

# MEGALOBlastic ANEMIA IN ADULTS WITH NEW-ONSET PANCYTOPENIA ON PERIPHERAL SMEAR

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## ABSTRACT

**Objectives:** To determine the frequency of megaloblastic anemia in patients with a new onset of pancytopenia on peripheral smear.

**Materials and Methods:** This cross-sectional study was conducted in the Department of Medicine, Khyber Teaching Hospital, Peshawar from 1<sup>st</sup> February 2021 to 31<sup>st</sup> July 2021. A total of 109 patients participated in the study after fulfilling the inclusion criteria. Patients with pancytopenia on peripheral smear underwent bone marrow biopsy. Megaloblastic anemia as the cause of pancytopenia was confirmed after bone marrow biopsy reports were available. The results were stratified into tables based on study participants' demographics. Data was analyzed by SPSS 23 and presented in tables.

**Results:** Megaloblastic anemia was observed in 42.2% of patients presenting with pancytopenia on peripheral smear. 66.1% of these were male and 33.9% were female.

**Conclusion:** A large number of patients with pancytopenia on initial investigations were diagnosed to be suffering from megaloblastic anemia in our study.

**Keywords:** Pancytopenia; Megaloblastic anemia; Peripheral smear; Bone marrow biopsy

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## INTRODUCTION

Megaloblastic anemia (MA) refers to a variety of anemias that share the features of having macrocytes on the peripheral blood smear and megaloblasts in the bone marrow.<sup>1</sup> Megaloblastic anemia's pathophysiology is mostly centered on poor DNA synthesis, which prevents nuclear division. Contrarily, cytoplasmic maturation has less of a problem. The huge size of megaloblasts is explained by the asynchronous maturation that results between the nucleus and cytoplasm of erythroblasts. The most common cause of megaloblastic anemia in our part of the world is undernutrition, particularly a deficiency in vitamin B12 and folate, which are essential for DNA synthesis. Adults require 50 to 100 ug of folic acid per day.<sup>2</sup>

The jejunum is where folic acid is largely absorbed. Folic acid can be stored by humans for 3–4 months on average.<sup>3</sup> Its lack is primarily caused by insufficient intake, such as in cases of malnutrition, either from starvation or

chronic alcohol abuse, or increased demand, such as in cases of pregnancy, hemolysis, hemodialysis, and malabsorption.

Pancytopenia which encompasses anemia, leucopenia, and thrombocytopenia is the hallmark of megaloblastic anemia. Pancytopenia occurs when the hemoglobin level is below 9 g/dl, the leucocyte count is below  $4 \times 10^3/l$ , and the platelet count is below  $100 \times 10^3/l$ .<sup>4</sup> Pancytopenia can be caused by several hematopoietic and non-hematopoietic conditions, including those that reduce the production of hematopoietic cells, cause the marrow to be replaced by abnormal cells, inhibit marrow growth and differentiation, cause hematopoiesis to fail and result in cell death, cause defective cell formation, cause antibody-mediated cell sequestration or destruction, or trap cells in an enlarged and overactive reticuloendothelial system.<sup>1</sup>

Due to genetic diversity and various ethnic communities, the prevalence of megaloblastic anemia as a cause of pancytopenia varies widely among studies, ranging from 16.67% to 74.04%.<sup>1</sup> Incidence of pancytopenia has a bimodal presentation that is typically found in children and adults in their third and fourth decades. Anemia, bicytopenia, or pancytopenia may be present. The mean corpuscular volume (MCV), which is often greater than 100fL, on the peripheral smear indicates anemia with macrocytosis in most cases.<sup>1,2</sup>

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This study is intended to ascertain the prevalence of megaloblastic anemia in persons with newly diagnosed pancytopenia on peripheral smears. It is also imperative to gather local evidence to determine the true burden of this disease because no previous research has been done on the subject. This study will open the door for additional investigation and assist in designing the diagnostic and treatment approach for patients with pancytopenia from megaloblastic anemia.

## MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Medicine, Khyber Teaching Hospital, Peshawar from 1<sup>st</sup> February 2021 to 31<sup>st</sup> July 2021. The Department of Medicine is a four-unit department with 24-hour emergency services and a daily outpatient department run from 9 am to 3 pm, Monday to Friday. A total of 109 patients were enrolled in the study. The sample size was calculated by using the expected frequency of megaloblastic anemia=16.67%<sup>1</sup> with a Margin of error of 7% and confidence level 95%. Non-probability consecutive sampling technique was used. Patients of both genders between 18-60 years of age with new onset pancytopenia on peripheral smear were included in the study. Patients with a history of malignancy, any bleeding disorder, decompensated chronic liver parenchymal disease, hypothyroidism, alcohol ingestion, and pregnant females (proven on ultrasound) were excluded from the study.

109 patients fulfilling the inclusion criteria from outdoor and in-door departments of Medicine, KTH, Peshawar were included in the study after permission from the ethical committee. Baseline demographic information of patients (age, gender, weight on the weighing scale) was taken. Informed consent was taken ensuring confidentiality and the fact that there was no risk involved to the patients while taking part in this study. Bone marrow biopsy was performed under aseptic conditions by a qualified pathologist. Data regarding megaloblastic anemia was noted as per the operational definition by the researcher and recorded on specially designed proforma. Data was entered and analyzed using the statistical analysis program SPSS version 23. Frequencies and percentages were computed for categorical variables like gender and megaloblastic anemia. Mean + SD was used to calculate quantitative variables like age and weight. Megaloblastic anemia was stratified for age, gender, and weight.

## RESULTS

The age range in this study was from 18 to 60 years with a mean age of 35.85 + 6.92 years and a mean weight of 79.49 + 9.84 kg. Male patients were 66.1% and females were 33.9%. Megaloblastic anemia was observed in 42.2% of patients as shown in Table 1. Stratification of megaloblastic anemia for age, gender, and weight are shown in Tables 2, 3, and 4 respectively.

**Table 1: Frequency of patients according to megaloblastic anemia n = 109**

Megaloblastic anemia	Frequency	%age
Yes	46	42.2%
No	63	57.8%
Total	109	100%

**Table 2: Stratification of megaloblastic anemia for age**

Age (years)	Megaloblastic anemia	
	Yes	No
18-40	22(28.9%)	54(71.1%)
41-60	24(72.7%)	9(27.3%)
Total	46(42.2%)	63(57.8%)

**Table 3: Stratification of megaloblastic anemia for gender**

Gender	Megaloblastic anemia	
	Yes	No
Male	28(38.9%)	44(61.1%)
Female	18(48.6%)	19(51.4%)
Total	46(42.2%)	63(57.8%)

**Table 4: Stratification of megaloblastic anemia for weight**

Gender	Megaloblastic anemia	
	Yes	No
<80	14(20.9%)	53(79.1%)
>80	32(76.2%)	10(23.8%)
Total	46(42.2%)	63(57.8%)

## DISCUSSION

A typical hematologic issue seen in clinical practice is pancytopenia. It is identified by the peripheral smear test results showing hemoglobin levels below 9 g/dL, total leukocyte counts below 4,000/uL, and platelet counts below 100,000/uL without a prior history of pancytopenia.<sup>2,5</sup> Its causes are varied. The evaluation of pancytopenia's etiology begins with a history, physical exam, and laboratory tests, including the fundamental hematological, biochemical, radiological, and histological tests. Pancytopenia's genesis can be broadly divided into two types: those that are central and involve production-related diseases, and those that are peripheral and entail greater destruction-related disorders. These factors may have an individual or combined effect on pancytopenia. While peripheral cell death can be linked to numerous autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, and splenic sequestration), pancytopenia caused by decreased production is typically secondary to dietary inadequacies. The severe acute respiratory syndrome coronavirus 2 has been linked to pancytopenia in the current COVID-19 pandemic (SARS-CoV 2).<sup>1</sup>

The evaluation of bone marrow is a quick and safe

invasive operation that is only somewhat uncomfortable to execute. It is a crucial diagnostic tool for assessing pancytopenia cases. In 75% of instances, a bone marrow aspiration confirms the pancytopenia diagnosis.<sup>6</sup> Megaloblastic anemia, hematological cancers, and hypoplastic marrow are the most frequent etiologies identified. According to a 2013 Indian study, the most frequent causes of myelosuppression are megaloblastic anemia, infections, hypersplenism, and myelosuppression brought on by cancer, chemotherapy, medication toxicity, or radiotherapy. Megaloblastic anemia, followed by aplastic anemia, was found to be the most common cause in an earlier study conducted in India.<sup>7</sup> These findings are seconded by a local study conducted in Karachi in 2013, which concluded that the most common cause of pancytopenia is megaloblastic anemia followed by acute myeloid leukemia and aplastic anemia.<sup>8</sup>

Megaloblastic anemia is identified by the simultaneous presence of MCV >100fL and MCH >32fL on a complete blood count and segmented neutrophils on a peripheral smear. According to a study by Hossain MZ, et al., persons with newly diagnosed pancytopenia had a 16.67% frequency of megaloblastic anemia.<sup>5</sup> Another study by Gayathri BN, et al. revealed that adults with newly diagnosed pancytopenia had a prevalence of megaloblastic anemia equal to 74.04%.<sup>4</sup> The two micronutrients, folate, and cobalamin, which work together to produce the thymidylic acid required for DNA synthesis, are involved in the pathogenesis of megaloblastic anemia. Therefore, a shortage in the use of folate is what leads to the megaloblastic arrest in cobalamin insufficiency. Vegetarianism-related dietary vitamin B12 insufficiency results in hyper-homocysteinemia, which ultimately becomes the cause of megaloblastic anemia.<sup>8</sup>

Since strict vegetarianism is not practiced in Pakistan, poverty, poor cooking practices, or food taboos are likely the root causes of vitamin B12 insufficiency, which still needs additional investigation. Physicians should treat patients who present with anemia symptoms including pallor and weakness and/or who are later confirmed with anemia with a high index of suspicion for vitamin B12 insufficiency.

The clinical-hematological and histological profiles of 109 patients with pancytopenia associated with megaloblastic anemia were examined in the current investigation. In our investigation, megaloblastic anemia was determined to be the cause of pancytopenia in 42.2% of the cases. Other local research has supported similar findings.<sup>8,10</sup>

Characteristic bone marrow results in our investigation allowed for the diagnosis of megaloblastic anemia. Megaloblastic anemia is becoming more common, which has been attributed to the increasing prevalence of nutritional anemia in India. Due to sociological and geographic

parallels, nutritional anemia may also be to blame for the rise of megaloblastic anemia in Pakistan. In Pakistan, vitamin B12 deficiency is more common than folate deficiency among nutritional anemias.<sup>11</sup> It was beyond the scope of this study to look into the causes of megaloblastic anemia. The Pancytopenia series from Tariq Aziz et al.<sup>12</sup> and Iqbal et al.<sup>13</sup> is roughly equivalent. Megaloblastic anemia was discovered to be the primary contributor to pancytopenia in each of these trials. Megaloblastic anemia was more common in these studies, which was likely a result of the high incidence of nutritional anemia in developing nations. According to our study, which was validated by other studies, the highest incidence of megaloblastic anemia occurs in the middle age group (41–60 years) with an equal sex ratio. In contrast, Khanduri et al. discovered in their study that the majority of patients with pancytopenia were in the age range 10-30 years (48%) and mostly females (71%).<sup>14</sup>

## CONCLUSION

In our study, a high majority of pancytopenia patients were initially found to have megaloblastic anemia. Global awareness of the effects of folic acid and vitamin B12 deficiency on health, including megaloblastic anemia, has grown. Despite having a vague or extremely diverse presentation, vitamin B12 insufficiency can cause serious health problems in humans that, if not treated or detected in time, can be fatal. Since strict vegetarianism is not practiced in Pakistan, likely, food taboos, poor cooking practices, and/or poverty are the root reasons for vitamin B12 deficiency, all of which require additional investigation. Intermittent vitamin B12 supplement dosing, more accurate assessments of B12 bioavailability in fermented vegetarian meals, and public knowledge of food preparation and handling practices to reduce the loss of vitamin B12 and folate are all areas that need further study.

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**Authors Contribution:**

Following authors have made substantial contributions to the manuscript as under

Authors	Conceived & designed the analysis	Collected the data	Contributed data or analysis tools	Performed the analysis	Wrote the paper	Other contribution
Razaq S	✓	✗	✓	✗	✓	✗
Badshah A	✓	✓	✗	✓	✓	✗
Rehman O	✓	✗	✗	✓	✗	✗
Munib N	✗	✗	✓	✓	✗	✓
Shafi M	✓	✗	✓	✓	✗	✗

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Ethical Approval:**

**This Manuscript was approved by the Ethical Review Board of  
Khyber Medical College, Peshawar Vide No. 908/DME/KMC.**

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