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# A study of hundred adults cases presenting with normoblastemia

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**Abstract**
**Introduction:** Normoblastemia is the presence of nucleated RBCs (nRBCs) in the peripheral blood. It signifies bone marrow damage or stress and potentially serious underlying disease. Various infiltrating & non-infiltrating conditions present with normoblastemia ranging from infections, sepsis, haemorrhage, haemolysis, anemias to leukemias, lymphomas & metastases.
**Aims and Objectives:** 1. To study the distribution of various conditions presenting with normoblastemia in different age groups and sex. 2. To categorize the spectrum of conditions presenting with normoblastemia into non-infiltrating and infiltrating conditions based on the mechanisms involved.
**Materials and Methods:** A total of 100 adult patients presenting with normoblastemia were studied from June 2018 to December 2018. The patient' s medical history, clinical and hematological findings along with the peripheral smear examination to look for the presence of normoblastemia were evaluated. Bone marrow study was done wherever required.
**Results:** A total of 100 adult patients were included. 26% cases were between the age group of 21-30 years, thus constituting the largest group. 52% were males and 48% were females. The spectrum of conditions presenting with normoblastemia were categorized into non-infiltrating and infiltrating cases. Majority of the cases were non-infiltrating (72%) as compared to that of infiltrating cases (28%). The various mechanisms involved in the non-infiltrating conditions were hyposplenism, anemia and compensatory erythropoiesis, hypoxia and other miscellaneous causes. Iron deficiency anemias (23/72) were the highest followed by megaloblastic anemias (22/72) and sepsis (6/72). Among the infiltrating conditions, highest cases were chronic myeloid leukemias (9/28) followed by acute myeloid leukemias (6/28).
**Conclusion:** Normoblastemia offers an invaluable insight into disease processes. Its presence may indicate that a bone marrow examination is necessary to rule out hematologic malignant neoplasms or unsuspected blood disorders. This study emphasizes on the importance of finding even single nRBC that may lead to more timely medical intervention, thus increasing the chance of a positive outcome.

**Keywords:** Normoblastemia, nucleated RBCs, peripheral blood, myelodysplasia, myelofibrosis

## Introduction

Normoblastemia" is defined as the presence of immature erythroid cells in the peripheral blood. Nucleated red blood cells (nRBCs) are early erythrocyte precursors not present in the peripheral blood of normal adults [1, 2]. Fenestrations in the bone marrow provide a physical filter to the release of the large nRBCs into the circulation, and the rare nRBC that escapes is rapidly cleared from peripheral blood by the spleen. The presence of circulating nRBCs in adults thus reflects extreme increase in erythropoietic activity or failure of the blood filtration mechanism [3, 4].

Normoblastemia in a general population is frequently caused by non-malignant disorders such as hemolysis, infection, haemorrhage, megaloblastic anemias, & combinations of infections, bleeding and hypoxia [5, 6]. The presence of nRBCs in the peripheral smear of the critically ill is associated with increased inhospital mortality [7, 8, 9, 10]. Their presence in peripheral blood of 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 for identifying abnormal cells, and the samples involved should be reviewed manually. Unfortunately, analyzers may not detect low levels of nRBCs. It is recommended that the WBC count with even 1 nRBC/100 WBCs should be corrected and reported as " occasional nRBC seen." This alerts clinicians for the significance of unexplained normoblastemia [1, 2].

Therefore, the present study was conducted to study the spectrum of various conditions presenting with normoblastemia and to categorize the spectrum into non-infiltrating and infiltrating conditions based on the mechanism involved.

## Materials and Methods

The present study was a prospective study conducted during the period of June 2018 to December 2018. A total of 100 adult patients above the age of 18 years who presented with normoblastemia either on manual peripheral smear examination or on detection with the help of automated analyzer flags were included in the study. The patient' s clinical history with all the relevant investigations were evaluated. All the findings were documented on a standard proforma. Bone marrow study (Aspiration and/or biopsy) was done wherever required. The data obtained was analyzed using the Microsoft Excel 2007 and SPSS statistical tool.

## Results

A total of 100 adult patients who presented with normoblastemia were included in this study. The distribution of the cases presenting with normoblastemia according to the age (Table 1) & sex (Table 2) were studied. Out of a total of 100 adult patients maximum number of cases, i.e, 26 cases were between the age group of 21-30 years. Hence, the patients in this age group constituted the largest group. There were 52 males and 48 females.

**Table 1:** Age specific distribution of the cases presenting with normoblastemia

| Age group (In years) | No. of cases |
|---|---|
| 18-20 | 08 |
| 21-30 | 26 |
| 31-40 | 16 |
| 41-50 | 22 |
| 51-60 | 12 |
| 61-70 | 16 |
| Total | 100 |

**Table 2:** Sex specific distribution of the cases presenting with normoblastemia

| Sex | No. of cases |
|---|---|
| Male | 52 |
| Female | 48 |
| Total | 10 |

**Table 3:** The spectrum of non-infiltrating conditions presenting with normoblastemia

| Sl. No | Mechanisms involved | Conditions presenting with normoblastemia | No. of cases |
|---|---|---|---|
| 1. | Hyposplenism | A] Autoimmune Hemolytic Anemia [AIHA] | 04 |
| | | B] Sickle Cell Anemia | 01 |
| | | C] Malaria | 02 |
| 2. | Anemia and compensatory erythropoiesis | A] Iron Deficiency Anemia | 23 |
| | | B] Megaloblastic Anemia | 22 |
| | | C] Haemorrhage | 04 |
| 3. | Hypoxia | Congestive Cardiac Failure | 02 |
| 4. | Miscellaneous | A] Uremia | 04 |
| | | B] Sepsis | 06 |
| | | C] Chronic Liver Disease | 04 |
| | Total | | 72 |

The spectrum of conditions presenting with normoblastemia were categorized into non-infiltrating and infiltrating cases (Table 3 and 4). The non-infiltrating cases were 72 constituting the majority of cases as compared to that of 28 infiltrating cases. The various mechanisms involved in the non-infiltrating conditions were hyposplenism, anemia and compensatory erythropoiesis, hypoxia and other miscellaneous causes. Iron deficiency anemia cases (23/72) were the highest followed by megaloblastic anemia cases (22/72) and sepsis (6/72) (Table 3). Among the infiltrating conditions, chronic myeloid leukemia (9/28) constituted the majority of cases followed by acute myeloid leukemia (6/28) (Table 4).

**Table 4:** The spectrum of infiltrating conditions presenting with normoblastemia

| Sl.no | Diagnosis | No. of cases |
|---|---|---|
| 1. | Acute myeloid leukemia (AML) | 06 |
| 2. | Acute lymphocytic leukemia (ALL) | 02 |
| 3. | Chronic myeloid leukemia(CML) | 09 |
| 4. | Chronic lymphocytic leukemia (CLL) | 02 |
| 5. | Myelodysplastic syndrome (MDS) | 02 |
| 6. | Lymphomas- non-hodgkin' s lymphoma (NHL) | 02 |
| 7. | Multiple myeloma | 02 |
| 8. | Myelofibrosis | 02 |
| 9. | Metastatic breast carcinoma | 01 |
| | Total | 28 |

Among the non-infiltrating conditions, 41/72 cases were seen in females. Iron deficiency anemia (23/72) cases were the highest and were common in the females between the age group of 21-30 years. 3 /4 cases of AIHAs were seen in the females (Table 5 and 6). One case of sickle cell anemia was seen in a female patient of 19 years who presented with

sickle cell crisis and had severe bone pain (Figure 1 and 5). Two cases of malaria also showed the presence of nucleated RBCs. Haemorrhage, congestive cardiac failure, uremia, sepsis and chronic liver disease were more in male patients than in females.

Among the infiltrating conditions, 21/28 cases were seen in males. 6/9 cases of CML were seen in males and 3/9 cases were in the age group of 41-50 years. 4/6 cases of AML were seen in males and 3/6 cases were in the age group of 41-50 years (Table 5). Both the cases of ALL (Figure 2), CLL, myelodysplastic syndromes, non-Hodgkin' s lymphoma and myelofibrosis were seen in males (Table 6). One case of metastatic breast disease was seen in a female aged 62 years who presented with multiple metastatic bone deposits and was diagnosed on bone marrow aspiration and biopsy. Both the cases of NHLs were diagnosed on bone marrow biopsy as the bone marrow aspirate was a dry tap. Bone marrow study was also done for the two cases of multiple myeloma which showed binucleated and trinucleated plasma cells on aspiration slides (Figure 3A and 3B). Dyserythropoietic features were significant in the myelodysplastic cases (Figure 4).

**Table 5:** Age specific distribution of the spectrum of conditions presenting with normoblastemia

| Sl. No | Conditions With Normoblastemia | Age Groups | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | 18-20 | 21-30 | 31-40 | 41-50 | 51-60 | 61-70 | |
| | I] Non-Infiltrating | | | | | | | |
| 1. | Autoimmune Hemolytic Anemias [AIHA] | - | 02 | - | - | - | 02 | 04 |
| 2. | Sickle Cell Anemia | 01 | - | - | - | - | - | 01 |
| 3. | Malaria | - | 01 | 01 | - | - | - | 02 |
| 4. | Iron Deficiency Anemia | 05 | 09 | 03 | 02 | 02 | 02 | 23 |
| 5. | Megaloblastic Anemia | 02 | 11 | 04 | 04 | 01 | - | 22 |
| 6. | Haemorrhage | - | - | 02 | 01 | 01 | - | 04 |
| 7. | Congestive Cardiac Failure | - | - | - | - | 02 | - | 02 |
| 8. | Uremia | - | - | - | 02 | 01 | 01 | 04 |
| 9. | Sepsis | - | 02 | 01 | 02 | - | 01 | 06 |
| 10. | Chronic Liver Disease | - | - | - | 01 | 03 | - | 04 |
| | | | | | | | | |
| | II] Infiltrating | | | | | | | |
| 1. | Acute Myeloid Leukemia | - | - | 02 | 03 | - | 01 | 06 |
| 2. | Acute Lymphocyic Leukemia | - | - | - | 02 | - | - | 02 |
| 3. | Chronic Myeloid Leukemia | - | - | 02 | 03 | 02 | 02 | 09 |
| 4. | Chronic Lymphocytic Leukemia | - | - | - | - | - | 02 | 02 |
| 5. | Myelodysplastic Syndrome | - | 01 | - | 01 | - | - | 02 |
| 6. | Lymphomas-Non-Hodgkin' s lymphoma | - | - | 01 | 01 | - | - | 02 |
| 7. | Multiple Myeloma | - | - | - | - | - | 02 | 02 |
| 8. | Myelofibrosis | - | - | - | - | - | 02 | 02 |
| 9. | Metastatic breast carcinoma | - | - | - | - | - | 01 | 01 |
| | Total | 08 | 26 | 16 | 22 | 12 | 16 | 100 |

**Table 6:** Sex specific distribution of the spectrum of conditions presenting with normoblastemia

| Sl. No | Conditions with normoblastemia | NO. of cases | | |
|---|---|---|---|---|
| | | Males | Females | Total |
| | I] Non-infiltrating | | | |
| 1. | Autoimmune Hemolytic Anemias [AIHA] | 01 | 03 | 04 |
| 2. | Sickle Cell Anemia | | 01 | 01 |
| 3. | Malaria | 02 | - | 02 |
| 4. | Iron Deficiency Anemia | 05 | 18 | 23 |
| 5. | Megaloblastic Anemia | 08 | 14 | 22 |
| 6. | Haemorrhage | 03 | 01 | 04 |
| 7. | Congestive Cardiac Failure | 02 | - | 02 |
| 8. | Uremia | 03 | 01 | 04 |
| 9. | Sepsis | 04 | 02 | 06 |
| 10. | Chronic Liver Disease | 03 | 01 | 04 |
| | II] Infiltrating | | | |
| 1. | Acute Myeloid Leukemia | 04 | 02 | 06 |
| 2. | Acute Lymphocytic Leukemia | 02 | - | 02 |
| 3. | Chronic Myeloid Leukemia | 06 | 03 | 09 |
| 4. | Chronic Lymphocytic Leukemia | 02 | - | 02 |
| 5. | Myelodysplastic Syndrome | 02 | - | 02 |
| 6. | Lymphomas-Non-Hodgkin' s lymphoma | 02 | - | 02 |
| 7. | Multiple Myeloma | 01 | 01 | 02 |
| 8. | Myelofibrosis | 02 | - | 02 |
| 9. | Metastatic breast carcinoma | - | 01 | 01 |
| | Total | 52 | 48 | 100 |

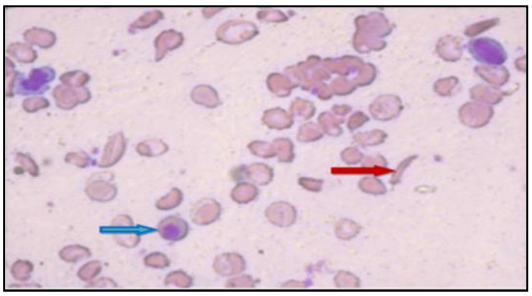

**Fig 1:** Peripheral smear of a Sickle cell disease patient showing nucleated RBC (blue arrow), sickle cells (Red arrow) and severe anisopoikilocytosis. (Leishman' s stain; 100X)

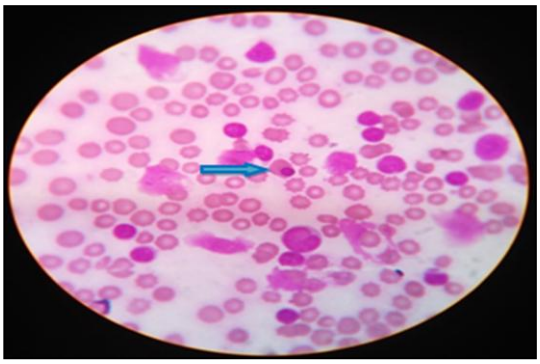

**Fig 2:** Peripheral smear of an acute lymphoid leukemia (ALL) patient showing nucleated RBC (Black arrow). (Leishman' s stain; 100X)

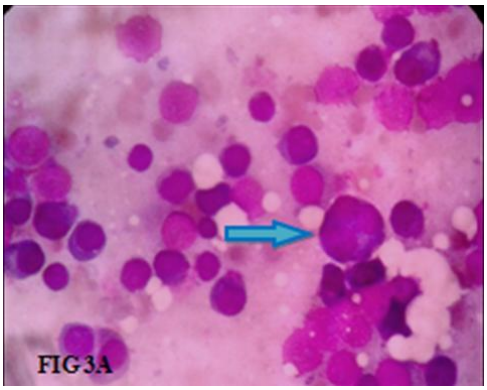


**Fig 3A:** Bone marrow aspirate of a patient with multiple myeloma patient showing trinucleate plasma cell (Blue arrow) (Bone marrow aspirate; Leishman' s stain; 400X).

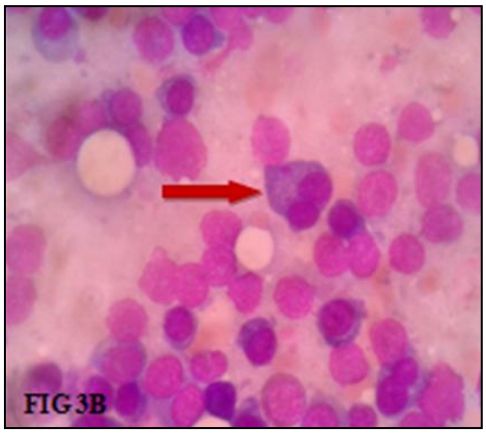


**Fig 3B:** Bone marrow aspirate of a patient with multiple myeloma patient showing binucleate plasma cell (Red arrow) (Bone marrow aspirate; Leishman' s stain; 400X).

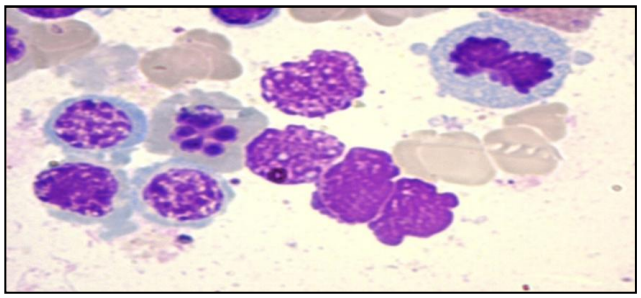

**Fig 4:** Bone marrow aspirate in a Myelodysplastic syndrome case showing features of dyserythropoiesis such as cytoplasmic blebbing, nuclear budding and abnormal mitotic figure. (Bone marrow aspirate; Leishman' s stain; 400X)

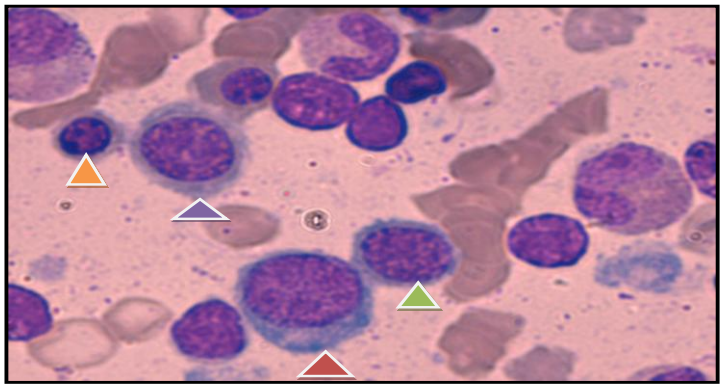

**Fig 5:** Bone marrow aspirate showing erythroid hyperplasia with normal maturation pattern of erythroid series in a Sickle cell disease patient. Proerythroblast with a perinuclear pale zone (Red arrow head), early erythroblast (Green arrow head), Intermediate erythroblast (Purple arrow head) and late erythroblast (orange arrow head). (Bone marrow aspirate; Giemsa stain; 400X).

## Discussion

Nucleated RBCs (nRBCs) are immature RBCs normally they are not seen in the peripheral blood after the neonatal period. Their presence in peripheral blood of 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 for identifying abnormal cells, and the samples involved should be reviewed manually [1, 2].

The presence of nRBCs in the peripheral blood is usually associated with malignant neoplasm' s, bone marrow diseases, and other serious disorders [11, 12, 13]. The bone marrow has a special architecture, its disruption leads to obvious changes. Normal mature bone marrow cells are deformable, so they can squeeze through small " portholes" in the endothelium to enter the peripheral circulation. [14] Normoblasts and immature granulocytes, however, are less deformable and rarely enter the circulation. Their presence in the peripheral blood indicates that the mechanism of bone marrow barrier has been disrupted or extramedullary hematopoietic mechanism has been activated.

The spectrum of haematological disorders in patients presenting with normoblastemia is very wide. Therefore, in the present study we categorized the patients presenting with normoblastemia into non-infiltrating and infiltrating

conditions based on the mechanisms involved. We also studied the distribution of the spectrum of conditions presenting with normoblastemia according to different age groups and sex.

The various mechanisms involved in non-infiltrating conditions were hyposplenism/asplenism, anemia and compensatory erythropoiesis, hypoxia and other miscellaneous causes. Normoblasts that escape from the marrow are normally cleared by the spleen, their presence in the peripheral blood suggests a hyposplenic state [15]. Marrow stress and release of many normoblasts can overcome 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 [12].

In our study, a total of 4 cases of AIHAs were reported and 3 out of 4 cases were females. The range of nRBCs in AIHAs was 1-25 nRBCs/100WBCs on peripheral smear (PS) examination. In Burkett *et al* study, out of a total of 42 cases of non-infiltrating conditions presenting with leukoerythroblastic blood picture, 11 (26%) cases were Hemolytic anemias which constituted majority of cases [16]. One case of sickle cell anemia was seen in a female patient of 19 years who presented with sickle cell crisis and had severe bone pain. The number of nRBCs were 35/100WBCs on PS examination. Among the non-infiltrating cases, the maximum number of cases (n=49) were under the anemia and compensatory erythropoiesis category. In every type of severe anemia i.e. hemolytic, nutritional or anemia of blood loss normoblastemia is caused by hypoxic erythropoietin-induced compensatory erythropoiesis [17].

Normoblastemia occurs in response to hypoxia in both anemia and cardiopulmonary disorders. In anemia, hypoxia results when the reduced hemoglobin concentration causes a corresponding decline in the oxygen carrying capacity of the blood [18, 19]. Cardiopulmonary hypoxia, however, may involve numerous 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 [20, 21]. In our study, two male patients in the age group of 51-60 years had congestive cardiac failure and presented with normoblastemia.

Sepsis evokes inflammatory response by stimulating the production of inflammatory mediators like interleukin, like interleukin-6 [1, 2]. In our study, 6 cases of sepsis showed neutrophilic leukocytosis and thrombocytopenia on PS examination. The range of nRBCs was 1-45/100WBCs. Retief prospectively studied 37 adults with leukoerythroblastosis & found that one-third were suffering from acute infections, and the rest had various hemolytic states and other nonmalignant disorders [19].

Marrow replacement can occur in leukemia, myeloma, or lymphoma. 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 [22].

Malignancies reveal always 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. In our study out of 28 infiltrating conditions, 9 cases were CML. The range of nRBCs in CML cases was 1-5 nRBCs/100WBCs. Two cases of NHLs were diagnosed on bone marrow biopsy as aspiration yielded a dry tap. In a study conducted by Conlan *et al*, 317 patients with NHL treated with chemotherapy were evaluated for the presence of hematologic abnormalities at diagnostic staging. Normoblastemia was present in 2% of cases [23].

In the present study, one case presenting with normoblastemia showed metastatic deposits in the bone marrow. This case had the highest number of nRBCs (35nRBCs/100WBCs) among all the infiltrative conditions followed by the two cases of myelofibrosis which had 8 and 10nRBCs/100WBCs. In a study conducted at the Mayo clinic, out of a total of 37 patients with leukoerythroblastic picture, 1/3$^{rd}$ of the patients had underlying malignancy [24]. In a study by Danise *et al*., a total of 478 patients were analyzed with the automated hematology analyzer and nRBCs were found in nearly all onco-hematological diseases at diagnosis [5].

NRBCs present in the peripheral blood of several hematological and non-hematological conditions, are usually associated with bad prognosis. Detection of nRBCs is an independent risk of poor outcome, where the mortality increases with the increasing nRBC concentration. Therefore, it is necessary to analyze the frequency of various causes in order to determine the value of normoblastemia as a diagnostic clue.

## Conclusion

The spectrum of haematological disorders in patients presenting with normoblastemia is very wide. Various infiltrating & non-infiltrating conditions present as normoblastemia ranging from infections, sepsis, haemorrhage, haemolysis, anemias to leukemias, lymphomas & metastases. Normoblastemia offers an invaluable insight into disease processes or progressions. 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. This study emphasizes on the importance of finding even single nRBC that may lead to more timely medical intervention, thus increasing the chance of a positive outcome.

**Abbreviations:** nRBC– Nucleated red blood cells, WBC-White blood cells, AML-Acute myeloid leukemia, ALL-Acute lymphocytic leukemia, CML- Chronic myeloid leukemia, CLL- Chronic lymphocytic leukemia, MDS-Myelodysplastic syndrome, NHL- Non-Hodgkin' s lymphoma, PS-Peripheral smear

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