Pancytopenia – A Clinico Hematological Evaluation

[1]Arun P Bakshi, [2]Pradnya S Bhadarge, [3]Asha Zutshi

[1]*Associate Professor, Indira Gandhi Government Medical College, Nagpur, Maharashtra.*
[2]*Assistant Professor, Indira Gandhi Government Medical College, Nagpur, Maharashtra.*
[3]*Consultant pathologist, Nagpur, Maharashtra.*

Abstract

Pancytopenia is a disorder composed of a triad of anemia, leucopenia and thrombocytopenia due to reduced hematopoietic cells in bone marrow. There are various causes leading to pancytopenia like infections, chemotherapy, drugs, nutritional deficiency, malignancy etc. Therefore, identifying the exact cause will help in implementing appropriate therapy. Aim and objectives: 1) To find out various causes of pancytopenia. 2) To determine age wise and sex-wise distribution of various causes of pancytopenia. 3) To study clinical manifestations and hematological parameters in pancytopenic patients. Material & methods: 100 pancytopenic patients were evaluated for their clinical presentation along with hematological parameters and bone marrow examination in the department of pathology at our institute. Results: Pancytopenia is seen in all age groups with preponderance in second, third and fifth decade with M:F ration being 1.63:1. Anemias are the commonest cause of pancytopenia with megaloblastic anemia (46%) topping the list followed by dimorphic anemia and hypoplastic anemia. Malaria (11%) is second most common cause for pancytopenia. Generalized weaknesses, fever, easy fatigability, pallor, hepatosplenomegaly are the common clinical presentation in pancytopenic patients. Routine hematological investigations were done in all cases. Bone marrow aspiration was done in 70 patients and bone marrow biopsy in 16 patients. Lowest hemoglobin level was of 1.2 g/dl was seen in megaloblastic anemia, lowest total leucocyte count of 500/mm3 was noted in hypersplenism and lowest platelet count of 1000 / mm^3 was observed in hypoplastic anemia. RBC morphology was dimorphic anemia (36%) followed normocytic normochromic anemia (27%). Conclusion: Megaloblastic anemia reflects higher prevalence of pancytopenia followed by malaria and aplastic anemia. These varied causes of pancytopenias presents with varied clinical picture and hematological parameters.

Keywords: *cause, hematological parameters, megaloblastic anemia, pancytopenia.*

I. INTRODUCTION

Pancytopenia is simultaneous presence of anemia, leucopenia and thrombocytopenia. It is not a disease entity in itself, but a triad of findings that may arise from a number of disease processes.[1] The presenting symptoms are attributable to anemia or thrombocytopenia. Leucopenia is an uncommon cause of initial presentation. However, it is the most serious complication during the course of the disease.[2] The diseases leading to pancytopenia vary depending upon differences in age, nutritional status and prevalence of infective disorders.[3] List of possible underlying etiologies are frequently provided with occasional discussion over most of the common causes of pancytopenia with a suboptimal investigative approach. Some experts suggest that bone marrow examination is essential for diagnosis of pancytopenia but it has not been established that whether the procedure is necessary in all patients.[4] Usually presentation of pancytopenia alarms for a possibility of either a bone marrow failure syndrome or acute malignancy especially when associated with lymphadenopathy or organomegaly.[5] This study highlights some other important causes of pancytopenia that may change the viewpoint of both the patient and treating physician.

II. AIM AND OBJECTIVES

1. To find out various causes of pancytopenia
2. To determine age wise and sex-wise distribution of various causes of pancytopenia
3. To study clinical manifestations and hematological parameters in pancytopenic patients.

III. MATERIAL AND METHODS

The present study carried out over a period of 2 years at department of pathology at our institute. Study subjects were patients of all ages and sexes coming to hematology section having all three of following parameters on complete blood count (CBC) ie. Hemoglobin (Hb) < 10gm/dl, total leucocyte count (TLC) < 4000/mm^3 and platelet count < 1,50,000/mm^3.[T]there were no exclusion criteria's. The clinical examination of the patient was done in detail. Following investigations were done:

1. CBC- The samples were run on automated blood cell counter (sysmex KX-21) and parameters like Hb, PCV, RBC count, MCV, MCH, MCHC, WBC count, platelet count were noted. Peripheral smear (PS) was stained with leishman's stain.[6]
2. Reticulocyte count [6]

3. Bone marrow aspiration (BMA)- BMA was done using method described by Bain BJ under all aseptic precautions. [6] Informed consent of patients was obtained. Bone marrow aspiration smears were examined for
   I) Cellularity
   II) M:E ratio
   III) Erythropoiesis
   IV) Myelopoiesis
   V) Thrombopoiesis
   VI) Parasites
   VII) Abnormal cells
4. Bone marrow biopsy (BMB)- BMA was done using method described by Bain BJ [6] under all aseptic precautions. Informed consent of patients was obtained.
5. Special stains- Special stains like Myeloperoxidase (MPO), Sudan Black B (SBB), Periodic Acid Schiff's (PAS) were performed wherever necessary. [7]

IV. RESULTS

100 patients who presented with pancytopenia were studied over a period of two years. Primary hematological procedures were carried out in all 100 patients. PS findings were noted. BMA was done in 70 cases and yielded adequate material in 63 cases where as dry tap was seen in 7 cases. In cases where BMA was a dry tap or inadequate, BMB was done and it was diagnostic. BMB was done in 16 cases which included in 3 cases of megaloblastic anemia and 2 cases of viral fever with dry tap on BMA, 3 cases of aplastic anemia and 6 cases of hypoplastic anemia for confirmation of diagnosis which included 1 case of hypoplastic anemia with dry tap on BMA and 2 cases of subleukemic leukemia which on BMA were reported as megaloblastic anemia and inadequate respectively.

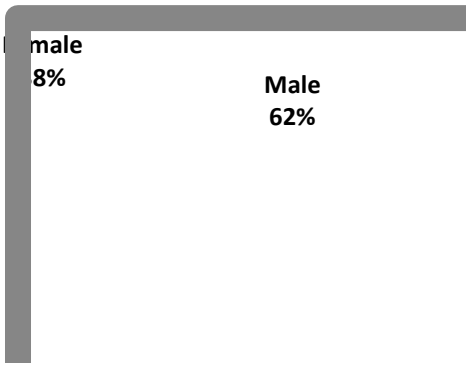
A. Age wise and sex wise distribution of cases of pancytopenia

The age of patient in the present study ranged from 2 years to 71 years. Maximum numbers of cases were seen in second decade (28%). (Table I) Maximum number of cases were seen in male patients (62%) compared to female patients (38%) with M:F ration of 1.63:1. (Graph I)

Table I- Age Wise Distribution of Cases in Pancytopenia

Age range in years	No of cases	Percentage
0-10	8	8
11-20	28	28
21-30	20	20
31-40	11	11
41-50	18	18
51-60	9	9
61-70	5	5
71-80	1	1
Total	100	100

GRAPH I- Sex Wise Distribution of Cases Of Pancytopenia



B. Clinical Presentation In Cases Of Pancytopenia-

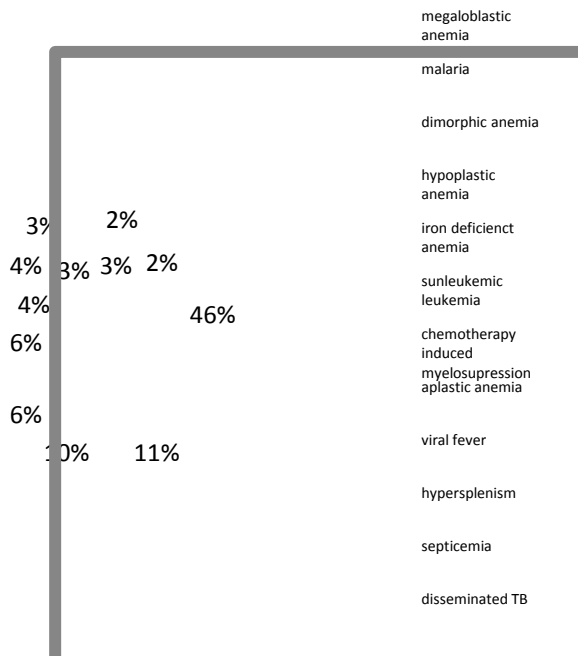
The commonest mode of presentation was generalized weakness followed by fever and easy fatigability. Pallor was noted in all the cases. The other clinical findings were hepatosplenomegaly. (Table II)

Table II- Showing Clinical Presentation Of Patients With Pancytopenia

Sr no	Presenting complaint	Percentage (%)	Clinical findings	Percentage (%)
1	Generalized weakness	77	Pallor	100
2	Fever	46	Splenomegaly	33
3	Easy fatigability	35	Hepatomegaly	29
4	Dizziness	29	Edema feet /POF	23
5	Breathlessness	27	Petechiae/purpura	14
6	Bleeding manifestations	16	Lymphadenopathy	8
7	Weight loss	12	Sternal tenderness	5
8	Total	100	Total	100

C. Causes Of Pancytopenia

In the present study anemia was the commonest cause for pancytopenia contributing 71% cases of which megaloblastic anemia was predominant with 46% cases followed by dimorphic anemia (10%). Other common causes were malaria (11%) followed by subleukemic leukemia (4%). (Graph 2)



GRAPH II- Showing Causes Of Pancytopenia

Table III- Hematological Parameters In Pancytopenic Patients

Diagnosis	Hematological parameters			
	Hb g/dl	TLC /mm^3	Platelet /mm^3	MCV fl
Megaloblastic anemia	3.24	2158.7	78086	105.12
Malaria	6.72	2936.36	70727.3	78.9
Dimorphic anemia	3.4	2200	73500	79.2
Hypoplastic anemia	3.34	2133	14833	92.5
Iron deficiency anemia	3.38	2083.3	114666	68.36
Subleukemic leukemia	4.48	2725	56500	91.25
Chemotherapy induced myelosupression	8.03	2000	69750	78.18
Aplastic anemia	4.73	2633.33	26666.6	98.4
Viral fever	4	2266.67	28333.33	98
Hypersplenism	4.33	900	31000	78.67
Septicemia	9.8	3050	100000	70.05
Disseminated TB	5.45	2100	15500	95.25

D. RBC Morphology In PS In Pancytopenic Patients

Dimorphic anemia was seen in 26% of cases followed by normocytic normochromic anemia (27%), macrocytic anemia (26%) and microcytic anemia (11%).

E. Bone Marrow Cellularity

BMA (n=70) in present study showed three distinct types of cellularity- hypercellular, hypocellular and normocellular. Hypercellular marrow was seen in 49 (70%) of cases, hypocellular in 9 (12.85%) and normocellular in 5 (7.15%) cases. In 7 (10%) of cases BMA was inadequate or dry tap.

D. Pancytopenia with hypercellular marrow

Pancytopenia with hypercellular marrow was seen in cases of megaloblastic anemia (63.27%), dimorphic anemia (18.37%), iron deficiency anemia (10.20%), subleukemic leukemia (4.08%) and hypersplenism (4.08%).

In the present study, megaloblastic anemia was the commonest cause of pancytopenia with hypercellular marrow. Maximum number of cases of megaloblastic anemia was seen in second decade and males were commonly affected. The patients presented with generalized weakness, dizziness, easy fatigability along with fever in 16 patients and bleeding manifestations in 5 patients. Pallor was seen in all the patients followed by edema feet / POF in 15 patients, Hepatomegaly in 5 and splenomegaly in 4. In majority of cases, RBC morphology was macrocytic (52.2%) and dimorphic picture (43.5%). BMA was satisfactory in 33 out of 36 cases with hypercellular smears. Cells of erythroid serious showed hyperplasia with megaloblastic reaction. Myelopoiesis revealed giant myelocyte and metamyelocyts. Megakaryopoieis was normal. In 3 cases BMA was dry tap. These cases on BMB showed hypercellular marrow with erythroid hyperplasia. (Figure 1)

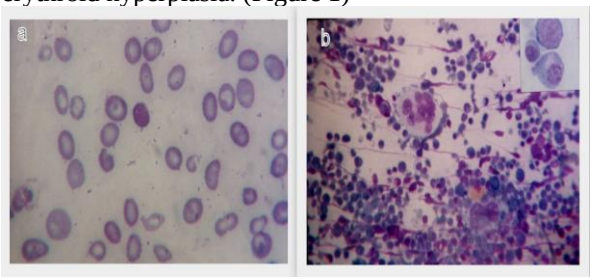


Figure 1: a) PS showing macro-ovalocytes (Leishman stain, 40X), b) BMA smear showing hypercellular marrow with erythroid hyperplasia and megaloblasts (Leishman stain, 40X) Inset : megaloblast (Leishman stain, 100X)

In the present study 10 cases of dimorphhic anemia were seen which presented with pancytopenia. The age of patient ranged from 14-45 years with 6 males and 5 females. Patients presented with generalized weakness, easy fatigability and dizziness along with pallor, edema in 2 cases and splenomegaly in 1 case. PS showed presence of both microcytic and macrocytic RBCs along with leucopenia and thrombocytopenia. BMA was done in all the cases and showed hypercellular marrow with micronormoblasts and megaloblasts in cluster. Myelopoiesis and thrombopoiesis were normal. (Figure 2)

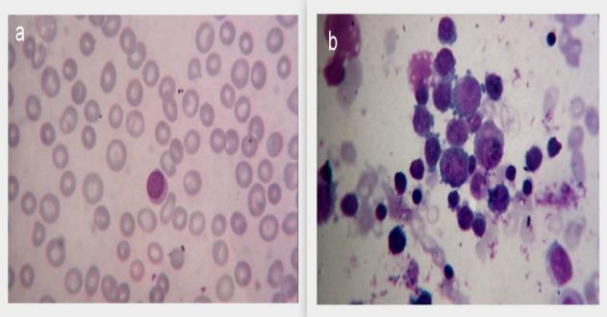


Figure 2: a) PS showing microcytes and macrocytes (Leishman stain, 40X), b) BMA smear showing both micronormoblasts and megaloblasts (Leishman stain, 40X)

6 cases IDA with pancytopenia were seen in the age range of 2nd to 7th decade. Presenting symptoms were generalized weakness, easy fatigability. Pallor was universal sign. PS showed anisopoikilocytosis, microcytes with moderate to sever hypochromia, tear drop cells and pencil cells were seen. BMA was done in 5 out of 6 cases and showed erythroid hyperplasia with micronormoblasts in clusters. Granulopoiesis and thrombopoiesis were normal. (Figure 3)

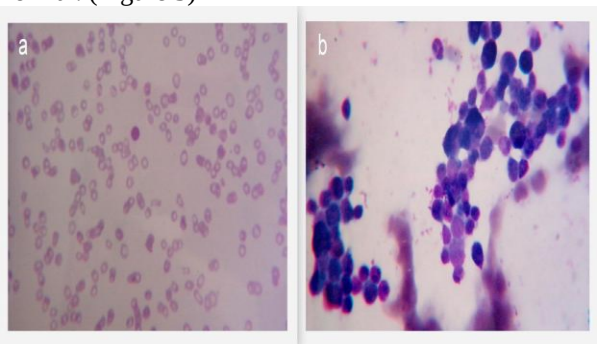


Figure 3: a) PS showing microcytic hypochromic RBC's (Leishman stain, 40X), b) BMA smear showing both micronormoblasts in clusters (Leishman stain, 40X)

4 cases of subleukemic leukemia were seen, 3 cases of AML and 1 case of ALL. Patients presented with fever, generalized weakness, easy fatigability and weight loss along with pallor and sterna tenderness. PS showed normocytic normochromic anemia with leucopenia and thrombocytopenia. Myeloblasts with auer rods constituted 6%, 14% and 19% of cells respectively in myeloblastic type and lymphoblastic type showed 18 % of lymphoblasts BMA in subleukemic AML showed hypercellularity in one case and 2 cases showed hypocellularity. Majority of cells were Myeloblasts with reduced erythropoiesis and thrombopoiesis. (Figure 4) Blasts were MPO and Sudan black B positive. BMA in subleukemic ALL showed hypercellular marrow with reduced erythroid, myeloid and megakaryocytic series. 90% cells were lymphoblasts which stained positive on PAS staining.

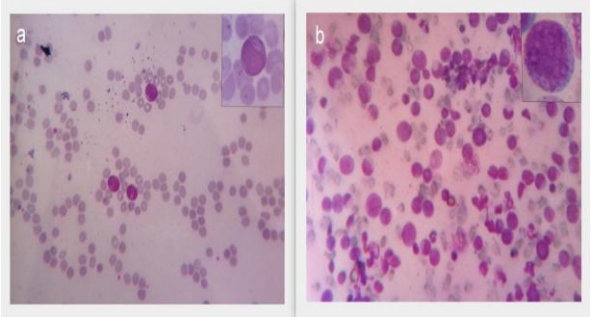


Figure 4: a) PS showing Myeloblasts (Leishman stain, 40X), Inset: myeloblast with auer rod(Leishman stain, 100X) b) BMA smear showing Myeloblasts (Leishman stain, 40X) Inset : Myeloblasts with 3-4 nucleoli (Leishman stain, 100X)

3 cases of hypersplenism with pancytopenia were seen. Presenting complaints were generalized weakness and distension of abdomen. On clinical examination severe pallor was present along with moderate to massive splenomegaly. PS showed dimorphic and megaloblastic anemia.

3 cases of viral fever presented with pancytopenia. Symptoms were high grade fever with bone pains and generalized weakness. Pallor was seen in all cases and splenomegaly in one case. Ps showed dimorphic anemia, leucopenia, thrombocytopenia and lymphocytosis. BMA tried in 2 cases was inconclusive. BMB was within normal limits in both the cases.

E. Pancytopenia associated with hypocellularity - hypoplastic / aplastic anemia

9 patients out of 100 cases of pancytopenia belonged to hypoplastic / aplastic anemia subgroup. Highest incidence of hypoplastic anemia / aplastic anemia was in 11-20 years age group with male predominance. Patients presented with generalized weakness and fever along with pallor, edema feet, and lymphadenopathy in one case. Normocytic normochromic anemia was the commonest blood picture seen in hypoplastic / aplastic anemia followed by dimorphic anemia. BM was hypocellular with increase in fat and decrease in all the three hematopoietic series. Causes of hypoplastic/ aplastic anemia were drug induced myelosupression secondary to intake of diclofenac sodium in 2 cases and post infectious hepatitis in 1 case. In remaining 6 cases cause could not be determined. (Figure 5)

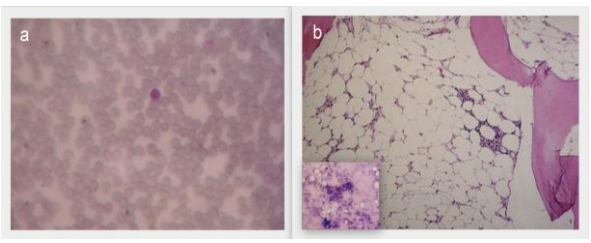


Figure 5: a) PS showing normocytic normochromic RBC's (Leishman stain, 40X), b) BMB smear showing hypocellular marrow with increase in fat cells (Hematoxaline & Eosine, 10X) Inset : BMA showing hypocellularity (Leishman stain, 40X)

Malarial infestation was seen in 11 cases. It formed the second common group of pancytopenia. Patients presented with fever with chills and rigor, vomiting, headache with pallor and hepatosplenomegaly. Ps showed normocytic normochromic anemia and gametocytes of plasmodium falciparum seen in 10 cases and 1 case showed gametocyte of plasmodium vivax. (Figure 6)

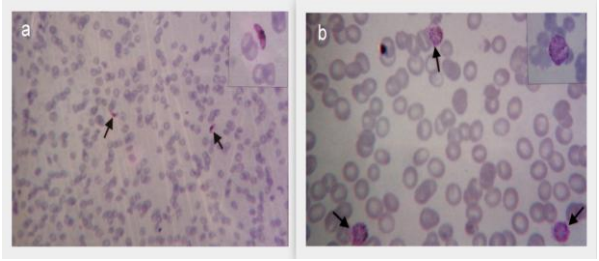


Figure 6: a) PS showing gametocyte of plasmodium falciparum (Leishman stain, 40X) Inset: gametocyte of Pl. falciparum (Leishman stain, 100X), b) PS showing gametocyte of plasmodium vivax (Leishman stain, 40X) Inset: gametocyte of Pl. vivax (Leishman stain, 100X)

2 cases of pancytopenia associated with septicemia were seen in 20 year old and 2 year old male patient. Both patients presented with high grade fever, generalized weakness and gram negative bacilli seen on culture. 2 cases of disseminated tuberculosis (TB), 1 each in 20 year old female and 55 years male were seen. Both patients gave history of low grade fever with evening rise of temperature, generalized weakness and weight loss. On examination both patients were pale and cachexic. X ray chest revealed bilateral pleural effusion in both cases. In one case septated ascitis with splenic nodules were seen while other case showed nodules on kidney. 4 cases of chemotherapy induced myelosupression were seen, 2 cases of AML and 1 case each of ALL and Hodgkin's lymphoma. Presenting complaint was generalized weakness mainly. PS showed normocytic normochromic anemia, leucopenia and thrombocytopenia. 2 cases, 1 each of AML and ALL showed presence of 10% and 16% blasts on PS.

V. DISCUSSION

Pancytopenia is a common clinical condition encountered in clinical practice. It should be suspected when a patient presents with anemia, prolonged fever and bleeding tendencies. Data regarding age, sex, presenting complaints, various causes of cytopenias and hematological parameters were noted and compared with those of other studies.

In the present study, the age of the youngest patients seen was 2 years which was similar to study by Gayathri BN et al (2011)[8] while in other studies done by Bharath C et al (2013)[9] , Dasgupta S et al (2015)[10], Jain A et al (2013)[11], Graham S et al (2015)[12] , Manzoor F et al (2014)[13] it was 16 years, 3 years, 2 months , 6 years, 8 years respectively. Age of oldest patient was 71 years while in other studies by Gayathri BN et al (2011)[8], Bharath C et al (2013)[9], Dasgupta S et al (2015)[10], Jain A et al (2013)[11], Graham S et al (2015)[12], Manzoor F et al (2014)[13] it was 80 years,58 years,84 years, 95 years,75 years, 69 years respectively. In the present study, M:F ratio was 1.63:1 which was coinciding with study of Manzoor F et al (2014)[13]. Other studies also showed male preponderance. Jain A et al (2013)[11]got higher M:F ratio of 2.6:1 while it was 1.2:1 in study by Gayathri BN et al (2011)[8]. Maximum number of cases in the present study was encountered in second and third decade (48%) which was similar to findings by Gayathri BN et al (2011)[8], Dasgupta S et al (2015)[10], Jain A et al (2013)[11], Makheja KD et al (2013)[14] and Graham S et al (2015)[12]. While in studies by Bharath C et al (2013)[9] and Manzoor F et al (2014)[13] maximum number of cases was seen in the second decade.

Generalized weakness was the commonest presenting complaint in the present study, seen in 76%. This finding is similar to the studies by Gayathri BN et al (2011)[8], Dasgupta S et al (2015)[10] , Manzoor F et al (2014)[13]. But fever was commonest presentation in studies by Bharath C et al (2013)[9] accounting for 63% and Graham S et al (2015)[12] accounting for 37%. Easy fatiguability and dizziness were next major symptoms which were seen in 35% and 29% patients respectively. Graham S et al (2015)[12] found fatigability and weakness as next common presenting complaints accounting for 20% each. While Gayathri BN et al (2011)[8] found dyspnea (43.2%) and fever (38.46 %) as another symptoms. Pallor was the commonest physical finding seen in all patients in the present study. This is similar with the findings of Gayathri BN et al (2011) [8], Bharath C et al (2013)[9], Dasgupta S et al (2015)[10], Manzoor F et al (2014)[13]. Splenomegaly was seen in 33% cases which was comparable to Gayathri BN et al (2011)[8] (35.57%). Manzoor F et al (2014)[13] found splenomegaly in 22% of cases. Third common finding was hepatomegaly seen in 29% of cases in the present study. Other studies showed lower incidence of Hepatomegaly as compared to the present study. Gayathri BN et al (2011)[8] and Manzoor F et al (2014)[13] found Hepatomegaly in 26.9% and 14% cases respectively. Lymphadenopathy in present study was noticed in 8% cases while Graham S et al (2015)[12] noticed lymphadenopathy in 10% of cases. In the present study 23% cases had edema feet or puffiness of face which is comparable to study by Aziz T et al (2010)[15] (24%). Incidence of petechiae

or purpura observed in 14% cases is low as compared to study by Aziz T et al (2010).[15]

Present study showed megaloblastic anemia (46%) to be the commonest cause for pancytopenia which is comparable with the studies done by Gayathri BN et al (2011)[8] (74.4%), Bharath C et al (2013)[9] (72%), Manzoor F et al (2014)[13] (56%), Makheja KD et al (2013)[14] (41.9%). While Dasgupta S et al (2015)[10] found aplastic anemia (33.47%) as most common cause followed by megaloblastic anemia (20.97%) and hypersplenism (13.71%) and leishmaniasis (13.71%). Jain A et al (2013)[11] found hypersplenism(29.2%) as most common cause of pancytopenia and Graham S et al (2015)[12] found normoblastic erythroid hyperplasia (30%) followed by megaloblastic anemia (20%). The second most common cause resulting in pancytopenia was malaria which is in contrast to studies by Gayathri BN et al (2011)[8] , Bharath C et al (2013)[9], Manzoor F et al (2014)[13] who found aplastic anemia as second most common cause. Makheja KD et al (2013)[14] found AML (27.4%) as second most common cause.

Hb level in megaloblastic anemia in the present study was 3.24 g/dl which was lowest level while in septicemia showed highest level of 9.8 g/dl. In other studies, Gayathri BN et al (2011)[8] , Dasgupta S et al (2015)[10], Manzoor F et al (2014)[13] Hb levels ranged from 1.8 to 9.2 g/dl, 1.4-9 g/dl, 2-9 g/dl respectively. TLC in the present study ranged from 900 g/dl in hypersplenism to 2936.36 /mm3in malaria while Gayathri BN et al (2011)[8] showed TLC ranged from 500 to 3900/mm3 in megaloblastic anemia while Dasgupta S et al (2015)[10] noticed TLC from 500 in leishmaniasis to 3900/mm3 in leishmaniasis and hypersplenism.

Mean platelet value in the present study ranged from 14833 in hypoplastic anemia to 114666 /mm3 in iron deficiency anemia in studies. While in study by Gayathri BN et al (2011)[8] platelet count ranged from 12,000/mm3 to 95000/mm3 and in study by Dasgupta S et al (2015)[10] it ranged from 10000 to 95000/mm3.

On PS dimorphic anemia was commonest finding accounting for 36 % which was comparable to study by Gayathri BN et al (2011)[8] (37.5%) while Manzoor F et al (2014)[13] found anisocytosis (58%) as commonest finding on PS. Second common finding in the present study was normocytic normochromic anemia (27%) followed by macrocytic anemia (26%). While Gayathri BN et al (2011)[8] found macrocytic anemia (31.7%) and Manzoor F et al (2014)[13] found normocytic normochromic anemia (34%) as second common finding on PS.

VI. CONCLUSION

Pancytopenia is not an uncommon hematological problem encountered in clinical practice. Physicians should have high index of suspicion when patient presents with unexplained anemia, fever and bleeding with hematological parameters like Hemoglobin < 10gm/dl, total leukocyte count (TLC) < 4000/mm^3 and platelet count < 1,50,000/mm^3. The present study concludes that complete clinical history, complete hematological work up along with bone marrow examination is important to rule out the cause and diagnose pancytopenia. Megaloblastic anemia and malaria followed by aplastic anemia constitute major causes of pancytopenia. Most of the causes were treatable. Therefore stringent diagnostic criteria and a general conceptual work up for determining the cause of pancytopenia is therefore necessary and a demand of time.

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