A CLINICAL STUDY OF CYTOPENIAS WITH SPECIAL REFERENCE TO MEGALOBLASTIC ANAEMIA IN A TERTIARY CARE CENTRE

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ABSTRACT

BACKGROUND

Peripheral cytopenia is defined as reduction in either of the cellular elements of blood, i.e. red cells, white cells, or platelets. The aetiology varies widely ranging from transient marrow suppression by viral infections to marrow infiltration by life-threatening malignancy. Megaloblastic anaemia is not uncommon in India. Diagnosing this disease assumes great clinical importance since it responds exceedingly well to treatment.

OBJECTIVES

To study the aetiology and clinical profile of patients with cytopenias with special reference being made for cytopenias in megaloblastic anaemia.

MATERIALS AND METHODS

An observational study was conducted on 149 patients who presented with cytopenias to the Dept. of General Medicine and Dept. of Haematology, GMCH, Guwahati, during the period of June 2014 to May 2015. Their clinical profile, complete haemogram, and bone marrow examination were studied.

RESULTS

A total of 149 patients with cytopenia were studied. The patients were predominantly males with mean age of 37 years. Bicytopenia (59.7%) was more commonly seen than pancytopenia (40.3%). The most common cause of cytopenia was Megaloblastic Anaemia (28.2%) followed by Acute Myeloid Leukaemia (22.1%). Majority of the patients presented with Generalised Weakness (94.6%) and Fatigue (74.5%). Most common physical finding was Pallor (94.6%) followed by Splenomegaly (40.3%) and Hepatomegaly (36.2%). Of the 42 patients with Megaloblastic Anaemia, majority of the patients had a macrocytic (71.5%) peripheral blood smear followed by dimorphic picture (21.3%) of which all but 7 patients had hypersegmented neutrophils. Bone marrow examination was done in 31 patients of megaloblastic anaemia, which showed mainly a hypercellular marrow (83.8%).

CONCLUSION

A detailed clinical history and meticulous physical examination along with a complete haemogram and bone marrow examination in patients presenting with cytopenias is useful in diagnosing the aetiology and initiating quick management.

KEYWORDS

Cytopenia, Bicytopenia, Pancytopenia, Megaloblastic Anaemia.

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INTRODUCTION: Peripheral cytopenia is defined as reduction in either of the cellular elements of blood, i.e., red cells, white cells, or platelets. Bicytopenia is reduction in any of the two cell lines and pancytopenia is reduction in all the three.[1] A study by Naseem et al (2011) defined cytopenia as: Haemoglobin <10 g/dL, Total Leukocyte Count $<4\times10^9$/L, and Platelet Count $<100\times10^9$/L.[2]

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In many patients, the cause of cytopenia is obvious and it is not difficult to establish the correct diagnosis after a first examination.[3] In some patients, cytopenia may be detected as an incidental finding, whereas other patients may be severely ill.[4] Traditionally, cytopenias have been classified as deficiency related (i.e. a nutritional or hormone deficiency), immune mediated, bone marrow failure based, or idiopathic cytopenias.[3] The aetiology of bicytopenia and pancytopenia varies widely ranging from transient marrow viral suppression to marrow infiltration by life-threatening malignancy. These may also be caused iatrogenically secondary to certain drugs, chemotherapy, or radiotherapy for malignancies. The frequency of pattern of diseases causing them varies in different populations.

The bone marrow picture may vary depending on the aetiology from normocellular with nonspecific changes to hypercellular being replaced completely by malignant cells. According to aetiology, degree, and duration of the impairment, clinically these can lead to fever, pallor, infection, or serious illness and death. Knowing the exact aetiology is important for specific treatment and prognostication,[2] there is considerable overlap between the causes and diagnostic approach of bicytopenia and pancytopenia.[2] Bone marrow evaluation is an invaluable diagnostic procedure, which may confirm the diagnosis of suspected cytopenias.[5] Megaloblastic anaemia is characterised by ineffective erythropoiesis with premature death of cells, a decreased output of Red Blood Cells (RBCs) from bone marrow, and consequently anaemia.[6] Megaloblastic anaemia is suspected in anaemic patients with macrocytic indices (Mean Corpuscular Volume [MCV] >100 fl). The earliest change is the development of macrocytosis and elevated MCV without anaemia.[7]

Diagnosis is usually based on Complete Blood Count (CBC) and peripheral smear, which may show macroovalocytes, hypersegmented neutrophils, and reticulocytopenia. In advanced cases, neutropenia and thrombocytopenia develop simulating aplastic anaemia or leukaemia. Megaloblastic anaemia is an important cause of cytopenias, but to best of our knowledge, there are not many studies quoting its incidence.[8]

MATERIALS AND METHODS: It is a Hospital-Based Observational, Cross-Sectional Descriptive Study. This study was conducted in the Department of Medicine and Department of Haematology, Gauhati Medical College and Hospital, Guwahati. Ethical clearance was obtained from ethical committee of Gauhati Medical College. The period of study is from 1st June, 2014, to 31st May, 2015. 149 patients with cytopenias who satisfied the laid down inclusion and exclusion criteria were selected and studied with the help of a proforma.

DEFINITION OF CYTOPENIA: Haemoglobin <10 g/dL, Total Leucocyte Count $<4\times10^9$/L and Platelet Count $<100\times10^9$/L.[2]

Inclusion Criteria:

Patients with any two or all of the following:

- Haemoglobin <10 g/dL.
- Total leucocyte count $<4\times10^9$/L.
- Platelet count $<100\times10^9$/L.

Exclusion Criteria:

- Prior exposure to chemotherapeutic agents.
- Prior exposure to radiation.

Study Design:

1. **Clinical:** The included patients were subjected to:
   a) A detailed history taking as per proforma.
   b) A detailed meticulous physical examination as per proforma.
2. **Investigations:**
   - Complete Haemogram.

Under all aseptic precautions 3 mL of blood was collected after venepuncture in an Ethylenediaminetetraacetic (EDTA) Vacutainer. The samples were sent to the lab for the Complete Haemogram, which were done by semi-automated electronic cell counter (Sysmex XT4000i, Transasia Bio-Medicals) and were again crosschecked manually during peripheral smear examination. Anaemia was defined as mild (Hb 9-10 gm%), moderate (Hb 5-9 gm%) and severe (Hb <5 gm%).[(9)] Leucopenia was defined as mild (leucocyte count 3,000-4000/mm3), moderate (leucocyte count 1,000-3,000/mm3) and severe (leucocyte count <1,000/mm3).[9] Thrombocytopenia was defined as mild (platelet count >50,000/mm^3), moderate (platelet count 20,000-50,000/mm^3) and severe (Platelet count <20,000/mm^3).[10]

- Peripheral Blood Smear.
- Bone Marrow Examination.

Bone marrow examination was done in cases where indicated. It was performed using Salah's Needle after obtaining a written consent for the procedure.

- Other investigations were done in indicated cases.

Liver Function Test, Serum Creatinine, Blood Glucose, Serum Electrolytes (Na, K, Ca, Mg), Prothrombin Time/INR, Bleeding Time/Clotting Time, Erythrocyte Sedimentation Rate (ESR), Urine for Analysis and Culture, Blood Culture, Rapid Diagnostic Test for Malaria/Typhoid, Sputum for Acid Fast Bacilli (AFB) and Culture, Serum Protein Electrophoresis, Serum Iron, Ferritin, Total Iron-Binding Capacity, ANA by Immunofluorescence, Vit B_{12} estimation, Viral Markers, Urine for Bence Jones Protein, Imaging, Lymph Node Excision Biopsy.

STATISTICAL ANALYSIS: Statistical analysis was performed using GraphPad InStat version 3.00 for Windows 7, GraphPad Software, San Diego, California USA, 'www.graphpad.com'. All the statistical graphs were prepared using Microsoft Excel 2010 and Microsoft Word 2010.

RESULTS AND OBSERVATIONS: A total of 149 patients who presented with cytopenias were studied. The age ranged from 13-75 years with the mean age of 37 years.

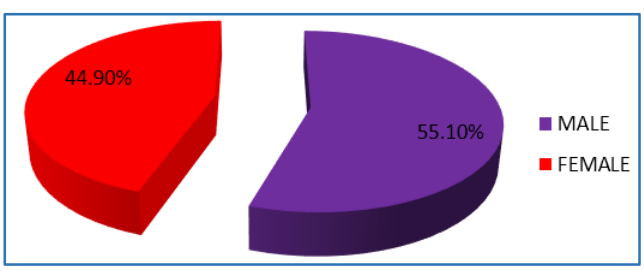

Figure 1: Sex Distribution of Patients with Cytopenias

Diagnosis	Bicytopenia	Pancytopenia	No. of Cases
Megaloblastic Anaemia	27	15	42
Acute Myeloid Leukaemia	26	7	33
Chronic Liver Disease	12	6	18
Aplastic Anaemia	2	11	13
Acute Lymphoblastic Leukaemia	7	5	12
Systemic Lupus Erythematosus	2	3	5
Myelodysplastic Syndrome	2	3	5
Septicaemia	2	2	4
Non-Hodgkin's Lymphoma	2	2	4
Malaria	2	1	3
Disseminated Tuberculosis	0	2	2
Metastasis	0	2	2
Idiopathic Thrombocytopenic Purpura	2	0	2
Chronic Myeloid Leukaemia	1	0	1
Multiple Myeloma	1	0	1
Myelofibrosis	0	1	1
Hodgkin's Lymphoma	1	0	1
Total	**89**	**60**	**149**

Table 1: Distribution of Cytopenias Based on Aetiology

The most common aetiology was found to be Megaloblastic Anaemia (28.2%) followed by AML (22.1%) and Chronic Liver Disease (12.1%). Bicytopenia was more commonly seen than pancytopenia.

Symptoms	No. of Cases (n=149)	Percentage (%)
Generalised Weakness	141	94.6
Fatigue/Malaise	111	74.5
Fever	63	42.2
Breathlessness/Palpitations	58	38.9
Abdominal Pain/Fullness	52	34.9
Bleeding Manifestations	37	24.8
Jaundice	29	19.4
Weight Loss	22	14.8
Bone Pain/Back Pain	13	8.7

Table 2: Presenting Symptoms in Patients with Cytopenias

From Table 2, we can see that generalised weakness (94.6%) is the most common symptom followed by fatigue (74.5%). Other symptoms include fever, breathlessness, and bleeding manifestations, which consists of 42.2%, 38.9%, and 24.8%, respectively.

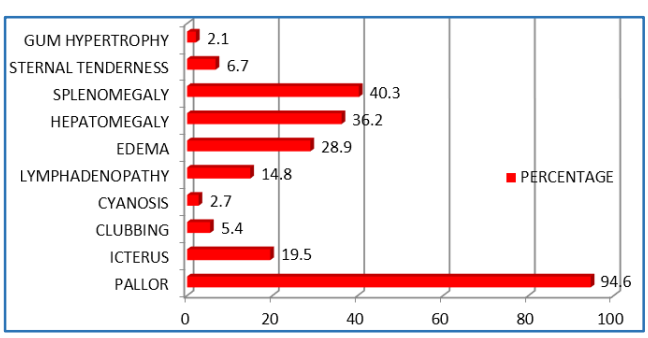

Fig. 2: Physical Findings in Patients with Cytopenias

In the 149 patients studied, the mean haemoglobin was found to be 6.7±2.3 g/dL, mean total leucocyte count was $2.74x10^9$/L and the mean platelet count was $60.6±34.3x10^9$/L. Majority of the patients in our study had normocytic and normochromic blood picture constituting 54.2% followed by macrocytic (23.5%) and microcytic hypochromic blood picture (13.4%). Dimorphic blood picture was seen only in 10.7% of the cases. Hypersegmented neutrophils were seen in all except 7 patients with megaloblastic anaemia.

Symptoms	No. of Cases (n=42)	Percentage (%)
Generalised Weakness	42	100
Fatigue/Malaise	32	76.2
Fever	11	26.2
Breathlessness/Palpitations	7	16.7
Abdominal Pain/Fullness	5	11.9
Bleeding Manifestations	4	9.5
Jaundice	6	14.3
Weight Loss	5	11.9
Bone Pain/Back Pain	0	0

Table 3: Presenting Symptoms in Patients with Megaloblastic Anaemia

From Table 3, the most common presenting symptom of megaloblastic anaemia was generalised weakness (100%) followed by fatigue and fever. Bleeding manifestation and jaundice was seen in 9.5% and 14.3% of patients respectively.

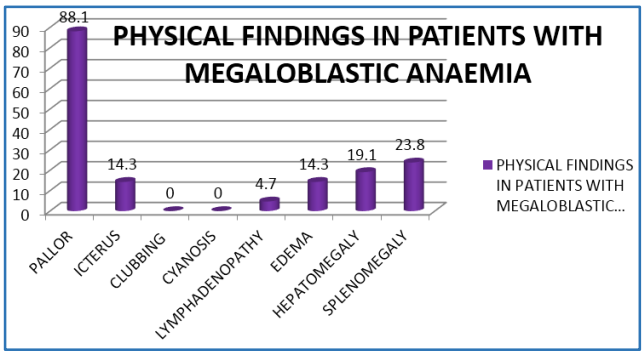

Fig. 3: Physical Findings in Patients with Megaloblastic Anaemia

The most common physical finding in patients with megaloblastic anaemia was pallor (88.1%) followed by splenomegaly (23.8%) and hepatomegaly (19.1%). Majority of the patients with megaloblastic anaemia has moderate anaemia (62.9%), mild leucopenia (53.3%), and mild thrombocytopenia (88.2%).

Haematological Parameter	Mean±SD
Haemoglobin (g/dL)	7.9±1.9
Total Leucocyte Count (x10^9/L)	3.6±1.6
Platelet Count (x10^9/L)	86.3±28.9

Table 4: Haematological Profile in Patients with Megaloblastic Anaemia

Bone Marrow Findings	No. of Cases (n=31)	Percentage (%)
Hypercellular	26	83.8
Normocellular	5	16.2
Hypocellular	0	0
Total	**31**	**100**

Table 5: Bone Marrow Findings in Patients with Megaloblastic Anaemia

Out of 42 patients with megaloblastic anaemia, bone marrow aspiration was done in 31 patients and bone marrow biopsy was done in 5 patients. Majority of the patients had hypercellular bone marrow (83.8%).

DISCUSSION: Megaloblastic anaemia is an anaemia that results from inhibition of DNA synthesis in red blood cell production. When DNA synthesis is impaired, the cell cycle cannot progress from the growth stage to mitosis stage. This leads to continuing cell growth without division, which causes nuclear-cytoplasmic asynchrony and presents as macrocytosis. The defect in red cell DNA synthesis is most often due to hypovitaminosis, specifically a deficiency of cobalamin or folate or both. Megaloblastic anaemia is a distinct type of anaemia characterised by macrocytic red blood cells and typical morphological changes in RBC precursors.[11,12] Majority of patients with cytopenias were in the age group of 31-40 years. The mean age was found to be 37 years, which is similar to other studies. Yadav et al (2015) found that the mean age of patients was 35 years.[13]

Santra et al (2010) found that the mean age was 36.9 years.[10] In the present study, the male-to-female ratio was 1.2:1, which is in concordance with other studies done by Jha et al (2013) and Santra et al (2010).[14,10] Of the 149 cases studied, megaloblastic anaemia was found to be the most common cause of cytopenia constituting 28.2% followed by Acute Myeloid Leukaemia (AML) (22.1%), Chronic Liver Disease (12.1%), and Aplastic Anaemia (8.7%). Sharif et al (2014) found that megaloblastic anaemia 41.9% was the leading cause of cytopenia in patients aged 13-60 years. This was followed by infective aetiology 19%, aplastic anaemia in 13.3%, and acute leukaemia in 10.5%.[15] Bhatnagar et al (2005) included 109 children in his study and found megaloblastic anaemia as the single most common aetiological factor in 28.4% followed by acute leukaemia and infection in 21% each and aplastic anaemia in 20% of the cases.[16]

Study	Country	Year	Sample Size	Most Common Aetiology	2nd Most Common Aetiology
Savage et al	Zimbabwe	1999	134	Megaloblastic (64%)	Aplastic (20%)
Bhatnagar et al	India	2005	109	Megaloblastic (28.4%)	Acute leukaemia (21%)
Chhabra et al	India	2012	111	Megaloblastic (31.8%)	Malignancies (25.2%)
Sharif et al	Pakistan	2014	105	Megaloblastic (41.9%)	Infective aetiology (19%)
Present study	India	2015	149	Megaloblastic (28.2%)	Acute Myeloid Leukaemia (22.1%)

Table 6: Aetiology Comparison with Other Studies

Bicytopenia was more common than pancytopenia constituting 59.7% and 40.3% respectively. Jha A et al (2013) in his study found that the frequency of bicytopenia and pancytopenia were 34.88% and 23.25% respectively.[14] Naseem et al (2011) in a study of 990 children found that 40% had bicytopenia and 17.7% had pancytopenia.[2] Sharif et al (2014) found that 62.9% had bicytopenia and 37.1% had pancytopenia on blood complete picture.[15]

Our study found that bicytopenia was more common than pancytopenia in megaloblastic anaemia. Gomber et al (1998) in a study of megaloblastic anaemia found that the incidence of pancytopenia and bicytopenia as 17.2% and 44.8% respectively[17] and Sarode et al (1989) found that the distribution of pancytopenia and bicytopenia was 43.8% and 80.5% respectively.[18]

Generalised weakness was the most common symptom constituting 94.6% of the patients. This was in concordance with other studies done by Gayatri et al (2011), Niazi et al (2004), and Khan et al (2013) in which generalised weakness constituted 100%, 62.8%, and 75% of the cases respectively.[19,20,21] The second most common symptom in our study was easy fatigability, which was seen in 74.5% of the patients. Santra et al (2010) and Sweta et al (2014) found easy fatigability in 74.7% and 84% of their patients respectively.[10,22] Fever was seen in 42.2% of the cases in our study. Niazi et al (2004) and Dahake et al (2014) found fever in 47.7% and 27% of the patient respectively.[20,23] Bleeding manifestations were seen in 24.8% of the cases in our study. Santra et al (2010) and Niazi et al (2004) found bleeding manifestations in 41.4% and 33.7% of the patients respectively. Dahake et al (2014) found bleeding manifestations in only 11.7% of the patients.[10,20,23]

The most common physical finding seen was pallor in 94.6% of the patients followed by splenomegaly and hepatomegaly and oedema seen in 40.3%, 36.2%, and 28.9% respectively. Gayatri et al (2011), Gupta et al (2008), and Khodke et al (2011) found pallor as the most common physical sign in their patients.[19,24,25] Splenomegaly was found to be more common than hepatomegaly in patients with cytopenias. Gayatri et al (2011) found splenomegaly in 35.57% and hepatomegaly in 26.92% of their patients.[19] Santra et al (2010) found splenomegaly in 44.14% and hepatomegaly in 24.32% of their patients.[10] Gupta et al (2008) found splenomegaly in 22.85% and hepatomegaly 18.57% of their patients.[24]

The mean haemoglobin in our study was 6.7±2.3 g/dL. Thakkar et al (2013) in their study of cases of pancytopenia revealed a mean haemoglobin concentration of 6.2 g/dL. Majority of the patients had moderate leucopenia (50.6%) followed by mild (40.6%) and severe (4.8%) leucopenia. The mean TLC was 2.74 x 10^9/L. This was also similar to the study done by Thakkar et al (2013).[9] Memon et al (2008) in their study have described the presenting features of megaloblastic anaemia with pancytopenia as pallor with varying degree of skin and mucosal bleedings. Bleeding manifestations were seen in 9.5% cases in the present study.[26] Sweta et al (2014) found bleeding manifestations in 23% of patients with megaloblastic anaemia.[22] In this study, 23.8% case and 9.1% cases of megaloblastic anaemia presented with splenomegaly and hepatomegaly. Sweta et al (2014) found splenomegaly and hepatomegaly in 29% and 11% of their patients' respectively.[22] Ishtiaq et al in their study found 15.4% and 17.9% of megaloblastic anaemia with splenomegaly and hepatomegaly respectively.[27]

In the present study, 71% cases of megaloblastic anaemia patients had macrocytic RBCs and 83.3% had hypersegmented neutrophils. Sweta et al (2014) found 74% of patients with megaloblastic anaemia had both macrocytic anaemia and hypersegmented neutrophils. Majority of the patients who had megaloblastic anaemia had hypercellular bone marrow. Sweta et al (2014) found that bone marrow aspiration showed hypercellular marrow with cellularity range from 85% to 96% in megaloblastic anaemia.[22]

CONCLUSION: The present study concludes that a detailed primary haematological investigation along with a bone marrow examination in cytopenic patients is helpful for understanding the disease process; to diagnose or to rule out the causes of cytopenias; and helpful in planning further investigations and management of cytopenic patients. The most common cause of cytopenia was megaloblastic anaemia, which indicates the high prevalence of nutritional anaemia in the region. However, there is limited number of studies available from Indian subcontinent on the frequency of various causes of cytopenias. The variation in the frequency of various conditions causing cytopenias can be attributed to difference in methodology and diagnostic criteria employed, geographic area, period of observation, genetic differences, and varying exposure to myelotoxic agents. Megaloblastic anaemia can present with varied clinical manifestations. Strong suspicion of megaloblastic anaemia should be entertained by clinicians to improve clinical outcome. Prompt diagnosis is important as megaloblastic anaemia is a completely curable condition. Long-term follow up and diet counseling should be done.

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