A cross sectional study of clinical and aetiological profile of pancytopenia at a tertiary care hospital in Bhopal

Nitin Rohira[1], Farah Jalaly Meenai[2,*]

[1]Post Graduate Student, [2]Professor, Dept. of Pathology, Chirayu Medical College and Hospitals Bairagarh Bhopal, Madhya Pradesh, India

***Corresponding Author: Farah Jalaly Meenai**
Email: farahjalaly@gmail.com

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Abstract

Introduction: Pancytopenia is an important clinico-haematological entity observed in our day to day clinical practice. It is a disorder in which all the three major formed elements of blood (red blood cells, white blood cells and platelets) are decreased in number. The causes of pancytopenia can be due to decrease in hematopoietic cell production in the marrow resulting from infections, toxins, malignant cell infiltration, post- chemotherapy or post-radiation.

Materials and Methods: 150 patients having pancytopenia were included in the present study. The study was conducted in the Department of Pathology of Chirayu Medical College & Hospitals, Bhopal. The study period was 1 July 2016 to 31 December 2017. Study was performed in patients attending outdoor and indoor departments of Chirayu medical college and hospitals, Bhopal. Informed consent was obtained from each of the patient fulfilling the inclusion criteria prior to their enrolment in the study. Those how had age<10 years and not giving consent were excluded. The patients were interviewed for relevant history including treatment history, history of drug intake, radiation exposure and examined for important physical findings such as pallor, icterus, hepatomegaly, splenomegaly, lymphadenopathy and ascites.

Results: This is a clinico-haematological study on Pancytopenia and its correlation with bone marrow aspiration carried out in the Department of Pathology over a period of one and half year from 1 June 2016 to 31 December 2017. A total number of 150 patients in all the age group presenting with pancytopenia were evaluated. Out of 150 cases 95 were males and 55 were females. The age of the patients ranged from 0 years to >70 years. 64% cases were observed in the age group of 11-30 years. Most of the patients were in the age group of 11-30 years. Megaloblastic anaemia was the commonest underlying etiology of pancytopenia in 50% patients. Next common cause was hypersplenism in 18% and aplastic anaemia in 11% cases. Acute leukaemia was the cause in 9%. MDS was seen in 10%. Nutritional anaemia was seen in 2% patients.

Conclusion: The present study concludes that detailed primary hematological investigations along with bone marrow aspiration in pancytopenic patients are helpful for understanding disease process and to diagnose or to the rule out causes of pancytopenia. These are also helpful in planning for further investigations and management.

Keywords: Pancytopenia, Bone marrow aspiration, Megaloblastic anemia, Aplastic anemia.

Introduction

Pancytopenia is an important clinico-haematological entity encountered in our day to day clinical practice. It is a disorder in which three major formed elements of blood (red blood cells, white blood cells and platelets) are decreased in number.[1]

The causes of pancytopenia can be due to decrease in hematopoietic cell production in the marrow resulting from infections, toxins, malignant cell infiltration, chemotherapies and radiation.[2]

Ineffective hematopoiesis with cell death in the marrow; formation of defective cells which are rapidly removed from circulation; sequestration and/or destruction of cells by the action of antibodies or trapping of normal cells in a hypertrophied and over-reactive reticuloendothelial system may result in pancytopenia. Patients usually present with complaints related to anemia, leukopenia and thrombocytopenia, which if not diagnosed at an early stage, may be fatal.[3]

Peripheral blood basically contains erythrocyte blood cells, platelets and leukocytes (granulocytes, lymphocytes and monocytes) within ranges of them. Pancytopenia is defined as a reduction of all the three formed elements of blood below the normal reference range. Pancytopenia is a temporary or permanent pathologic finding in the peripheral blood that is a result of a disease, not a disease.

The causes of pancytopenia are bone marrow-originated causes (aplastic anemia, myelodysplastic syndrome, etc), bone marrow infiltration (myelofibrosis, acute leukemia, multiple myeloma, metastatic carcinoma, hairy cell leukemia), splenomegaly (congestive splenomegaly, hematological malignancies splenic infiltration, storage diseases, primary splenic pancytopenia), paroxysmal nocturnal hemoglobinuria, tuberculosis, brucellosis, Q fever, Legionnaires' dis-ease, fungal infection and septicemia, and other rea-sons (sarcoidosis, systemic lupus erythematosus, anorexia nervosa, alcoholism, vitamin B12, folic acid deficiency, coagulopathy).[4]

In published articles from different countries, megaloblastic anemia was the most reported cause of pancytopenia, followed by aplastic anemia and other hematological diseases, respectively Male to female ratios varied in those articles and found to be more common in the age group of 10 to 40 years.[5,6]

Careful assessment of the blood elements is often the first step in assessment of hematologic function and diagnosis of disease. Physical findings and peripheral blood picture provides valuable information towards the work up of

pancytopenic patients and help in planning investigations on bone marrow samples.[7] Bone marrow aspiration remains the essential tool in the diagnosis of aplastic anaemia and malignant disorders.[8]

Bone marrow evaluation is an invaluable diagnostic procedure which may confirm the diagnosis of suspected cytopenia, from the clinical features and peripheral blood examination. It may occasionally give a previously unsuspected diagnosis.[9]

The spectrum of disorders primarily or secondarily affecting the bone marrow may manifest with peripheral pancytopenia.[10]

A detailed history, physical examination, and review of blood film remains fundamental to the diagnosis.[11]

The present study is intended to evaluate the various causes of pancytopenia, in patients admitted to Chirayu Medical College and hospitals and correlate the clinical and haematological findings with bone marrow aspiration.

Aims and Objectives

The study was undertaken with the aim of studying clinicohaematological correlation of pancytopenia, Furthermore, to find out peripheral blood smear findings, bone marrow aspirate and to correlate them. The etiopathological causes of pancytopenia in patients admitted to Chirayu medical college and hospitals Bairagarh Bhopal.

Materials and Methods

The present study was conducted in the Department of Pathology, Chirayu Medical College and Hospitals, Bhopal over a period of one and half year from 1 June 2016 to 31 December 2017. All the OPD and indoor patients admitted were included in the study.

Inclusion criteria were as follows:

Presence of two or all three of the following:

1. Hemoglobin < 11.5 gm/dl in females, and < 13.5gm/dl in males
2. Total leukocyte count(TLC) < 4000/ul
3. Platelet count < 100000/ul

Exclusion criteria were as follows:

1. Patients who have already been diagnosed with pancytopenia.
2. Patients who do not give consent for bone marrow aspiration and biopsy.
3. Patients who have recently received blood transfusions.
4. Patients who were on chemotherapy/radiotherapy.

Methodology

The study was performed in patients attending outdoor and indoor departments of Chirayu medical college and hospital, Bhopal (CMCH). Informed consent was obtained from each of the patient fulfilling the inclusion criteria prior to their enrolment in the study. The patients were interviewed for relevant history including treatment history, history of drug intake, radiation exposure and examined for important physical findings such as pallor, icterus, hepatomegaly, splenomegaly, lymphadenopathy and ascites.

Sample collection was carried out under strict aseptic precaution 3 ml of blood was collected by vene puncture. The sample was put in an ethylenediamine tetra-acetic acid (EDTA) coated vial and, at the same time, a drop of blood was used to prepare peripheral blood smear on a glass slide. Complete hemogram was performed with collected EDTA anticoagulant blood on automated cell counter analyser (BC 5380, 5-part differential cell counter). Blood and bone marrow smears were stained with various stains as per requirement.

Results

The present study evaluated 150 patients with pancytopenia who fulfilled the inclusion criteria and consented to enrollment in the study. In our study we performed bone marrow aspirate examination in 150 cases which presented in the peripheral blood film with pancytopenia (i.e. leucopenia, anemia and thrombocytopenia).

Our study has also included the correlation with physical findings like ascitis, bleeding, icterus, lymphadenopathy, hepatomegaly, edema, pallor and splenomegaly. We also correlated with the sign and symptoms (complainls) of the patient presented in CMCH. Major complains in the cases of pancytopenia were abdominal distention, abdominal pain, back pain, bleeding, breathlessness, fever, hemoptysis, hematemasis, hematuria, joint pain, loose motion, swelling, weakness and vomiting.

Complete hemogram and peripheral smear examination was performed in all the 150 patients. Bone marrow aspiration was performed in all 150 patients.

Megaloblastic anaemia was observed in 75 (50%) patients. Hypersplenism was seen in 27(18%) cases. Aplastic anaemia was detected in 17(11%) and acute leukaemia was detected in 13(9%). The other etiology of pancytopenia included myelodysplastic syndrome which was seen in 15(10%) and nutritional anaemia see in 3(2%) patients. Megaloblastic anaemia was the most common etiology observed in pancytopenic patients and hypersplenism was the second common cause of paneytopenia in our study.

Table 1: Distribution of different causes of pancytopenia

Etiology	Number of patients					
	M	**%**	**F**	**%**	**Total**	**%**
Megaloblastic Anaemia (MA)	46	48	29	53	75	50
Hypersplenism (HS)	20	21	7	13	27	18
Aplastic Anaemia (AA)	10	11	7	13	17	11
Acute Leukaemia (AL)	8	8	5	9	13	9
Myelodysplastic Syndrome (MDS)	9	9	6	11	15	10
Nutritional Anaemia (NA)	2	2	1	2	3	2
Grand Total	**95**	100	**55**	100	**150**	100

Out of the 150 patients included in the present study, the percentage distribution of females was 55% and of males was 95 % were males with an overall approximate Male: Female ratio of 1.7:1.

Table 2: Age distribution in different causes of pancytopenia

Age Group (in Years)	Pancytopenia							
	MA	**HS**	**AA**	**AL**	**MDS**	**NA**	**n**	**%**
1-10	1	1	0	0	2		4	3
11-20	14	3	8	4	1	2	32	21
21-30	17	6	4	1	4		32	21
31-40	9	3	0	3	5		20	13
41-50	9	7	3	1	2		22	15
51-60	12	3	1	4	1		21	14
61-70	10	1	1	0	0	1	13	9
> 70	3	3	**0**	0	0		6	4
Total	**75**	**27**	**17**	**13**	**15**	**3**	**150**	**100.0**

Abbreviations: MA: Megaloblastic anemia, HS: Hypersplenism, AA: Aplastic anemia, AL: Acute leukaemia, MDS: Myelodysplastic syndrome NA: Nutritional anemia

The age range of the 150 pancytopenic patients included in the study was 1->70 years. 64 cases were observed in the age group of 11-30 years and found to be the most common age group of patients with pancytopenia.

Table 3: Presenting complaints in the different causes of pancytopenia

Symptoms	No. of Patients						Percentage
	MA	**HS**	**AA**	**AL**	**MDS**	**NA**	
Abdominal Distension	2	2					1
Abdominal Pain	7	7	3	1		4	8
Back Pain	2						1
Bleeding	1		2				1
Breathlessness	8	10	10	5	5	2	14
Fever	33	11	14	7	9	7	29
Hemoptysis	2						1
Hematemesis	2						1
Hematuria		1	2	1			1
Joint/Bone Pain				1			0
Loose motion	1						0
Loose stools	1						0
Nasal bleeding				2			1
Swelling	2	1	1		9	1	5
Weakness	43	14	14	3	7	10	33
Vomiting	2	1	2			2	3

MA: Megaloblastic anemia, HS: Hypersplenism, AA: Aplastic anemia, AL: Acute leukaemia, MDS: Myelodysplastic syndrome, NA: Nutritional anemia

Table 4: Physical findings in the different causes of pancytopenia

Physical examinations	No. of Patients						Percentage
	MA	HS	AA	AL	MDS	NA	
Ascites	1						0
Bleeding	1	3					1
Icterus	4	3	2		2	14	8
Lymphadenoapthy		5	3				3
Hepatomegaly	17	14	2	3	5	8	16
Oedema	5		2	1	7	5	7
Pallor	55	20	12	10	15		38
Splenomegaly	30	21		7	5	16	27

MA: Megaloblastic anemia, HS: Hypersplenism, AA: Aplastic anemia, AL: Acute leukaemia, MDS: Myelodysplastic syndrome, NA: Nutritional anemia

Pancytopenia with hypercellular marrow was observed in 78(52s%) patients, whereas 42(28%) and 30(20%) patients exhibited normocellular and hypocellular marrow respectively.

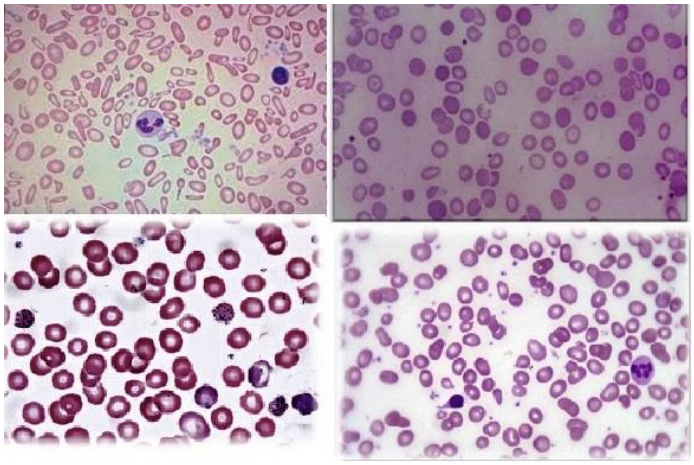

Fig 1. Peripheral smear showing (a) microcytic hypochromic anemia with pencil cells ,tear drop cells and severe anisopoikilocytosis in iron deficiency anemia (Leishman X 100); (b) Dimorphic anemia with macrocytes and microcytes (Leishman X100); (c) Basophilic stippling in case of megaloblastic anemia (LeishmanX 100) (d) Numerous oval macrocytes and hypersegmented neutrophils in megaloblastic anemia (Leishman X 100)

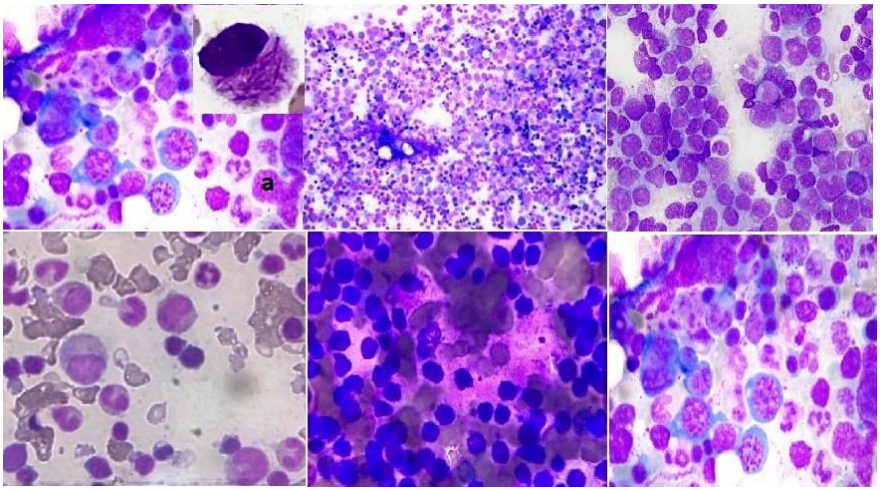

Fig. 2: (a): Peripheral smear with myeloblast having auer rod in AML (Leishman X 100); (b): Bone marrow smear showing hypercellular marrow (leishman's stain 10x x 100x) (c): Bone marrow aspirate showing erythroid hyperplasia with megaloblastic maturation (sieve like nuclear chromatin (Leishman X 100); (d): Smears showing giant metamyelocytes (Leishman X 100); (e): Blast cells in acute leukemia (Leishman X 100); (f): Megaloblasts with open chromatin (Leishman X 100)

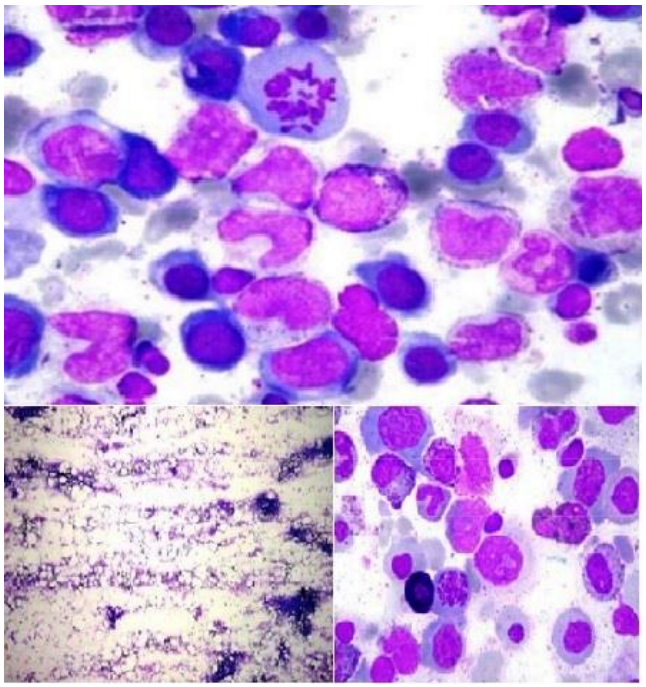

Fig 3. (a): Bone marrow aspiration smear showing giant metamyelocyte and mitosis (Leishman X 100); (b): Bone marrow smear showing increased number of fat cells (Leishman X 100); (c): Bone marrow smear showing dyserythropoiesis and blast (Leishman X 100)

Discussion

The present study analyzed the clinico-haematological and etiological profile of 150 patients of pancytopenia. Age, gender, clinical features and haematological findings including complete hemogram, peripheral smear and bone marrow examination findings among different causes of pancytopenia were compared with various studies published previously in the English literature.

The age of the patients in the present study ranged from 1 to more than 70 years. The highest incidence was observed in the age group of 11-30 years (64%). These findings were comparable to the age distribution observed in most studies conducted in the Indian subcontinent.[3,5,7,12] In the present study, the male female ratio was 1.73, which correlated well with the male preponderance noted in other studies from the Indian subcontinent. This could be attributed to the increased health concern for the males in India.[2]

The most common presenting symptom in the present study was fever in 81 cases (54%) followed by breathlessness in 40 cases (26.7%). These findings were comparable to the previous studies reported from the Indian subcontinent,[7,13] Study by Kumar et al in 2012 reported weakness in 91 patients followed by fever as the second most frequent symptom in 40 patients.[14]

Pallor was the most common physical finding observed in 112 (74.7%) patients in the present study. Splenomegaly was the second most common sign in 47 cases (31.3%) followed by hepatomegaly in 22 (14.7%) patient. A single case of hypersplenism was observed which could be attributed to portal hypertension. The physical findings were comparable to other studies reported from the Indian subcontinent.[3,7,15] Pallor was the commonest sign observed in all the patients in most studies reported from the Indian subcontinent. Splenomegaly was the second most common finding reported by Tasreem et al and Khodke et al.[3,7] Hepatomegaly was the next most frequently observed finding in the studies by Tasreem et al and Thakkar et al.[3,16]

The variations in the frequency of various diagnostic entities causing pancytopenia has been attributed to difference in methodology and stringency of diagnostic criteria, geographic area, study period, genetic variations and difference in exposure to myelotoxic agents, etc.[16]

In the present study megaloblastic anaemia constituted the most frequent underlying etiology in 75(50%) patients of pancytopenia followed by hypersplenism in 27(18.0%) cases. Aplastic anaemia was reported in 17(11.3%), Acute leukemia in 13 (8.7%), MDS in 15 (10.0%) and nutritional anaemia in 3(2.0%) cases. The commonest cause of pancytopenia, reported from various studies throughout the world has been aplastic anaemia.[5,8,9]

On the contrary most studies conducted in the Indian subcontinent observed megaloblastic anaemia to be the major cause of pancytopenia[3,7,8,17,18,30] However, occasional studies reported from India observed aplastic anaemia as the most common underlying etiology of pancytopenia with megaloblastic anaemia being the second common cause. Haematological malignancies constituted the third common etiology of pancytopenia in the studies from the Indian subcontinent by Tasreem et al, Nanda *et al*, Singh et al in.[3,12,20] Hypersplenism was the second and fourth most, common cause of pancytopenia reported by previous studies.[21,22] Myelodysplastic syndrome and nutritional anaemia as underlying cause of pancytopenia were also reported in various studies from the Indian subcontinent.[3,5,7,23]

Table 7: Comparison of the findings of this study with studies carried out outside India

S. No.	Study	Country	Year	No. of Cases	Commonest Cause	Second Most common cause
1	Gayathri *et al*[1]	India	2011	104	Megaloblastic anaemia (74%)	Aplastic anaemia (18%)
2	Jha *et al*[05]	Nepal	2008	148	Hypoplastic anaemia (29.5%)	Megaloblastic Anaemia (23.64%)
3	Khunger *et al.*[13]	India	2001	200	Megaloblastic anaemia (72%)	Aplastic anaemia (14%)
4	Kumar R et al.[17]	India	2001	166	Aplastic anaemia (29.5%)	Megaloblastic anaemia (22.3%)
5	Osama Ishtiaq *et al.*[27]	Pakistan	2002	100	Megaloblastic Anaemia (39%)	Hypersplenism (19%)
6	Memon *et al*[28]	Pakistan	2008	230	Aplastic anaemia	Megaloblastic Anaemia (13.04%)
7	Present study	India	2018	150	Megaloblastic Anaemia (50%)	Hypersplenism (18%)

The incidence of megaloblastic anaemia observed in the West varies from 0.8% to 32.26% of all pancytopenic patients.[9,23] The incidence of megaloblastic anaemia noted in the present study was 50%. This correlated with the high incidence ranging from 44% to 74.04% reported by various Indian studies. The increased incidence of megaloblastic anaemia reflects the high prevalence of nutritional deficiency in the Indian subjects. As facilities for estimating folic acid and vitamin B12 levels are not routinely available in most centers in India, the exact deficiency remains unidentified most of the time.[24]

Pancytopenia was attributable to hypersplenism in 18% of our cases. Portal hypertension consequent to cirrhosis was the underlying cause in eight patients, haemolytic anaemia in four patients, and the cause remained undiagnosed in four patients. This correlated with the 11.4% incidence observed by an Indian study in 2001 which reported portal hypertension in, thalassemia in four and unspecified haemolytic anaemia in two patients as the underlying cause for hypersplenism.[25] A study from Pakistan in 2004 observed hypersplenism in 14% of all pancytopenia patients whereby portal hypertension constituted the commonest cause of hypersplenism in 12 patients followed by three cases of chronic malaria.

The incidence of aplastic anaemia among pancytopenic patients quoted in the western literature ranges from 10% to 52.7%.[26] This is much higher than observed in the Indian subcontinent which ranged from 7.7% to 29.6%. The incidence of aplastic anaemia in our study was 11% which correlated with the incidence observed by other studies reported from the Indian subcontinent. Most of the cases of aplastic anaemia in the present study were idiopathic. History of drug intake was present in one case. Preceding history suggestive of viral hepatitis was forthcoming in six patients of aplastic anaemia. History suggestive of viral hepatitis was elicited in eight out of 49 patients of aplastic anaemia in an Indian study reported in 2001.[7] Drug induced marrow suppression was identified in four out of six patients diagnosed with aplastic anaemia in a study reported from India.[14]

We diagnosed acute leukaemia in 9% of the patients presenting with pancytopenia which was comparable to 12.04%, 19.6% and 18.5% incidence of acute leukaemia reported by a study reported from India in 2001, Nepal in 2008 and 2012 respectively.[19,5,26] In the present study, acute lymphoblastic leukaemia and acute myeloid leukaemia was the FAB morphological type diagnosed in 63,6% and 36.4% patients of acute leukaemia respectively.

The diagnosis of MDS has been reported to be 10% in the present study, which was comparable to the incidence observed by other studies also. MDS is second most common cause of pancytopenia in studies by International agranulocytosis and aplastic anaemia group. A study by Jha et al[5] from Nepal reveals MDS as a cause of pancytopenia in 6.8% patients which is nearly similar to our study. Another study in Abbottabad 6 patients (7.05%) out of 85 patients having MDS present as pancytopenia which is comparable to our study.

Osama Ishtiaq et al.[27] studied 100 patients having panytopenia and encountered five cases of iron deficiency anaemia (5%) as 4th common cause in his study which was comparable with our study where we also encountered 3% cases of nutritional anaemia manifesting with pancytopenia all are due to iron deficiency. Iron deficiency anaemia is the second most common cause of nutritional deficiency in USA. Iron deficiency ajaaemia can be associated with pancytopenia. Though iron deficiency is associated with a reactive thrombocytosis, increasing severity of iron deficiency leads to normalisation and occasionally even decrease platelet counts. The exact mechanism of this is unclear but may be related to the alteration in the activity of iron dependant enzymes in thrombopoiesis and leucopoiesis.[28]

In the present study, the overall hemoglobin percentage ranged from 1 gm% to >10 gm%, total leukocyte count ranged from 100->5100 cells/cumm and platelet count

ranged from 0->1,00,000 cells/cumm. In the major causes of pancytopenia haematological parameters show overlap without any clue to the diagnosis. Similar results have been reported by other studies form the Indian subcontinent.[29]

In the present study, the bone marrow was hypercellular with a reduction of fat cells in most of the patients 77(51%). Bone marrow is normocellular in 42(28%) and hypocellular in 20% cases. Erythroid hyperplasia with megaloblastic maturation was seen in all the patients.

Patients with hypersplenism revealed normocellular marrow 93% of patients while the rest had hypercellular 7% marrow. In aplastic anaemia cellularity of bone marrow is very much reduced. It may be hypocellular or acellular. Lymphocytes and plasma cells are prominent, In a previous study analysis of 50 cases reported 74% of patients with hypocellular marrow, 16% of patients with normocellular marrow which later became hypocellular and 10% with acellular marrow.[23] In the present study, bone marrow was mostly hypocellular and the aspirate was composed of fat cells in all the patients. There was a relative increase in plasma cells and lymphocytes. In most of the cases of MDS**,** aspirate was hypercellular with erythroid hyperplasia and features of dyserythropoiesis, dysmyelopoiesis and large hypolobulated megakaryocytes were observed. Similar results have been reported by previous author.[27,28] In acute leukaemia bone marrow was hypercellular in most (85%) of the patients. Myeloid hyperplasia was observed in patients of AML and lymphoid hyperplasia in patients of ALL.

Conclusion

Pancytopenia is not an uncommon haematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anaemia, prolonged fever and tendency to bleed. The etiological spectrum of pancytopenia is diverse. Megaloblastic anaemia, hypersplenism and aplastic anaemia are the most frequently diagnosed underlying cause. Other important etiologies include hematological malignancies, MDS, nutritional anaemia, myclofibrosis, PNH and infections such as malaria, kala-azar, disseminated tuberculosis, HIV/AIDS.

Majority of the studies reported from Indian subcontinent report megaloblastic anaemia as a predominant cause of pancytopenia in contrast to western studies where aplastic anaemia and malignancies are common.

In India there is a high prevalence of nutritional anaemia. Ours is a rural medical college and patients visiting this hospital came from low socio-economic background, therefore, this is probably the reason that our study shows high prevalence of megaloblastic anaemia. The physical findings and peripheral blood picture play an important role in planning the investigations in pancytopenic patients. Clinical and haematological parameters show considerable overlapping, thus requiring specific tests to arrive at a final diagnosis.

Bone marrow examination is an important diagnostic tool in confirming the underlying diagnosis. It is also helpful in differential diagnosis of other diseases and excluding a primary marrow involvement and suggesting alternative investigations for diseases like hypersplenism, PNH, leukaemia, MDS etc.

Megaloblastic anaemia diagnosed in 50% patients constituted the commonest etiology of pancytopenia in the present study followed by hypersplenism in 18%, aplastic anaemia in 11%, acute leukaemia in 09%, MDS in 10% and nutritional anaemia in 2% patients.

The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patients. Megaloblastic anaemia which is amenable to treatment, so an, early and accurate diagnosis is life-saving.

Conflict of Interest: None.

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