

MORPHOLOGICAL SPECTRUM OF BONE MARROW IN PANCYTOPENIA – A RETROSPECTIVE STUDY IN A TERTIARY CARE CENTREKalpana Chandra¹, Praveen Kumar²**HOW TO CITE THIS ARTICLE:**

Kalpana Chandra, Praveen Kumar. "Morphological Spectrum of Bone Marrow in Pancytopenia – A Retrospective study in a Tertiary Care Centre". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 04, January 27; Page: 1056-1064, DOI: 10.14260/jemds/2014/1945

ABSTRACT: Pancytopenia is a hematological condition characterized by anemia, leucopenia and thrombocytopenia. We conducted a retrospective study on pancytopenia to evaluate various causes of pancytopenia based on bone marrow morphology. We included cases of more than 14 years of age with Hb <10gm/dl; TLC <4000/ μ L and Platelet <1, 00, 000/ μ L and without any prior hematological disorder or on chemotherapy or on immunosuppressant. We report 83 cases of pancytopenia out of which 48 were males and 35 were females. They were in the age group of 15 to 80 years with mean age of 35.7. There was hypercellular marrow in 57, hypocellular in 14 and normocellular in 12 cases. Megaloblastic anemia was most common etiology present in 25.30% cases. 15.67 % cases were having acute leukemia and 13.25% were having hypoplastic anemia. We conclude that pancytopenia is commonly caused by nutritional deficiency and can be diagnosed by bone marrow examination along with routine hematology and clinical details.

KEYWORDS: Bone marrow aspiration cytology, pancytopenia, megaloblastic anemia, hypoplastic/aplastic anemia.

INTRODUCTION: Pancytopenia is triad of findings characterized by reduction in all three major formed elements of the blood: erythrocyte, leukocytes and platelets. Pancytopenia exist in the adult when the hemoglobin level is less than 13.5 gm./dl in males, or 11.5 gm./dl in females; the leukocyte count is less than 4×10^9 /L and the platelet count is less than 150×10^9 /L.¹

Pancytopenia is a hematological problem with extensive differential diagnosis. Pancytopenia may be associated with decrease in hematopoietic cell production in bone marrow due to destruction of marrow tissue by toxins, replacement by abnormal or malignant tissue, or suppression of normal marrow growth and differentiation. It may be associated with normocellular or even hypercellular bone marrow without any abnormal cell and is due to ineffective hematopoiesis with cell death in marrow, formation of defective cells that are rapidly removed from circulation, sequestration or destruction of cells by the action of antibodies and trapping of normal cells in a hypertrophied and overactive reticuloendothelial system.¹

Pancytopenia is commonly insidious in onset. It is commonly characterized by signs and symptoms of anemia and thrombocytopenia. Sometimes pancytopenia is detected as an incidental feature in a patient who presented with symptoms of a disorder that is capable of depressing the level of all cellular elements in the blood.²

The essential investigations required to make a diagnosis of pancytopenia are routine hematology and bone marrow examination. Other investigations required in selected cases are radiological, microbiological, immunological and biochemical.

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The present study has been undertaken to study the bone marrow morphology due to various causes of pancytopenia. This will help in establishing the various etiologies, prognosticating pancytopenia and planning the management.

OBJECTIVE OF THE STUDY: The aim of present study is to evaluate the various causes of pancytopenia based on bone marrow morphology.

METHODS AND MATERIAL: The study was conducted on patients admitted in SRMS-IMS through OPD or emergency from July 2011 to June 2013. The patients were selected as per protocol based on inclusion and exclusion criteria.

Inclusion criteria: All new patients above 14 years of age with

- 1) Peripheral pancytopenia (Hb <10gm/dl; TLC <4000/ μ L and Platelet <1, 00, 000/ μ L).
- 2) Bone marrow aspiration study was done.

Exclusion criteria:

- 1) Patient presenting with pancytopenia but bone marrow study was not done.
- 2) Patient with pancytopenia already diagnosed to have hematological disorder/ malignancy or on treatment with chemotherapy and other immunosuppressive agents.

This is a retrospective analysis of charts of patients admitted to a tertiary care hospital during July 2011 to June 2013. Patients for this study were selected from hospital records based on inclusion and exclusion criteria. Data of the selected patients were collected from medical records from record room. Complete history, clinical findings and investigations as in medical records were noted down.

RESULTS: A total of 83 cases were included in the study admitted during July 2011 – June 2013 who were fulfilling the inclusion criteria.

Out of 83, 48 were males and 35 were females. They were in the age group of 15 to 80 years with mean age of 35.7 and majority was in the age range of 15 to 25 years (Table-1).

Age range	Frequency
15-25	38 (45.78%)
26-35	13(15.66%)
36-45	06(7.22%)
46-55	11(13.25%)
56-65	09(10.84%)
66-75	03(3.61%)
76-85	03(3.61%)

Table – 1(Age wise distribution)

Common presenting complaints were generalized weakness, fever and bleeding. Pallor was present in all cases. (Table -2)

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Symptoms/Signs	Frequency in %
Pallor	100%
Generalized weakness	58.80%
Fever	36.70%
Splenomegaly	33.73%
Bleeding manifestation	24.40%
Hepatomegaly	22.89%
Gastrointestinal symptoms	12%
Cough	8%
Dyspnea	6%

Table – 2(Clinical features)

Hemoglobin ranges from 1.9 to 9.8 gm. /dl with mean value of 5.9 gm. /dl. TLC ranges from 200 to 3900/ μ L with mean value of 2300/ μ L. Platelet ranges from 5000 to 98000/ μ L with a mean value of 40000/ μ L. Reticulocyte count ranges from 0.3 to 4%. ESR ranges from 17 to 91 mm in 1st hour. (Table-3)

Variables	Frequency
Hb	
Range	1.9 to 9.8 gm./dl
Average	5.9gm/dl
TLC	
Range	200-3900 / μ L
Average	2300/ μ L
Platelet	
Range	5000-98000/ μ L
Average	40,000/ μ L
Reticulocyte count (range)	0.3-4%
ESR (range)	17-91 mm in 1 st hour (Wintrobe's method)

Table – 3 (Lab parameters)

Peripheral smear commonly showed mild to moderate anisopoikilocytosis. In majority of cases of macrocytic anemia, macrocytes along with macro ovalocytes and hypersegmented polymorphs were characteristics findings. In few cases occasional megaloblast were also seen. This was followed by dimorphic blood picture comprising dual populations of macrocytes and microcytes with hypochromia. Cases of acute leukemia and hypoplastic anemia showed predominantly normocytic normochromic picture. Anisocytosis and poikilocytosis were of moderate degree in acute leukemia but less marked in aplastic anemia. In acute leukemia either occasional atypical cells were seen or the entire smear was filled with blasts. Aplastic anemia showed characteristically pancytopenia with reticulocytopenia and relative increase in lymphocytes. Rouleaux formation was noted in cases of multiple myeloma. Hypogranular neutrophils were found in some cases of myelodysplastic disorders.

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Giant platelets were found in some cases of acute leukemia with normal distribution width in aplastic anemia.

Bone marrow aspiration was done in all cases and slides were stained with MGG and special stains in selected cases. Smears were categorized as hypercellular, normocellular and hypocellular on the basis of the cellularity of the fragments which were adequate in number.

In the present study, 57 cases with hypercellular marrow were identified. Out of which megaloblastic anemia was the most common etiology found in 21 cases. Bone marrow in these cases of megaloblastic anemia was hypercellular with characteristic megaloblastic erythropoiesis overrepresented by early erythroid cells in comparison with mature forms due to ineffective erythropoiesis. Features of dysmyelopoiesis were evident in the form of giant metamyelocytes and band forms. Megakaryocytes were hyperlobated. 6 cases of combined deficiency nutritional anemia were identified where many features of megaloblastic anemia were masked by iron deficiency anemia. In about 12 cases, hypercellular marrow was because of heavy infiltration by leukemic blasts. Normal hematopoietic cells were markedly reduced in number but were morphologically normal. All these cases of acute leukemia taken in the study revealed pancytopenia on peripheral smears. 7 cases constituted hypercellular marrow with reversed M: E ratio because of erythroid hyperplasia due to hypersplenism. Other causes of hypercellular marrow included 4 cases of myelodysplastic syndrome, 4 cases of granulocytic hyperplasia due to infectious pathology and 1 case of leishmaniasis, multiple myeloma and lymphoproliferative disorder each.(Table -4).

Disease	Frequency
Megaloblastic anemia	21(25.30%)
Acute leukemia	12(14.45%)
Erythroid hyperplasia	7(8.43%)
Combined deficiency nutritional anemia	6(7.22%)
MDS	4(4.81%)
Granulocytic hyperplasia	4(4.81%)
Multiple myeloma	1(1.20%)
Leishmaniasis	1(1.20%)
Lymphoma	1(1.20%)

Table – 4 (Bone marrow morphology - Hypercellular)

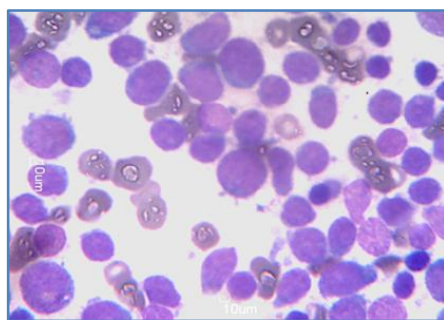


Fig. 1: Hypercellular marrow packed with blasts – Acute myeloid leukemia (Oil immersion)

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In the present study total 14 cases of hypocellular marrow were identified. 11 cases showed hypoplastic marrow suggestive of aplastic anemia. Only bone marrow aspiration was performed. Smears having adequate number of fragments showed decrease in cellularity varying from moderate reduction to complete absence and increased fat to cell ratio. Cell trails from hypoplastic fragment were either hypocellular or absent with trilineage suppression of hematopoiesis. Plasma cells, reticulum cells and lymphocytes were relatively prominent. Two cases of metastatic tumor to the bone marrow were identified. One case of acute myeloid leukemia with hypocellular marrow was documented where the patient was an elderly female. (Table – 5).

Disease	Frequency
Hypoplastic anemia	11(13.25%)
Metastatic tumor	2(2.40%)
Acute leukemia	1(1.20%)

Table – 5 (Bone marrow morphology - Hypocellular)

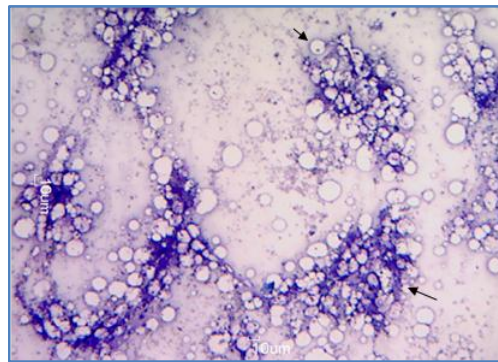


Fig. 2: Hypoplastic marrow particles (MGG 4X)

Total of 12 cases of normocellular marrow were identified. Out of which 5 cases showed normal study. This was followed by 3 cases of partially treated nutritional anemia and 2 cases of multiple myeloma. One case each of granulomatous inflammation and leishmaniasis were found. (Table-6).

Disease	Frequency
Normal study	5(6.02%)
Combined deficiency nutritional anemia	3(3.61%)
Multiple myeloma	2(2.40%)
Leishmaniasis	1(1.20%)
Granulomatous inflammation	1(1.20%)

Table –6 (Bone marrow morphology - Normocellular)

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Fig. 3: Normocellular marrow with LD bodies (Oil immersion)

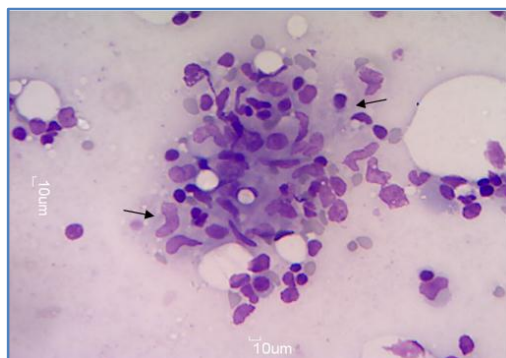


Fig. 4: Normocellular marrow with granulomatous inflammation (MGG 40x)

DISCUSSION: The study was conducted on 83 patients admitted in SRMS-IMS, Bhojipura, Bareilly. This was retrospective observational study.

In present study pancytopenia was observed in the age group of 15 to 80 years with a mean age 35.7 year and maximum affection in the age group of 15 to 25 years (45.8%). Males were affected more commonly than female with M: F ratio 1.37:1. B N Gayathri et al. observed pancytopenia in the age group of 2-80 years with mean age of 41 year and M: F ratio 1.2:1.³ Jha A. et al. observed pancytopenia in the age group of 1-79 years with a mean age of 30 years and M: F ratio 1.50:1.⁴ Lakhey A. et al. observed pancytopenia in the age group of 5-82 years with a mean age of 40 years and M: F ratio 2.6:1.⁵ Kishor Khodke et al. observed age range of 3-69 years with M: F ratio 1.3:1. Maximum numbers of cases were found in the age group of 12-30 years (44%).⁶ Osama Ishtiaq et al. observed age range of 12 to 82 years with mean age of 36.7 in which 53% were male.⁷ Rangaswamy M et al. observed M:F ratio of 1.6:1 and most of the patients were in the age group of 10-30.⁸

In present study the commonest symptoms were generalized weakness and fever in 58.8% and 36.7% cases respectively. Bleeding manifestation was present in 24.4% cases. Pallor was the most common sign and was present in 100% cases. Splenomegaly was present in 33.7% and hepatomegaly in 22.8% cases. B N Gayathri et al. observed fever and generalized weakness as common symptoms and pallor as the commonest sign.³ Rangaswamy M et al. observed generalized weakness and fatigue (88%) as the commonest presenting complaints.⁸ Kishor Khodke et al. observed fever as the commonest presentation in 40% cases followed by weakness in 30% cases and bleeding manifestation in 20%

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cases. Pallor was present in all patients, splenomegaly in 40%, hepatomegaly in 38% and petechial hemorrhage in 28%.⁶

In present study, hypercellular marrow was present in 68.67% patients followed by hypocellular in 16.86% and normocellular in 14.45% cases. Rangaswamy M et al. observed hypercellular bone marrow in 75%, hypocellular in 14% and normocellular in 11% of the patients.⁸

In present study, nutritional deficiency was the most common factor causing pancytopenia in 36.14% patients. Megaloblastic anemia was the most common cause constituting 25.3%. Neoplastic etiology contributed in 22.89% patients. Acute leukemia was the most common cause. B N Gayathri et al. observed megaloblastic anemia (74.04%) as a commonest cause followed by aplastic anemia in 18.26%.³ Kishor Khodke et al. observed megaloblastic anemia in 44% cases followed by aplastic anemia in 14% and kala azar in 14%.⁶ Osama Ishtiaq et al. observed megaloblastic anemia as the most common cause followed by hypersplenism secondary to portal hypertension.⁷ Rangaswamy M et al. observed megaloblastic anemia (33%) as the commonest cause followed by nutritional anemia (16%), aplastic anemia (14%), hypersplenism (10%), sepsis (9%) and leukemia (5%).⁸ Nafil H et al. observed megaloblastic anemia in 32.2%, marrow blasts in 23.7% and aplastic anemia (15.2%).⁹ Jha A et al. observed hypoplastic bone marrow (29.05%) as a commonest bone marrow findings followed by megaloblastic anemia (23.64%) and hematological malignancy (21.62%).⁴ Lakhey A et al. observed hypoplastic bone marrow in 29.69%, hematological malignancy in 27.78% and megaloblastic anemia in 24.10%.⁵ Kumar R et al. observed aplastic anemia in 49, megaloblastic anemia in 37, aleukemic leukemia or lymphoma in 30 and hypersplenism in 19 cases.¹⁰

In our study isolated megaloblastic anemia was the most common cause. Megaloblastic anemia is a group of disorder characterized by the presence of distinctive morphologic appearances of the developing red cell in the bone marrow. The commonest cause of megaloblastic anemia is folate and cobalamine deficiency and rarely by genetic or acquired abnormalities affecting the metabolism of the vitamin or because of defect in DNA synthesis not related to cobalamine or folate.¹¹ Sarode R. et al. conducted a study on 139 cases of nutritional megaloblastic anemia and observed 71 male and 68 female patients were affected. 76% were having vitamin B12 deficiency, 6.8% were having folate deficiency, 8.8% were having combined deficiency and rests were having normal vitamins level. All patients were having anemia, 80.5% were having thrombocytopenia and 43.8% were having neutropenia as well as thrombocytopenia.¹²

In the present study, acute leukemia presenting as pancytopenia was found in significant number. Acute leukemia constituted 15.67 % including 14.45% with hypercellular marrow and 1.2% with hypocellular marrow. Sultan et al. observed 1000 – 4000 WBC count with majority of blast cells (commonly in M2 and M3 type of AML) in 25% of case of acute leukemia.¹³ Hoelzer D, et al. reported hypocellular variant of AML in 5 – 10 % of patients.¹⁴

In current study hypoplastic marrow was found in 13.25 %. In many cases the possibilities of aplastic anemia was suggested on the basis of clinical findings, peripheral smears finding and bone marrow aspiration. The reported incidence of aplastic anemia varies considerably between countries e.g. from 0.7 to 4.1 per million per year in one study. Incidence is lower in Europe and North America than in various other parts of the world e.g. Asia.¹⁵

CONCLUSION: Pancytopenia is an important clinical condition commonly presenting as generalized weakness, fever and bleeding manifestations. Bone marrow study along with basic hematological

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investigations and clinical details can quickly diagnose and categorize the pancytopenic patients who commonly present with reversible treatable etiologies such as nutritional deficiencies.

Hb	HAEMOGLOBIN
WBC COUNT	WHITE BLOOD CELL COUNT
TLC	TOTAL LEUKOCYTE COUNT
ESR	ERYTHROCYTE SEDIMENTATION RATE
MGG	MAY-GRUNWALD'S STAIN
MDS	MYELODYSPLASTIC SYNDROME
M: F ratio	MALE TO FEMALE RATIO
OPD	OUT PATIENT DEPARTMENT
LIST OF ABBREVIATIONS	

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