

## PANCYTOPENIA: MEGALOBLASTIC ANEMIA IS STILL THE COMMONEST CAUSE

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### ABSTRACT

**Objectives:** To find out the frequency of the different causes of Pancytopenia and also to specifically detect the percentage of vitamin B<sub>12</sub> deficiency amongst these patients.

**Methodology:** It is a prospective study carried out in Medical Unit I (Ward 5) of Jinnah Postgraduate Medical Centre Karachi from March to August 2007. A total of 88 patients were included after a detailed history and examinations the information was recorded on Proforma. Findings of aspiration and trephine biopsies were interpreted in the light of history, clinical examination and peripheral blood findings.

**Results:** Out of 88 patients suffering from Pancytopenia, a large number (40.90%) were diagnosed as Megaloblastic Anemia, out of which 77.77 % had vitamin B12 deficiency. Aplastic anemia was found in 28 (31.88%) patients followed by other less common causes.

**Conclusion:** Megaloblastic anemia was found in largest number of patients who were found to have Pancytopenia on initial investigations and majority of such patients were found to be deficient in Vitamin B<sub>12</sub>.

**KEY WORDS:** Pancytopenia, Megaloblastic Anemia, Vitamin B<sub>12</sub> deficiency.

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## INTRODUCTION

Cytopenia is a reduction in the number in any of the three types of peripheral blood cell. A reduction in all three types of cellular components is termed pancytopenia and this involves anemia, leucopenia, and thrombocytopenia.<sup>1</sup> Initially, mild impairment in marrow function may go undetected and pancytopenia may become apparent only during times of stress or increased demand (e.g., bleeding or infection). As severity increases, the peripheral blood count decreases even in the steady state. The basic investigations in a suspected case of pancytopenia include Complete Blood Count with peripheral blood film and Reticulocyte count. In peripheral film, blast cells may be evident in patients where pancytopenia is due to malignant infiltration. Neutrophils might show

absent granulation and nuclear abnormalities suggestive of pre-leukemic or myelodysplastic states. Bone marrow examination is indicated in all cases of pancytopenia where the underlying cause is not obvious. This is particularly needed to exclude leukemia or other malignant infiltration.

Megaloblastic anemia has been found to be the most common cause of Pancytopenia worldwide. Diagnosis of megaloblastic anemia requires only complete blood count, peripheral blood smear and bone marrow cytology, which is cost effective. Nutritional factors, recurrent infection and deficiencies of vitamin B<sub>12</sub> and folate seem to be associated strongly with megaloblastic anemia.<sup>2</sup>

Megaloblastic anemia and aplastic anemia are important causes of pancytopenia in India. Since both may have presence of macrocytes, peripheral smear examination alone may pose a difficulty in distinction between the two in the absence of macro-ovalocytes and hyper segmented neutrophils.<sup>3</sup> Evidence in previous studies suggests that myeloperoxidase index measurement may assist differentiation of megaloblastic from aplastic anemia.<sup>4</sup>

There is increased worldwide concern about the consequences of folic acid and vitamin B<sub>12</sub> deficiencies on health, which includes megaloblastic anemia.<sup>5</sup> The breast-fed infant of a vitamin B<sub>12</sub>-deficient mother is also at risk of developing severe developmental abnormalities, growth failure, and anemia. Dietary deficiency of vitamin B<sub>12</sub> due to vegetarianism is increasing and also causes hyperhomocysteinemia. Elevated methylmalonic acid and/or total homocysteine have been found to be sensitive markers of vitamin B<sub>12</sub>-deficient diets.<sup>6</sup>

Vitamin B<sub>12</sub> deficiency has a broad spectrum of etiology such as inadequate dietary intake, impaired absorption in the setting of either intrinsic factor deficiency (pernicious anemia) and/or generalized malabsorption syndromes such as Crohn's disease, intestinal infestation by the fish tapeworm *Diphyllobothrium*, ileal resection and hereditary causes such as severe MTHFR deficiency, homocystinuria, and transcobalamin deficiency. Inadequate dietary

vitamin B<sub>12</sub> intake is one of the common causes of deficiency amongst vegetarians as vitamin B<sub>12</sub> is known to occur mostly in animal products. Latest research is focused on intermittent vitamin B<sub>12</sub> supplementation as well as detecting bioavailability of B<sub>12</sub> in fermented vegetarian foods so as to find out the appropriate diet to reduce or eliminate this deficiency. Moreover, vitamin B<sub>12</sub> deficiency is difficult to pick up clinically as it presents with vague complaints such as decreased mental and/or physical work capacity, reduced attention span, memory loss, irritability and low mood.<sup>7</sup>

The objective of this study was to find out the frequency of the different causes of Pancytopenia and also to specifically find out the number of vitamin B<sub>12</sub> deficient patients in our study group.

## METHODOLOGY

This study was carried in Medical Unit-I (Ward 5) of Jinnah Postgraduate Medical Centre Karachi from March 2007 to August 2007. A total of 88 Patients were included in the study fulfilling the criteria of pancytopenia by using the technique of time based sampling. This was done under simple random sampling design. Detailed history was recorded which include detailed questions on diet with special focus on intake of animal products such as meat, eggs and milk, any episodes or nausea, vomiting abdominal pain, loose and/or bulky stools, episodes of worms in stool, any diagnosed co-morbid diseases, prior drug intake, prior infections and surgeries, radiation exposure and examinations were done and recorded on Proforma. Patients on chemotherapy were excluded.

Blood counts obtained prior to transfusion were conducted on an automated blood analyzer (Sysmex). Along with this manual smear were also obtained. Differential leukocyte count and red cell morphology was done manually by staining the blood smears by Giemsa stains. Serum was sent for RBC folate and B<sub>12</sub> levels, reticulocyte counts were obtained and Hepatitis serology was performed. Bone marrow aspiration and wherever required, a trephine biopsy was also performed, both of which were

independently reviewed by one investigator who was unaware of the patient's clinical presentation. Anisocytosis and poikilocytosis were graded according to the degree of variation in size and shape.

Findings of aspiration and trephine biopsies were interpreted in the light of history, clinical examination and peripheral blood findings. Bone marrow examination was done in 60 patients whereas, in rest of the patients, bone marrow examination could not be done either because they were very ill or were meeting other criteria of diagnosis. Statistical methods including descriptive statistics (mean, median,) were applied and data analysis was done on SPSS v10 for windows.

## RESULTS

Eighty eight patients were enrolled in the study. The patients' age ranged from 15 years to 60 years with mean of 32.6 years. The mean age was 26.6 years for those in which we found aplastic anemia and 38.6 years for those in which megaloblastic anemia was discovered. The majority of the patients (59%) were females while males made up rest of the 41%. Quite interestingly aplastic anemia was found in 20 out of the 28 male patients.

Out of the 88 patients, 36 (40.90%) were diagnosed with megaloblastic anemia, out of which 28 (77.77%) had vitamin B<sub>12</sub> deficiency and eight patients (22.33%) were found to be deficient in folate. Amongst the patients with vitamin B<sub>12</sub> deficiency the 22 patients (78.57%) had a history of inadequate intake of animal products with a predominantly vegetable and fruit-based

Table-I: Etiology of Pancytopenia

<i>Etiology</i>	<i>No. of cases (%)</i>
Megaloblastic Anemia	36 (40.90)
Aplastic Anemia	28 (31.88)
Acute Leukemia	08 (09.99)
Hypersplenism	06 (06.81)
Chronic Malaria	04 (04.55)
Myelodysplastic syndrome	04 (04.55)
None	02 (02.77)

diet, three patients (10.71%) reported an intake of anti-ulcer medications over a prolonged period of time, two patients (7.14%) had a history of ileal resection due to subacute intestinal obstruction because of abdominal tuberculosis while one patient (3.57%) reported malabsorption syndrome on history.

Aplastic anemia was noted in 28 patients (31.88%) out of whom five patients (17%) gave history of drug intake. Acute myeloid leukemia was recorded in eight (9.99%) patients. Six patients (6.81%) had Hypersplenism, while Chronic Malaria was found in four patients (4.55%). Another four patients were found to have myelodysplastic syndrome, while no cause was found in two patients (2.77%) (Table-I).

Pallor and weakness was the most common symptom (98%) followed by shortness of breath (88%), abdominal pain (56%), mass in the abdomen (54%), bone pains (44%), petechial hemorrhages (36%), jaundice (30%), edema (24%), lymphadenopathy (10%), ascites (5%) (Table-II).

## DISCUSSION

We found that megaloblastic anemia was the most common cause of Pancytopenia at 40.9% which falls in the wide range of results reported in other local studies that vary from 38% to 72%.<sup>8-11</sup> In a study conducted in Malaysia,

Table-II: Clinical features of Pancytopenia(%)

<i>Clinical Features</i>	<i>%</i>
Pallor	98
Weakness	98
Shortness of Breath	88
Abdominal Pain	56
Mass in Abdomen	54
Bone Pain	44
Petechial Hemorrhages	36
Jaundice	30
Edema	24
Lymphadenopathy	10
Ascites	05

pancytopenia was found in 64% patients with megaloblastic anemia.<sup>12</sup> In the West, pancytopenia has become less common in patients with megaloblastic anemia, as only 13.7% of cases were reported in a study done in New York.<sup>7</sup>

Most of the patients gave the history of poor eating habits i.e. food taboos, poor quality of food and self-avoidance of necessary foods. The high prevalence of nutritional anemias in India has been cited for the increased frequency of megaloblastic anemia. Because of geographical and social similarities, nutritional anemias may also be responsible for increased frequency of megaloblastic anemia in northern region of Pakistan. Among the nutritional anemia's, vitamin B<sub>12</sub> deficiency is more prevalent than folate deficiency in Pakistan<sup>13</sup> and our study reported similar results.

The second most common cause of pancytopenia in this study was aplastic anemia (31.8% patients) while in other similar studies it varied from 38% to 41%<sup>11,14,15</sup>, although it was higher than Aplastic Anemia in the West which is reported to be between 10-25%. Aplastic anemia is thought to be more common in the Orient than in western world which may be related to environmental factors such as increased exposure to toxic chemicals rather than genetic factors as this increase is not seen in people of oriental ancestry presently living in US.<sup>16,17</sup> In addition, easy availability of over the counter medications in Asian countries particularly in the developing world could be implicated in higher percentage of aplastic anemia patients as studies from Thailand implicate pesticide exposure as a common etiological agent for aplastic anemia.<sup>18,19</sup> As Pakistan is also an agricultural country, pesticide may be an important factor in the high incidence of aplastic anemia. History of drug exposure prior to the development of symptoms of pancytopenia is another risk factor observed in our study in those patient found to have aplastic bone marrow.

Acute leukemia was found to be the third most common cause of Pancytopenia in our study which is similar to a study conducted by Savage et al<sup>20</sup> who observed that the most common cause of pancytopenia was megaloblastic

anemia followed by aplastic anemia, acute leukemia, AIDS and hypersplenism, and another study by Kumar who reported the causes of pancytopenia in order of frequency as Aplastic Anemia at 29.5%, megaloblastic anemia at 22%, Aleukemic Leukemia or lymphoma (18%) and hypersplenism at 11.4%.<sup>8</sup>

In our study pallor and weakness were the most common presentations (98%) with which patients presented to the physicians. Similar results have been reported in previous studies.<sup>11,13</sup> The frequency of other clinical features was variable and different from those of other studies possibly due to the broad spectrum of etiologies or disorders behind Pancytopenia.

## CONCLUSIONS

A large number of patients with pancytopenia on initial investigations were later diagnosed to be suffering from Megaloblastic anemia in our study mainly because of vitamin B<sub>12</sub> deficiency and in some cases due to folate deficiency, while Aplastic Anemia surprisingly came second followed by Acute Leukemia and Hypersplenism. There is increased worldwide concern about the consequences of folic acid and vitamin B<sub>12</sub> deficiencies on health, which include megaloblastic anemia. Dietary deficiency of vitamin B<sub>12</sub> due to vegetarianism is increasing and it also causes hyperhomocysteinemia. Thus vitamin B<sub>12</sub> deficiency, though having vague or highly variable presentation, yet can lead to many complications in the human body which can prove fatal if not diagnosed in time or left untreated. As much physicians should have a high index of suspicion for Vitamin B<sub>12</sub> deficiency when dealing with patients presenting with symptoms of anemia such as pallor and weakness and/or diagnosed with pancytopenia on further workup.

In Pakistan strict vegetarianism is not in practice so probably poverty, bad cooking habits or food taboos may be the causes behind vitamin B<sub>12</sub> deficiency which need further research. Areas for research also include intermittent vitamin B<sub>12</sub> supplement dosing and better measurements of the bioavailability of B<sub>12</sub> in fermented vegetarian foods and awareness in population



about the process and handling of food to prevent the loss of vitamin B<sub>12</sub> and folate.

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### Authors Contribution:

Dr. Tariq Aziz & Dr. Liaquat Ali conceived, designed and did statistical analysis & editing of manuscript. Dr. Tahir Ansari, Dr. Hammad Bin Liaquat, Dr. Shahnaz Shah did data collection and manuscript writing while Dr. Jamal Ara reviewed the manuscript before its submission for publication.