CASE SERIES

# A Study of Bone Marrow Examination in Cases of Pancytopenia

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**Abstract:**

Bone marrow examination (aspiration and biopsy) carried out in 30 cases having pancytopenia, had megaloblastic anemia as the commonest cause (46.6%) of pancytopenia. Other common conditions presenting as pancytopenia were micro-normoblastic erythroid hyperplasia (16.6%), aplastic anaemia (13.3%). Uncommon causes of pancytopenia were Acute Leukemia (AL), Myelodysplastic Syndrome (MDS), Myelofibrosis (MF) and Multiple Myeloma (MM).

**Keywords**: Pancytopenia, Bone Marrow Aspiration, Biopsy

**Introduction**:

Pancytopenia may be a manifestation of a wide variety of disorders, which primarily or secondarily affect the bone marrow [1]. This may be due to ineffective erythropoiesis, decreased cell production, increased peripheral utilization and increased destruction without an adequately matching compensatory increase in the cell production. The cause of pancytopenia may be thus lie in the bone marrow, periphery or both, Various factors encompassing geographic distribution and genetic disturbances may cause variation in the incidence of disorders causing pancytopenia [2-4]. Prognosis in pancytopenia depends upon the underlying pathology and determines the management. We present 30 cases of pancytopenia along with clinical and haematological features.

**Case Series**:

The present study was carried out over a period of one year (2015-2016) at Shridevi Institute of Medical Sciences and Research Hospital, Tumkur. Total 30 cases of various haematological disorders were randomly selected for bone marrow aspiration and biopsy study. These cases had pancytopenia on peripheral smear examination. Bone marrow aspiration and biopsy was performed using Jamshidi trephine biopsy needle from posterior superior iliac crest. Inclusion Criteria: All patients who fulfilled criteria for diagnosis of pancytopenia. Exclusion Criteria: Patients on chemotherapy, radiotherapy and drugs causing pancytopenia. Leishman stain was done for aspiration smears. H and E and other special stains like Prussian blue, MPO, PAS, Reticulin were done wherever necessary. Various clinico-hematological parameters were noted.

**Results**:

Thirty cases of pancytopenia were reported. Age ranged from 18-82 years with M: F ratio being 2:1(20/10). Maximum number of cases was found in age group of 20-50 years (70%). Criteria for diagnosis of pancytopenia were: Hb <10gm%, Total Leucocytes Count (TLC) <3500cells/cumm and platelet count < 1, 00,000/cumm [7].

The commonest presenting complaint was fever in 20(66.6%) cases followed by fatigue in 12 (40%) patients. Bleeding manifestation and bone pain in 2(6.66%) cases each were seen (Table 1)

**Table 1: Clinical Spectrum of Various Disorders**

| Diagnosis based on bone morrow examination | Number of cases | Fever | Hepato-splenomegaly | Petechiae | Lymphadeno-pathy | Bone pain |
|---|---|---|---|---|---|---|
| **Megaloblastic anemia** | 14 | 12 | 11 | 1 | - | - |
| **Micronormoblastic erythroid hyperplasia** | 5 | 3 | 2 | - | - | - |
| **Aplastic anemia** | 4 | 2 | - | 1 | - | - |
| **Myelofibrosis** | 3 | | | - | - | - |
| **Acute leukemias** | 2 | 2 | 1 | - | 1 | 1 |
| **MDS** | 1 | 1 | 1 | - | - | - |
| **Multiple Myeloma** | 1 | - | - | - | - | 1 |
| **Total** | 30 | 20 | 15 | 2 | 1 | 2 |

Pallor was present in all the patients. Majority of patients 15 (50%) had hepatosplenomegaly.

Peak range of Hb: 5-8gm%

Peak range of TLC: 3000-3900 cells/cumm

Peak range of platelet count: 50,000-1.3l cells/cumm

Absolute Reticulocytosis was seen in one case. Peripheral blood findings of all the cases were noted (Table 2).

The commonest cause of pancytopenia was megaloblastic anemia which was seen in 14 (46.6%) cases, followed by iron deficiency anemia (16.6%), aplastic anemia (13.3%).

The other causes of pancytopenia were acute leukemia (6.6%), myelofibrosis (10%), myelodysplastic syndrome (3.3%) and multiple myeloma (3.3%).

**Table 2: Peripheral Blood Findings of Various Disorders**

| Diagnosis | No. of cases | Aniso-cytosis | Tear drop cells | Polychro masia | nRBC | Rouleaux formation | Neutrophils with five lobes | Immature cells | Relative lympho cytosis | Absolute Reticulo-Cytosis |
|---|---|---|---|---|---|---|---|---|---|---|
| **Megaloblastic anemia** | 14 | 12 | 4 | 8 | 2 | - | 14 | - | - | 1 |
| **Micronormoblastic erythroid hyperplasia** | 5 | 4 | 4 | 4 | - | - | - | - | - | - |
| **Aplastic anemia** | 4 | 1 | - | - | - | - | - | - | 4 | - |
| **Myelofibrosis** | 3 | 2 | 3 | - | 3 | - | - | - | - | - |
| **Acute leukemias** | 2 | 1 | 1 | - | 2 | - | - | 2 | - | - |
| **MDS** | 1 | 1 | 1 | - | 1 | - | - | 1 | - | - |
| **Multiple Myeloma** | 1 | 1 | 1 | - | - | 1 | - | - | - | - |

Bone marrow aspiration and biopsy was done in all cases. Further analysis was done based on cellularity of bone marrow.

I Hypocellular marrow:

A. Aplastic anemia: Peripheral smear of all the 4 cases showed pancytopenia with relative lymphocytosis. It was the only group of cases which showed reduced cellularity of marrow and marked reduction in erythroid, myeloid and megakaryocytic series with predominance of lymphocytes and plasma cells. Mean age of the patients was 20yrs and M: F=3:1. Trephine biopsy showed reduced cellularity with fat cells occupying more than 75% of marrow. Scattered rests of erythropoietic cells seen in paratrabecular region, with relative increase in number of lymphocytes and plasma cells.

II Hypercellular marrow

Hypercellular marrow was seen in anemias, leukemias, MDS, myelofibrosis, multiple myeloma.

A. MDS: A single case had hypercellular marrow with M:E ratio being 1:1. Dyserytropoietic features included multinuclearity, asynchrony of maturation between nucleus and cytoplasm, cytoplasmic vacuolations, nuclear budding, karyorrhexis and mitotic figures. A diagnosis of refractory anemia was made as the patient had not responded to any treatment for the past six months. No evidence of Abnormal Localization of Immature Precursors (ALIP) seen in biopsy.

B. Myelofibrosis: Marrow aspirate was dry tap in all the 3 cases. Biopsy showed moderate cellularity with decrease in erythroid and myeloid series of cells. Megakaryocytes had abnormal nuclear-cytoplasmic ratios, abnormal chromatin clumping with hyperchromatic nuclei. Increased fibrosis was seen. Reticulin stain was done for grading of fibrosis. All were in cellular phase.

C. Multiple myeloma: A 60yr old patient presented with bone pain, backache and loss of weight. Aspiration was done to rule out secondaries. Marrow was hypercellular with 80-90% of plasma cells infiltrating the marrow. Patient had a multiple lytic lesions, hypercalcemia, presence of "Bence Jones" protein in urine and raised albumin, ESR and 2 microglobulin, all of which was complementary to marrow findings for a final diagnosis.

**Discussion:**

Pancytopenia develops due to decrease in hematopoietic cell production as a result of destruction of the marrow tissue by toxins, replacement by abnormal tissue or suppression of normal growth and differentiation. There are limited number of studies on the frequency of pancytopenia. Limited data has been reported from the Indian sub-continent.

In the present study, commonest cause of pancytopenia was megaloblastic anemia (46.6%). A study by Retief revealed that bone marrow failure was the commonest cause of pancytopenia and severe infections (9.7%) was the second common cause [5]. In one study, pancytopenia was seen in 52.7% of aplastic anemia and 10.5% of MDS patients [2]. Verma and Dash found aplastic anemia in 40.6% and megaloblastic anemia in 23.26% of patients [6]. Megaloblastic anemia (68%) was the commonest cause of pancytopenia followed by aplastic anemia (7.7%) in a study by Tilak and Jain [7]. This increased incidence of megaloblastic anemia correlates with the high prevalence of nutritional anemias in Indian population as well as in developing countries. The most common causes leading to pancytopenia on

bone marrow examination are hypoplastic (AA) bone marrow (29.05%), megaloblastic anemia (MA) (23.64%), haematological malignancies i.e. Acute Myeloid Leukemia (AML) (21.62%), and Erythroid hyperplasia (EH) (19.6%) [8].

The second most common cause of pancytopenia in the present study was aplastic anemia (13.3%) This was seen in the study done by Gayathri and Rao [9] and Khodke *et al.* [10]. All were idiopathic. No history of exposure to radiation/drugs was obtained. The incidence of aplastic anemia in west is much higher than that studied by us. Micronormoblastic erythroid hyperplasia with peripheral pancytopenia was seen in 16.6% of our cases. Iron stores were decreased. Iron deficiency anemia presenting as pancytopenia is uncertain.

A study by Mahfuz *et al.* [11] showed micro-normoblastic erythroid hyperplasia in 29.5% and 10.66% in a study by Parajuli[12]. In a study done by Ahmad *et al.* [13], 23.8% cases were microcytic hypochromic anemia and diagnosed as iron deficiency anemia. Patients responded well to iron therapy. No case of drug induced pancytopenia with bone marrow depression was encountered in the study.

Leukemias can present with pancytopenia [8]. Bone marrow aspiration helps in diagnosis and biopsy becomes mandatory in cases of dry tap. Aspiration and biopsy helped to arrive at diagnosis of AML and ALL in our study. Pancytopenia is known to occur in MDS. It is the least common finding in MDS as compared to mono and bicytopenia [14]. In a study of 31 patients of MDS by Kini, bicytopenia was the commonest finding and pancytopenia was common in the subtypes RAEB and RAEB-t.

Patients with multiple myeloma can develop pancytopenia due to replacement of bone marrow by immunoproliferative cells [15]. Tilak and Jain reported one case of pancytopenia due to multiple myeloma in their study. A study by Pudasini S *et al* showed pancytopenia in 3.5% of the cases studied [16]. In the present study, patient had multiple lytic lesions, hypercalcemia, increased Bence Jones proteins and infiltration of marrow by plasma cells.

Pancytopenia due to myelofibrosis occurs due to various etiological factors [17]. Myelofibrosis causes hypersplenism leading to pancytopenia [18]. Pancytopenia is a common finding in advanced AIDS. Fibrosis of marrow is seen in 20-50% making aspiration difficult [19]. In the present study, patient was HIV negative. Aspirate was a dry tap and biopsy showed increased fibrosis.

Variation in the frequency of disorders causing pancytopenia has been ascribed to differences in methodology, stringency of diagnostic criteria, geographic area, and period of observation, genetic differences and varying exposure to cytotoxic agents.

**Conclusion**:

Pancytopenia is relatively a common entity. Hence, appropriate physical examination and peripheral blood findings are relevant in planning investigations in pancytopenic patients. Bone marrow aspiration and biopsy is a must in cases of pancytopenia to arrive at the diagnosis and patient management. Most common causes of pancytopenia are megaloblastic anemia, aplastic anemia, erythroid hyperplasia. However, uncommon and rare causes such as multiple myeloma, myelofibrosis, should be kept in mind during complete work up. A comprehensive clinical and haematological study of patients with pancytopenia will usually help in the identification of underlying cause.

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