or metastatic tumor cells, or extramedullary hematopoiesis. Their presence indicates the extent to which bone marrow reacts to stress and disease.

A recent technological breakthrough enables new hematology analyzers to identify NRBCs separately from WBCs.[33,34] With this technology, more cells per specimen are characterized, and the new data might show that "rare" NRBCs occur more frequently than previously thought and that the significance of this should be revisited. Moreover, except for grossly abnormal results, manual correction of WBC counts may become unnecessary.

The classification of mechanisms associated with normoblastemia (see Table), although useful, is oversimplified because it emphasizes only the predominant cause of the disorders listed. In many conditions, more than one mechanism is operative. The best example is severe hemolytic anemia of the newborn (erythroblastosis fetalis) in which the severe stress of anemia and hypoxia on marrow erythropoiesis is the primary cause of normoblastemia. The combination of marrow stress with the immaturity (hyposplenism) of the reticuloendothelial system and the availability of extramedullary hematopoiesis probably accounts for the extreme normoblastemia or leukoerythroblastosis. Similarities to this are evident in leukemia, myelophthisic anemia, or myelofibrosis; although the primary cause of normoblastemia in these conditions is the crowding out of hematopoietic cells or the disruption of marrow architecture, concurrent anemia, hyposplenism, or extramedullary hematopoiesis may also contribute to normoblastemia. Furthermore, in cardiopulmonary disorders, normoblastemia is more pronounced when anemia is also present. Therefore, it should be easier to differentiate one disorder (mechanism) from the other by considering the total clinical picture.

Although studies show that even 1 NRBC in the peripheral blood of adults may indicate a serious disease,[5,38] clinicians and laboratory professionals do not agree on its clinical significance, especially when unsupported by other data. The differing views are probably due more to perception than reality. In primary health care units, normoblastemia is rare and may signify a pathologic condition. In contrast, normoblastemia is a common finding in an acute care hospital. As a result, NRBCs may be perceived as ordinary cells of questionable clinical significance; in these cases, the importance of normoblastemia is relative and depends on the type of hospital and patient population.

We believe that unexplained normoblastemia is important because it offers invaluable insight into disease processes or progressions that occur in conditions such as metastatic carcinoma, bone marrow conditions, systemic infections, and cardiopulmonary complications. The presence of normoblastemia with certain clinical conditions may indicate that a bone marrow examination is necessary to rule out hematologic malignant neoplasms or unsuspected blood disorders. When viewed in this context, 1 innocuous NRBC may lead to more timely medical intervention, thus increasing the chance of a positive outcome.

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