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Pathology

Study on Bone Marrow Profile of Patients with Pancytopenia in a Tertiary Care Centre

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Abstract: Pancytopenia is a common haematological entity that is characterized by the simultaneous presence of anemia, leukopenia and thrombocytopenia. A multitude of disorder primarily or secondarily affecting the bone marrow manifest with various haematological derangement, which is reflected in the peripheral blood, commonly as pancytopenia. Aspiration of bone marrow is an indispensible adjunct to the study haematopoietic disorder and is primarily utilized for cytological assessment. On the other hand, trephine biopsy allows for studies of the marrow's overall cellularity, detection of focal lesions and extends of infiltration by various pathologic entities.The present study was undertaken to evaluate the etiology of pancytopenia, was focused on clinical and bone marrow profile of each patient.In this cross-sectional study, A total of 102 patients with pancytopenia admitted in Calcutta National Medical College & Hospital in the Department of General Medicine and Department of Pediatric over a period of 1 year from August 2015 to July 2016 and met the inclusion criteria, were studied.Total of 102 patients, of whom 54 patients (53%) were male and 48 patients (47%) were female, were included in this study.The commonest age group affected was 16-30 years followed by 46-60years. The most common presenting complaint was fatigue and fever. The commonest physical findings were pallor followed by splenomegaly and hepatomegaly. Megaloblastic anemia (31%) was the commonest cause of pancytopenia, followed by aplastic anemia (22.5%), leukemia (13%).The present study concludes that detailed primary haematological investigations along with bone marrow examination of the patients with pancytopenia is helpful for understanding of the disease process, to diagnose or rule out the causes of pancytopenia and also in planning further investigations and management of these patients.
Keywords: Pancytopenia, Bone marrow aspiration, Bone marrow biopsy.

INTRODUCTION

Pancytopenia is a common haematological entity in which all three major cellular elements of blood are decreased in number. 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 [1]. Pancytopenia is a feature of some reversible condition as well as many life threatening conditions. The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patients [2]. The present study has been undertaken to evaluate the etiology of pancytopenia, focused on clinical and bone marrow profile of each patient to establish the etiological diagnosis. Thereby, this study would help in planning the diagnostic and therapeutic approach in patients with pancytopenia.

MATERIALS AND METHODS

The present study was conducted at the Department of Pathology in collaboration with the Department of General Medicine and the Department of Pediatrics, Calcutta National Medical College and Hospital, Kolkata during a period from August, 2015 to July, 2016. A total of 102 patients who met the inclusion and exclusion criteria were included in the study.

Inclusion Criteria

Patients of all age group with hemoglobin <10gm/dl, total count of white blood cells <4000/cmm and platelets < 100000/cmm [3]

Exclusion Criteria

Patients with bleeding diathesis, local site (hip area) infection/ sepsis and those unwilling to participate in the study. All patients were subjected to detailed history, general physical examination and investigations (complete hemogram, total count, differential count, ESR, corrected reticulocyte count, routine urine, liver function test, Chest X-ray, ultrasound abdomen, bone marrow aspiration and biopsy.

Cell count was performed by automated SYSMEX KX 21 cell counter. Values were correlated by direct peripheral blood smearexamination and also checked by Neubaur's counting chamber.

A few drops of EDTA-anticoagulated patient's venous blood were incubated with new methylene blue solution (supravital stain). A thin smear was prepared on a glass slide from mixture and reticulocytes were counted under microscope. Corrected reticulocyte count=Reticulocyte count x (Measured Hematocrit/ Normal Hematocrit).

Bone marrow aspiration and biopsy were subsequently carried out under aseptic precaution after obtaining written consent from the patient or guardian.

RESULTS

On the basis of criteria described, 102 patients with pancytopenia were studied and male preponderance (53%) was noticed with male: female ratio of 1.125.Majority of patients were young adult (11- 30 years).The commonest symptom was easy fatigability (91%) followed by fever (80%), petechie/purpura (23%), bleeding gum (18%). Other symptoms hemetemesis and malena were accounting for 14 and 10 % respectively.Pallor was present in all the patients (100%) followed by splenomegaly (34%), hepatomegaly (27%), glossitis (24.5%), pigmentation (21.6%), lymphadenopathy (17.7%), sternal tenderness (9.8%).

Table-1: Haemoglobin level in patient's withpancytopenia

Sr.no	Hbgm%	Severity of anemia	No of Patients	%(n=102)
1	≤4	Severe	33	32.35
2	4.1 to 7	Moderate	57	55.88
3	7.1 to 10	Mild	12	11.76

Haemoglobin level ranged from 2.3 gm% to 9.4 gm%. The mean hemoglobin level was 6.35 gm%. Majority of patients (56%) had moderate anaemia followed by severe anaemia in 32% and mild anaemia in 12% ofpatients.

Table-2: Distribution of Leucocyte count in patients with pancytopenia

Sr. No.	Leucocyte count (/cmm)	Total no of patients	% (n= 102)
1	≤1000	4	3.92
2	1000-3000	67	65.68
3	3000-4000	31	30.39

Total leucocyte count ranged from 500 to 3900 & mean was 2170/mm^3. Majority of the patients 67(66%) had Moderate degree of Leucopenia and 30% of the patient had mild leucopenia followed by severeleucopenia 4%.

Table - 3: Distribution ofAbsolute Neutrophil Count (ANC) in patients with pancytopenia.

Sr. No.	ANC	Total no.	%(n=102)
1	0-500	17	16.67
2	501-1000	48	47.06
3	1001-1500	28	27.45
4	>1500	09	08.82

Absolute neutrophil count ranged from 180 cells to 1620 cells/cmm. Majority (47%) had Absolute neutrophil count between 501 to 1000 cells/cmm followed by 27% had between 1001 to 1500 cells/cmm and 17% had ≤500 cells/cmm.

Table-4: Distribution of Platelet count in patients with pancytopenia

Sr. No.	Platelet count (/cmm)	Total no of patients	% (n= 102)
1	≤20000	11	10.78
2	21000-50000	44	43.14
3	51000-100000	47	46.08

Platelet count ranged from 10000 to 95000/cmm. Majority (46%) patients had platelet count

between 51000 to 100000 /cmm ,43 % patients had between 21000 to 50000 /cmm and 11 % had less than or equal to 20000/cmm.

Table-5: Distribution of corrected reticulocyte count in patients with pancytopenia

Sr. No.	Corrected Reticulocyte Count	Total no.	%
1	Low(<0.5%)	83	81.37
2	Normal(0.5-1.5%)	16	15.69
3	High(>1.5%)	03	2.94

Majority (81%) of patients had low corrected reticulocyte count followed by 16% patients had normal and 3% had high corrected reticulocyte count (Table-5).

Majority (58.82%) of the patients had hypercellular bone marrow followed byhypocellular (23.53%) and normocellular(17.65%) (Table-6).

Table - 6: Bone marrow cellularity in patients with pancytopenia

Sr. no.	Bone Marrow cellularity	No of patients	%
1	Hypocellular	24	23.53
2	Hypercellular	60	58.82
3	Normocellular	18	17.65

Table -7: Etiology of pancytopenia in the study population

Sr. No	Etiology	No. of Patients	%
1	Megaloblastic Anaemia	32	31.37
2	Hypo/Aplastic Anaemia	23	22.55
3	Acute leukemia	13	12.75
4	Infective	12	11.76
5	Myelodysplastic Syndrome	4	3.92
6	Metastasis	4	3.92
7	Multiple myeloma	3	2.94
8	Chronic liver disease	2	1.96
9	NHL	2	1.96
10	Hypersplenism	2	1.96
11	SLE	1	0.98
12	Myelofibrosis	1	0.98
13	Drug induced	1	0.98
14	Gaucher disease	1	0.98

The most common cause of pancytopenia was Megaloblasticanemia (31%) followed by Hypoplastic anemia (23%), Acute Leukemia (13%), Infective (12%) and MDS, Metastasis,Multiple myeloma. Other etiologies of pancytopenia are shown in the table.

DISCUSSION

Pancytopenia refers to the reduction in all three formed elements of blood i.e. erythrocytes, leucocytes and platelets. It is not a disease entity rather a triad of findings in a peripheral blood that may result from a number of disease processes.

102 patients with pancytopenia were included in the study during the period of one year and bone marrow aspiration and bone marrow biopsy and other relevant investigations were performed to ascertain probable etiology.

In the present study of 102 patients there were 54(53%) males and 48(47%) females with male to female ratio 1.125:1. The age of the patients range from 11 months to 78 years. Majority of patients (30%) in the present study were in the 11 to 30 years age group i.e. young adults.

Kumar R *et al.* studied 166 patients with pancytopenia and found mean age at presentation 30.6 years (range 12 – 73 years) with male preponderance (67.47%)[3].

Kishore Khodke *et al.* [5] noted male to female ratio 1.3:1; another study by khunger *et al.* [10] had male to female ratio 1.2:1 which are approximately similar to the present study.

Common presenting symptoms in present study were easy fatigability in 91%. Fever observed in 80% of patients. 41% patients presented with the bleeding tendencies in the form of petechie/purpurae (23%), Bleeding gums (18%), hematemesis (14%) and

malena(10%). Hemetemesis and Malena are mainly associated with chronic Liver disease.

A study including 30 patients of pancytopenia showed fatigue as the most common (86%) presenting symptom followed by fever (70%) as common presenting symptoms [4]. A study conducted by Khodke K et al with 50 cases of pancytopenia presented with fever (40%) followed by weakness (30%) and bleeding manifestations (20%)[5].

The presenting symptoms were usually attributed to anaemia, or thrombocytopenia. In the present study pallor was universally present in all the patients. 34% of the patients had splenomegaly and 27% had hepatomegaly, Lymphadenopathy in 18 % of cases and sternal tenderness in 10% cases. Knuckle pigmentation due to megaloblastic anemia was observed in 21% of cases. All the cases of CLD had icterus because of hepatocellular injury. Angular stomatitis and glossitis (25%) were observed due to nutritional deficiency.

One Indian study found pallor in all the patients followed by splenomegaly (40%), hepatomegaly (38%), purpuric spots (28%) and lymphadenopahty (12%)[5].

In the present study majority (56%) of patients had moderate anemia (Hb 4.1 to 7 gm%) followed by severe anaemia(≤4gm%) and mild anaemia. (7.1-10gm%)

Kumar *et al*. [3] had reported mild anaemia in 5 and moderate to severe anaemia in 16 patients out of 21 patients in his series without any particular reference to age and sex.

Total leucocyte count ranges from 500 to 3900. Mean 2170/mm3. Majority of patients (66%) in this study had moderate leucopenia (1000-3000) and 30% had severe leucopenia(<1000) followed by mild(>3000) leucopenia(4%) these findings are similar to those reported by scott *et al*. (1959) with mild and moderate leucopenia in 33.33% and 64.10% respectively, while Kit-fai-Wong *et al*. (1991) reported a still higher figure(83.33%) of moderate leucopenia and 16.67%mild leucopenia.

Absolute neutrophil count ranged from 180 cells to 1620 cells/cmm.

In present study majority of patients (47%) had Absolute neutrophil count between 501 to 1000 cells/cmm followed by 27% had between 1001 to 1500 cells/cmm and 17% had ≤500 cells/cmm.

A study by kondal Reddy and Saikrishna K.March2015 shows 30% patients with ANC between 0-600; 45% between 601 -1200 and 25% in 1201-1800. 75% of these developed fever due to infection and the risk is high if ANC is <500/cmm [4].

In the present study platelet count ranged from 10000 to 95000/cmm. Majority (46%) patients had platelet count between 51000 to 100000 /cmm with no clinically significant bleeding manifestation ,43 % patients had between 25000 to 50000 /cmm and 11 % had less than or equal to 25000/cmm.

Severe thrombocytopenia was recorded in 43.59% patients in his series by scott *et al*. with 35.89%moderate and 20.51% mild thrombocytopenia. Kit-Fai-Wong *et al*. [19] reported 83.33% of mild and 16.67% of moderate thrombocytopenia, while none had severe thrombocytopenia.

Majority of patients had corrected reticulocyte count low to normal; very few had high value in this study. Bone marrow examination was of great diagnostic value in patients of pancytopenia. Bone marrow cellularity has been examined in all 102 patients. In the present study bone marrow was hypercellular in majority (59%) of patients, hypocellular in 24% of patients and normocellular in 17% of patients. This is quite similar to that reported 51.72 % by Metikurke *et al*. in a series of 58 patients with pancytopenia. Al-Eissa *et al*. reported 87.5% hypercelllular and 12.5%normocellular bone marrow picture in a series of 16 patients with pancytopenia[6].

In the present study, the most common cause of pancytopenia was Megaloblastic anemia (31%) followed by Aplastic anemia (23%), Acute Leukemia(13%), Infective(12%). Other causes included myelodysplastic syndrome (4%), metastatic carcinoma (4%) and multiple myeloma (3%).

Most patients with megaloblastic anemia showed macrocytic erythrocyte in PBS examination.BM examination revealed hypercellular marrow with reversal of myeloid to erythroid ratio. Erythroid precursors showed megaloblastic features. Giant and abnormally shaped immature myeloid cells and enlarged hyperpolyploid megakaryocytes were also found. Vitamine B12 deficiency was found to be more common than folate deficiency in this patient. This is consistent with the result of similar studies conducted in India and its neighboring countries.

All cases of Aplastic anemia (22.5%) had hypoplastic/aplastic marrow. After bone marrow trephine biopsy examination, 20 cases were hypoplastic anemia and only 3 cases were confirmed as aplastic anemia. The etiology of aplastic anemia was idiopathic.

All thirteen cases of leukemia (12.75%) had hypercellular marrow. Blast cells were seen in all the cases. After detailed marrow examination seven cases

turned out to be acute lymphoblastic leukemia(FAB-ALL-L1/L2) and six case turned out to be acute myeloid leukemia among which two cases was diagnosed as acute promyelocytic leukemia and one as acute erythroid leukemia.

Among the infective etiology, 3 patients were diagnosed to be suffered from malaria, 2 patients each from leishmaniasis, dengue fever, hepatitis, typhoid fever and one was from disseminated tuberculosis.

Four patients of refractory anemia (4%), on doing bone marrow study/trephine biopsy turned out to be MDS. Bone marrow of these patients shown normo to hypercellularity with increased number of immature myeloid precursor cells and presence of ring sideroblasts with dyserythropoetic and/ or dysmegakaryocytic changes.

Bone marrow examination involving 148 patients shows hypoplastic bone marrow (29.05%), megaloblastic marrow (23.64%), hematological malignancies (21.62%), erythroid hyperplasia (19.6%) and normal bone marrow (6.09%)[7].

In the present study among four cases of metastatic carcinoma, three were deposit from prostatic adenocarcinoma (corroborated by raised serum PSA levels) and one from mixed germ cell tumor(corroborated by raised serum HCG and LDH levels).

In the present study 3 cases of Multiple myeloma had hypercellular marrow with >20% plasma cells and Plasmablasts with presence of M band on protein electrophoresis.

In the present study of 102 patients it was observed that megaloblastic anemia(31%) was the most common cause of pancytopenia. The incidence of megaloblastic anemia varies from 8% to 74% as a cause of pancytopenia in various studies [2,3,8].

A 1989 study based in India found that of 139 patients with megaloblastic anemia, 76% had B12 deficiency, 6.8% had folate deficiency,and 8.8% had a combination of both. Of this entire group,43.8% had pancytopenia.[9]

One Indian study involving 200 pancytopenic patients found megaloblastic anemia in 72% of cases as most common cause [10]. Another indian study found megaloblastic anemia to be the commonest cause (74.04%) of pancytopenia in 104 patients [11].

The second most common cause of pancytopenia in this study was aplastic anemia, which accounted for 22.5% of the cases. Similar results were observed by Reddy *et al*. who reported 26.2% incidence. The incidence of aplastic anemia worldwide is said to vary between 10% - 52.7%. In the study by Agarwal et al, aplastic anemia was the second most common cause of pancytopenia accounting for 14.28%. In several other studies, Aplastic anemia was the most common cause of pancytopenia [12,13].

In the present study, acute leukemias were the cause of pancytopenia in 12.75% cases and were the third most common cause of pancytopenia. One study reported 13.3% of cases of acute leukemias presenting with pancytopenia [14].

Among the infective cause, 3 cases of malarial fever, 2 cases of each for dengue fever, typhoid fever, leishmaniasis and viral hepatitis, observed in our study as the cause of pancytopenia with normo/ hypercellular marrow. One case of disseminated tuberculosis presented with pancytopenia with hypercellular bone marrow. All these cases were reversible and responded well to the treatment with restoration of cytopenias.

Comparing with other studies, In a study by Jalaee khoo et al. in Iran, the MDS was the forth common cause of pancytopenia after acute leukemia, AA, MA in a study of 188 adult patients i.e. 9.5%[13].

The Present study reported 2 cases(4%) of multiple myeloma 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[2,10,5].

Comparing the present study which has 2 cases of Alcoholic Chronic Liver Disease, in a study of the 250 cases of pancytopenia 27 were known cases of alcoholic liver cirrhosis[15].

Present study had 1 cases of SLE with hypocellular marrow. Santra G *et al*. studied 8 cases of SLE out of which 3 cases had hypocellular marrow and 5 cases had cellular marrow [16].

Awasthi and Ram [18] reported 22 patients with pancytopenia out of which 2 were due to hypersplenism comparable to our study.

Bhandari and Satyanarayan reported 6 patients with pancytopenia secondary to falciparum parasitemia. Patient presenting with pancytopenia had diverse etiologies and might have either cellular, hypocellular or hypercellular bone marrow morphology and there are few studies in the literature that explore the various etiological factors of pancytopenia with hypercellular or cellular marrow [17]. Hence present study conducted bone marrow study in all cases of pancytopenia along with other relevant investigations in order to know the etiology so that early intervention can be taken for the patient and enhance the survival rate.

CONCLUSION

Pancytopenia is a common problem encountered in clinical practice. As its etiology is varied so peripheral blood smear and bone marrow study helps us to reach a conclusive diagnosis. Megaloblastic anemia, which is a treatable and reversible disease, was found to be commonest underlying cause of the pancytopenia among adults. This can be attributed to the fact that undernutrition, malabsorption and practice of strict vegetarianism are more common in this part of our country.

So it is essential to work up all cases of pancytopenia so that curable disease can be identified and treated. Rapid diagnosis also helps to reduce morbidity and mortality in life threatening disease by early intervention. Bone marrow aspiration and biopsy examination gives a fairly accurate diagnosis of pancytopenia in a short period of time and may prevent unnecessary burden on already stressed laboratory in developing country like ours.

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