Pancytopenia: A Clinico Hematological Study

* Dr. Anjali Phatake, ** Dr. Prajakta Ghatage, ** Dr. Sharada Aher, *** Dr.Sunil Mhaske,

* Assistant Professor Department of Pathology, ** Resident, Department of Paediatrics, *** Dean, Dr. Vithalrao Vikhe Patil Foundation's Medical College,Ahmednagar.

Corresponding Author : Dr. Prajakta Ghatage

Mail ID: prajaktaghatage38@gmail.com

Mobile No.: 7276613919

Address : Department of Pathology, Dr. Vithalrao Vikhe Patil Foundation's Medical College, Ahmednagar.

Abstract :

Background : Pancytopenia is a relatively common hematological condition. It is a significant feature of many serious and fatal illnesses. It is starting from simple drug-induced bone marrow hypoplasia, megaloblastic anemia to fatal bone marrow aplasias and leukemias. The severity of pancytopenia and causative pathology determine the management and prognosis. Thus, the identification of the correct cause will help in implementing appropriate therapy. **Objectives :** To study the clinical presentations in pancytopenia due to various causes; and to evaluate hematological parameters which also comprise of the bone marrow aspiration. **Material and Methods :** It was a prospective study, and 100 pancytopenic patients were evaluated clinically. Also along with their hematological parameters and bone marrow aspiration in Department of Pathology. **Results :** Out of 100 cases studied, age of patients ranging from 2 to 80 years with a mean age of 41 years, and male predominance. Majority of the patients presented with generalized weakness and fever. The most common physical finding was pallor, succeeded by splenomegaly and hepatomegaly. Dimorphic anemia was the predominant blood picture. Bone marrow aspiration was conclusive in all cases. The commonest marrow finding was hypercellularity with megaloblastic erythropoiesis.And the most common cause of pancytopenia was found to be megaloblastic anemia (75%), followed by aplastic anemia (18%). **Conclusion:** The present study gives conclusion that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients are helpful for understanding of the progression of the disease and to diagnose or to rule out the causes of cytopenia. These are also helpful in establishing the further line of investigations and management.

Keywords : Bone marrow aspiration, megaloblastic anemia, pancytopenia

Introduction : Pancytopenia is an important clinico-hematological entity encountered in our day-to-day clinical practice. There are varying trends in its clinical pattern, treatment modalities, and outcome.[1] It is a disorder in which all three major formed elements of blood (red blood cells, white blood cells and platelets) are decreased in number.[2]It is not a disease entity but a triad of findings that may result from a number of disease processes — primarily or secondarily involving the bone marrow.[3] The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patients.[4]

In India, the causes of pancytopenia are not well defined, so the present study has been undertaken to evaluate the various causes and to correlate the peripheral blood findings with bone marrow aspirate.[5] Thereby, this data would help in planning the diagnostic and therapeutic approach in patients with pancytopenia. Hematological disorders are quite frequent in all age group. Most of this hematological disorder first present as anemia. Bone Marrow Aspiration plays a major role in the diagnosis of its underlying cause. Most of the time the diagnosis can be arrived at by detail clinical examination and few simple investigations. Without bone marrow examination the diagnosis is usually not a confirmatory. Bone marrow examination also gives explanation for unexplained cytopenias and leukemia.[6] It gives a more complete picture of the reaction of the hemopoietic tissue to anemia than can be gained from peripheral blood smear (PBS) alone.[7]

Bone marrow aspiration (BMA) is the most frequent and safe invasive procedures done routinely in the hospitals

for the diagnosis and management of hematological disorder.8 Patients of all age groups and both sexes were included. Case selection was based on clinical features and supported by laboratory evidence, which included peripheral blood counts for hemoglobin, leukocytes and platelets. Inclusion criteria were presence of all 3 of the following: hemoglobin, <9 g/dL; total leukocyte count (TLC), <4,000/μL; platelet count, <100,000/μL.5

Material and Methods : The present prospective study was undertaken patients of all age groups and both sexes were included. Case selection was based on clinical features and supported by laboratory evidence, which included peripheral blood counts for hemoglobin, leukocytes and platelets. Inclusion criteria were presence of all 3 of the following: hemoglobin, <9 g/dL; total leukocyte count (TLC), <4,000 / μL; platelet count, <100,000/μL.5

Patients on myelotoxic chemotherapy were excluded. Two milliliters of EDTA (ethylene diamine tetra-acetic acid) anticoagulated blood was collected and processed through ABX MICROS 60 automated hematology analyzer; and 9 hematological parameters were obtained, which included hemoglobin, red blood cell count, total leukocyte count, differential leukocyte count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), packed cell volume (PCV). Erythrocyte sedimentation rate (ESR) was estimated in all cases by Westergren's method. Peripheral smear was stained by Leishman stain for all the cases and examined in detail. Bone marrow aspiration was subsequently carried out under aseptic precaution after obtaining written consent from the patient or guardian.

Result : A total of 100 patients who presented with pancytopenia were studied. They consisted of 60 males and 40 females with a male-to-female ratio of 1.5:1. The age of patients ranged from 2 to 80 years (mean age, 41 years). Out of 100 cases, pancytopenia was observed in 28 pediatric patients (2-18 years); they consisted of 13 males and 15 females. No familial disease was observed in association with pancytopenia. Presenting complaints and physical findings are:

Sr. no	Presenting complain & physical findings	No. of cases	Per-centages
1.	Generalized weakness	100	100
2.	Dyspnea	45	45
3.	Fever	38	38
4.	Bleeding manifestations	5	5
5.	Weight loss	4	4
6.	Chills and rigors	2	2
7.	Pallor	100	100
8.	Splenomegaly	35	35
9.	Hepatomegaly	25	25
10.	Jaundice	5	5
11.	Body tenderness	2	2
12.	Lymphadenopathy	1	1

The commonest mode of presentation was generalized weakness; other main symptoms were dyspnea, fever, weight loss. Pallor was noted in all cases.

Splenomegaly and hepatomegaly were seen in cases of megaloblastic anemia, followed by subleukemic leukemia and malaria. Bony tenderness was seen in multiple myeloma. Lymphadenopathy was noted in subleukemic leukemia–lymphoblast type.

Hematological parameters in the 3 subgroups of pancytopenia are shown in Table 2.

Table 2

Parameters	Megaloblastic anemia	Aplastic anemia	Subleukemic leukemia
Hb (g/dL)	1.8-9.2	2-8.6	2.8-6
TLC (µL)	500-3,900	700-3,800	600-3,200
Platelets (µL)	12,000-95,000	10,000-92,000	15,000-85,000

The predominant blood picture was dimorphic anemia (37.5%), followed by macrocytic anemia (31.7%); peripheral smear showed macro-ovalocytes with hypersegmented neutrophils Figure 1. Normocytic normochromic anemia constituted 15.3% of the cases; and normocytic hypochromic anemia, 15.3%. Leucopenia and thrombocytopenia were seen in all cases.

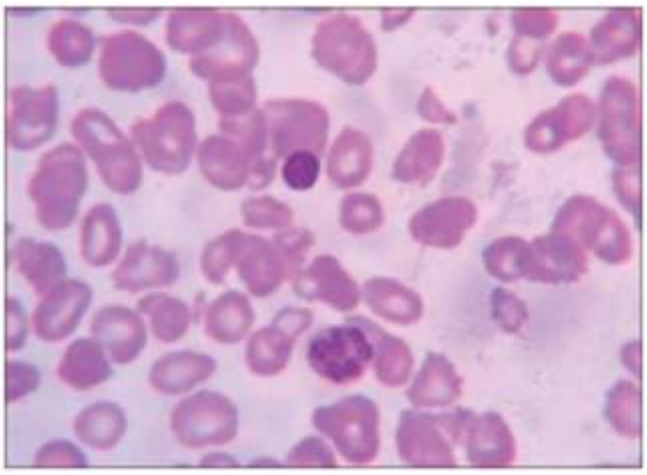


Figure 1

The causes of pancytopenia and case distribution are shown in Table 3

Sr. no	Presenting complain & physical findings	No. of cases	Per-centages
1	Megaloblastic anaemia	75	75
2	Aplastic anaemia	18	18
3	Subleukemic leukemia	2	2
4	Malaria	3	3
5	Multiple myeloma	1	1
6	Storage disease	1	1
	Total	**100**	**100**

Megaloblastic anemia was observed in 41 males and 34 females, their age ranging from 4 to 80 years, with a mean age of 42 years. Four patients had evidence of malabsorption syndrome. Six patients had clinical neurological deficits: subacute combined degeneration (SACD) of spinal cord in 4 and sensory ataxia in 2 patients. In the remaining 65 cases, the underlying disorder could not be established. Since B12 and folate levels could not be estimated as a routine, both folic acid and parenteral hydroxycobalamine therapies were administered to all, and they showed complete clinical and hematological remission. Bone marrow aspiration showed megaloblastic erythroid hyperplasia. Megaloblasts had the characteristic feature of sieved nuclear chromatin, asynchronous nuclear maturation and bluish cytoplasm with cytoplasmic blebs [Figure 2]. Giant metamyelocytes and band forms were predominant in granulocyte series.

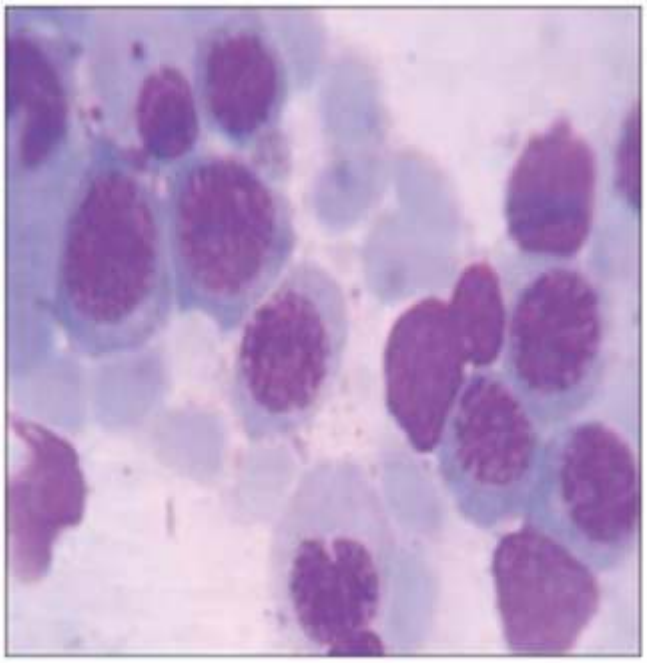


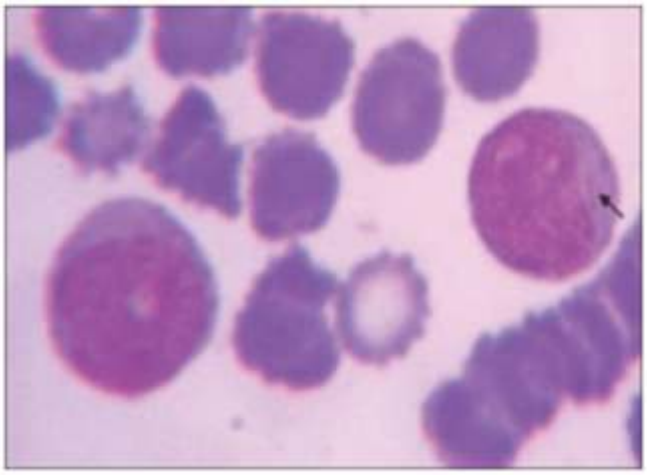
Figure 2

Aplastic anemia was seen in 10 males and 8 females; their age ranged from 2 to 50 years, with a mean age of 26 years. In the present study, out of 18 cases of bone marrow hypoplasia, cause was not known in 16 cases and was grouped under idiopathic bone marrow hypoplasia. Only 1 patient had history of hepatitis infection. Another patient gave history of reatment with carbamazepine for epilepsy. One being, a known case of hyperthyroidism, was on antithyroid medication. Bone marrow (BM) showed hypocellularity with suppression of

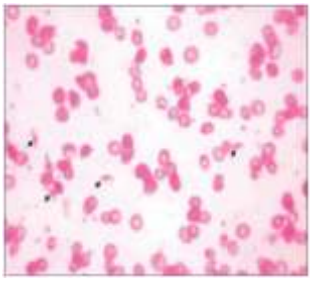
erythropoiesis, myelopoiesis and megakaryopoiesis with relative lymphoplasmacytosis.

We came across 2 patients of subleukemic leukemia; their age ranging from 4 to 30 years. Three cases were of AML-M2 (acute myeloblastic leukemia) and 1 case was of ALL-L2 (acute lymphoblastic leukemia). Bone marrow was hypercellular in all cases. Erythroid and megakaryocytic series were reduced. Majority of cells were myeloblasts and lymphoblasts, constituting more than 40% and 30% of cells in marrow, respectively. Bone marrow aspirate showed myeloblasts with Auer rods.

Malarial infestation was seen in 1 male patients aged 5 years and 25 years. Peripheral blood picture showed pancytopenia, and gametocytes of plasmodium falciparum were seen in blood smear in both cases. BM was hypercellular with megaloblastic change. No malarial parasites were seen on bone marrow smears. The patient recovered after antimalarial treatment and folic acid therapy. Multiple myeloma was diagnosed in a 41-year-old female, who presented with weakness and bony tenderness. BM showed abnormal proliferation of plasma cells, constituting >40% of marrow cells, including good number of binucleate and trinucleate forms.



Bone marrow showing myeloblast showing Auer rods.



PBS showing plasmodium falciparum.

We encountered 1 case of storage disorder in a 15-year-old male, who presented with fever, pallor, hepatosplenomegaly. BM showed good number of large cells with peripherally placed relatively small nucleus and abundant multivacuolated foamy cytoplasm and was PAS (periodic acid Schiff) negative. Hence diagnosis of Niemann-pick disease was considered.

Discussion : A total of 100 cases of pancytopenia were studied. Age, gender-wise incidence, presenting complaints, peripheral blood picture, bone marrow aspiration smears and various causes of pancytopenia were studied in all cases, and observations were compared with those in studies published in the literature.The age of the patients ranged from 2 to 80 years, with a mean age of 42 years. Cytopenias were observed more in males (60%) than females (40%), with male-to-female (M: F) ratio of 1.5: 1. Age and sex distribution was compared with other studies as shown in Table 4.

Sr. no	Authors	No. of cases	Age range	Age range
1	Khunger JM et al.	200	2-70	1.2:1
2	Kumar R et al.	166	12-73	2.1:1
3	Tilak Vet al.	77	5-70	1.14:1
4	Khodke et al.	50	3-69	1.3:1
5	Present study	100	2-80	1.5:1

The most common cause of pancytopenia, reported in various studies all over the world has been aplastic anemia. This result contradicting with the results of our study, which concludes the commonest cause of pancytopenia was found to be megaloblastic anemia. Similar findings were observed in other studies conducted in India. This seems to reflect the higher prevalence of nutritional anemia in Indian subjects.

Incidence of megaloblastic anemia was 75% in our study. Incidence of 72% was reported by Khunger JM et al.; and

68%, by Tilak V et al. All the above studies have been done in India, and they stress the importance of megaloblastic anemia being the major cause of pancytopenia. It is a rapidly correctable disorder and should be promptly notified. Although bone marrow aspiration studies are uncommon in suspected cases of megaloblastic anemia, if the diagnosis does not appear straightforward or if the patient requires urgent treatment and hematological assays are not available, bone marrow aspiration is indicated. As facilities for estimating folic acid and vitamin B12 levels are not routinely available in most centers in India, the exact deficiency is usually not identified.

Incidence of aplastic anemia varies from 10% to 52% among pancytopenic patients. The incidence of hypoplastic anemia in our study was 19%, which correlated with the corresponding figures in studies done by Khodke K et al. and Khunger JM et al.,Both observed an incidence of 14%. A higher incidence, viz., 29.5%, was reported by Kumar R et al.

In our study, we came across 31 pediatric pancytopenic cases; again megaloblastic anemia was the common cause for pancytopenia, followed by aplastic anemia. Similar results were reported by Bhatnagar et al.8 However, in a study by Gupta and colleagues, 105 patients aged 1.5 to 18 years, with a mean age of 8.6years, were included in the study. Aplastic anemia was themost common cause of pancytopenia (43%), followed by acute leukemia(25%). Infections were the third most common cause of pancytopenia,of which kala-azar was the most common. Megaloblastic anemiawas seen in 6.7% of the patients.[9] In another study, 64 children were identified with diagnosis of pancytopenia. The most common cases were infectious in origin (64%), followed by hematological (28%) and miscellaneous (8%) etiologies.[10]

We encountered 2% incidence of subleukemic leukemia, compared to 5% reported by Khunger JM et al.[5,6] Kumar R et al.[6] reported 12% incidence of aleukemic leukemia. Pancytopenia was the common feature in our study; this correlated with the corresponding finding in the studies by Kumar R et al. and Khunger JMet al. The diagnosis of AML was based on bone marrow aspiration study, and we reported 3 cases of AML-M2 and 1 case of ALL-L2. Khodke K et al. reported a single case of AML-M2 out of 50 cases of pancytopenia. Kumar R et al. reported 5 cases of ALL, 13 cases of AML, 2 cases of hairy cell leukemia out of 166 cases of pancytopenia, over a 6-year study period.

We encountered 2 cases of malaria in our study, constituting 3% of total cases – compared to [5] Khunger JM et al., who have reported an incidence of 1%; Tilak V et al., who have reported an incidence of 3.9%; and[6] Kumar R et al., who have reported an incidence of 3% of the total cases.

We encountered 1 case of multiple myeloma, constituting 1% of total cases – compared to Khodke K et al., who have reported an incidence of 4%; Tilak V et al., who have reported an incidence of 1.3%; and Khunger JM et al., who have reported an incidence of 1% in their studies.[4,5,6] Patients present study presented with generalized weakness, fever and bony tenderness. ESR was 92 mm at the end of 1 hour by Westergren's method. Plasmablasts with increased N:C (nuclear- cytoplasmic) ratio, multinuclearity and nuclear lobulation were seen. Terpstra et al. reported >50% of plasma cells in the bone marrow in 12 of 54 patients with multiple myeloma in their study.[11]

We have reported a single case of storage disorder (Niemann-pick disease), in a 15-year-old boy, who presented with hepatomegaly, splenomegaly and pancytopenia. BM was with multiple myeloma in their study.[11]

We have reported a single case of storage disorder (Niemann-pick disease), in a 15-year-old boy, who presented with hepatomegaly, splenomegaly and pancytopenia. BM was normocellular with normoblastic erythropoiesis. Aspirated smears showed collection of large foamy histiocytes (Niemann-pick cells) dispersed throughout the smear. Kumar R et al., Khunger JM et al. and [7] Khodke K et al have not reported any case of storage disorder as a cause of pancytopenia in their studies.

The causes of pancytopenia were treatable in 70% of the patients, who fully recovered from cytopenia. Death occurred in 20% of the cases, which was due to severe pancytopenia and overwhelming infections.

Conclusion : Pancytopenia is not an uncommon hematological problem encountered in clinical practice

and should be suspected on clinical basis.,when a patient presents with unexplained anemia, prolonged fever and tendency to bleed. The present study conclusion is that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients are helpful for understanding the disease process; to diagnose, or to rule out the causes of, cytopenia; and in scheduling further investigations and management of cytopenic patients. Severe pancytopenia is a significant relation with the clinical outcome. It can be used as a prognostic indicator.

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