Clinico-hematological evaluation of pancytopenic adults in a tertiary care institution

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Abstract
Introduction: Pancytopenia is an important clinico-hematological entity encountered in our day-to-day clinical practice from a number of disease processes primarily and secondarily involving bone marrow. This study was carried out to evaluate bone marrow findings in patients with pancytopenia.
Materials and Methods: This is a prospective cross sectional study carried out on 140 pancytopenia patients over the period of one and half years. Relevant clinical details were recorded, followed by screening of patients for routine blood investigations included a complete blood count, peripheral blood smear examination, reticulocyte count. Bone marrow aspiration was done in all cases and bone marrow biopsy performed whenever necessary and Perl's Prussian blue stain for grading of bone marrow iron stores were done in all cases. Data analysed was compared with various studies published in literature.
Results: The maximum cases of pancytopenia were in the age group of 31 to 40 years with male preponderance. Dimorphic anemia (49.3%) was found to be the most common etiology of pancytopenia followed by megaloblastic anemia (35%), iron deficiency anemia (5.7%). We encountered two cases of non-Hodgkin's lymphoma and one case each of multiple myeloma, acute lymphoblastic leukemia, aplastic anemia and anemia of chronic disease. Most common clinical presentation was pallor followed by fatigue and fever.
Conclusion: Present study concludes that basic primary hematological investigations along with bone marrow aspiration/trephine bone biopsy in the pancytopenia patients are helpful in understanding the disease process. This plays a key role in planning the further management.

Keywords: Adults, Bone marrow, Dimorphic anemia, Megaloblastic anemia, Pancytopenia.

Introduction

Pancytopenia is an important clinico-hematological entity encountered in our day-to-day clinical practice from a number of disease processes primarily and secondarily involving bone marrow.[1]

Pancytopenia is the simultaneous presence of anemia, leucopenia and thrombocytopenia. It exists in adults when hemoglobin concentration is less than 13.5 g/dl in males, 11.5 g/dl in females, the leucocyte count <4000/Cumm and platelet count <1.5 lakhs/cumm.[2]

The presenting symptoms are often attributable to the anemia or thrombocytopenia. Leucopenia is often seen in the subsequent course of the disorder.[3] Anemia leads to fatigue, dyspnea and cardiac symptoms. Thrombocytopenia leads to bruising, mucosal bleeding and neutropenia to sharply increased susceptibility to infection.

Varieties of hematopoietic and non-hematopoietic conditions manifest with features of pancytopenia. The underlying mechanisms are decrease in hematopoietic cell production, marrow replacement by abnormal cells and suppression of marrow growth and differentiation, ineffective erythropoiesis with cell death, defective cells formation which are removed from the circulation, antibody mediated sequestration or destruction of cells and trapping of cells in a hypertrophied and overactive reticuloendothelial system.[4]

Various studies done in India stress the importance of megaloblastic anemia as being the major cause of pancytopenia which may present acutely in the critically ill.[5] Higher number of megaloblastic anemia seems to reflect high prevalence of nutritional deficiency in our country [6]

The another causes include combined nutritional deficiencies of iron and vitamin B12 that presents as dimorphic anaemia which is characterized by two distinct red cell population. In this one cell population is of microcytic hypochromic cells and another is of normocytic normochromic cells or macrocytic cells. [7]

Early diagnosis reduces the mortality and morbidity in the patients. Causes of pancytopenia can be from simple treatable disease to serious life threatening condition. So, it is important to evaluate these patients to provide them appropriate and correct treatment.

Aim of the study is evaluate the clinico-hematological profile and causes of pancytopenia in adult patients from the population of this region.

Materials and Methods

This prospective cross sectional study was carried out from March 2016 to September 2017 in the Department of Pathology, on 140 adult patients of pancytopenia irrespective of the cause fulfilling the

inclusion criteria (i.e. Hemoglobin <13.5 g/dl in male and <11.5 g/dl in female, Leucocyte count <4000/cumm. Platelet count < 1.50 lakhs/cumm.[2]). The patients exposed to chemotherapy and/or radiotherapy were excluded from the study. An institutional ethics committee clearance (IECC) was obtained before the start of the study. Informed and written consent was taken from the patients included. Relevant clinical details were recorded. Followed by screening of patients for routine blood investigations included a complete blood count including hemoglobin, total leucocyte count, differential leucocyte count, platelet count, red blood cell indices and peripheral blood smear examination, reticulocyte count. Bone marrow aspiration was done in all cases and bone marrow biopsy performed whenever necessary by the standard technique from posterior superior iliac spine under local anaesthesia with standard aseptic precautions. Leishman stain was used to stain all bone marrow aspiration smears and perl's Prussian blue stain for grading of bone marrow iron stores were done in all cases. Bone marrow biopsy specimens were fixed in Bouin's fixative and hematoxylin and eosin (H &E) stained sections were examined. Qualitative data was summarized using proportions and percentages and quantitative data will be summarized using mean and standard deviation. Data analyzed was compared with various studies published in literature.

Result

Total 140 adult patients, who presented with pancytopenia were included in the study. Patient's age ranged from 19 to 80 years. Mean age was 41yrs. Maximum numbers of cases were in the age group of 31- 40 years (25%). Followed by age group of 21-30yrs (22.9%) and least age group affected was above > 70 years. (Table 1)

Male patients were 67.9% and females were 32.1%, accounting for a male to female ratio of 2.1:1.

The most common presenting feature was pallor with 100%, followed by fatigue 95.7%, fever 22.9%, bleeding tendency 12.9%. The physical findings included, splenomegaly seen in 20% and hepatomegaly in 10% and lymphadenopathy in 3.6%.

In the present study, the most common cause of pancytopenia was dimorphic anemia (49.3%). followed by Megaloblastic anemia (35%). Less common cause were ALL, multiple myeloma, Aplastic anemia and anemia of chronic disease. Other causes were shown in the Table 2.

Mean MCV was high in the Aplastic anemia is 123.5fl, followed by megaloblastic anemia is 114.4±13.7 fl, and dimorphic anemia is 96±18.4fl. Lowest MCV was found in Iron deficiency anemia is 77.0±15.7fl.

Bone marrow cellularity was evaluated on bone marrow aspiration, imprints and biopsy. Majority of patients had hypercellular bone marrow (88%) followed

by normocellular (11%) and hypocellular (1%) bone marrow.

In the present study, iron store grade in the bone marrow aspiration smears was evaluated. It is observed that in the iron deficiency anemia it is in the range of 0-1, in megaloblastic anemia it is 1-4, in cases of dimorphic anemia it is in the range of 0-3, in aplastic anemia it is grade 1, in hypersplenism in the range of 0-2, in the normocellular bone marrow ranges from 1-3 and in the ACD iron grade is 3. Table 6

We observed reticulocyte count was ranging from 0% to 4% in pancytopenic patients. Mean Reticulocyte count was 1.15±0.4%. Reticulocyte count was normal in 95% of cases, high in 3.6% of cases and low in 1.4% of cases. In the cases of dimorphic anemia 92.8% are showing normal reticulocyte count and 5.8% are high and 1.4% was showing low reticulocyte count. In megaloblastic anemia 97.9% of cases show normal reticulocyte count and 0.3% cases shows high reticulocyte count. Aplastic anemia case shows low reticulocyte count.

Table 1: Age distribution among patients with pancytopenia

Age (Year)	Frequency	Percent (%)
≤ 20	16	11.4
21 – 30	32	22.9
31 – 40	35	25.0
41 – 50	18	12.9
51 – 60	18	12.9
61 – 70	12	8.6
> 70	9	6.4
Total	140	100.0

Table 2: Causes of pancytopenia in study population

Causes of Pancytopenia	Frequency	Percent (%)
DA	69	49.3
MA	49	35.0
IDA	8	5.7
HS	4	2.9
NM	4	2.9
LYM	2	1.4
MM	1	0.7
ALL	1	0.7
ACD	1	0.7
AA	1	0.7
Total	140	100.0

DA: Dimorphic anemia. MA: Megaloblastic anemia. IDA: Iron deficiency anemia.
HS: Hypersplenism. NM: Normal Bone Marrow. LYM: Lymphoma. MM: Multiple Myeloma. ALL: Acute Lymphoblastic Leukemia. ACD: Anemia of Chronic Disease.
AA: Aplastic anemia.

Table 3: Age and sex distribution in comparison with other studies

S. No.	Authors	Age distribution	No. of cases	Predominant Age group affected	M:F ratio
1	Khodke et al. (2001) [6]	3-69yrs	50	12-30yrs	1.3:1
2	Khunger et al. (2002) [8]	2-70yrs	200	21-30yrs	1.2:1
3	Hamid et al. (2008)[9]	3-85yrs	75	16-30yrs	1.03:1
4	Desalphine et al. (2014)[10]	6-78yrs	50	10-30yrs	1.8:1
5	Dagdia et al.(2016)[7]	1-80yrs	75	21-40yrs	0.87:1
6	Present study	19-80yrs	140	31-40yrs	2.1:1

M: Male, F: Female

Table 4: Comparison of most common causes of pancytopenia in different studies conducted in different countries

Study	Country	Year	No. of cases	Most common cause (%)	Second most common cause (%)	Third most common cause (%)
Kale p et al[13]	India	1991	70	Hypersplenism (47.6)	Megaloblastic (25.4)	Acute Leukemia (14.5)
Tilak et al[14]	India	1999	77	Megaloblastic (68)	Aplastic anemia (7.7)	Others (24.3)
Kumar et al[15]	India	2001	166	Aplastic anemia (29.5)	Megaloblastic (22.2)	Acute Leukemia (18.0)
Khunger et al[8]	India	2002	200	Megaloblastic (72)	Aplastic anemia (14)	Subleukemic Leukemia (5)
Ishitaq O et al[16]	Pakistan	2004	100	Megaloblastic (39)	Hypersplenism (19)	Aplastic anemia (10)
Hamid et al[9]	Yemen	2008	75	Hypersplenism (45.3)	Megaloblastic (14.7)	Aplastic anemia (13.3)
Jha et al[5]	Nepal	2008	148	Hypoplastic marrow (29)	Megaloblastic (23)	Hematological malignancy (21)
Santra et al[11]	India	2010	111	Aplastic anemia (22.72)	Hypersplenism (11.7)	Kala azar (9)
Gayathri et al[12]	India	2011	104	Megaloblastic (74)	Aplastic anemia (18)	Subleukemic Leukemia (3.85)
Vandana R et al[17]	India	2012	80	Megaloblastic (41.2)	Dimorphic anemia (8.7)	Aplastic anemia (8.7)
Weinzierl et al[18]	USA	2013	250	MDS (44)	AML (31)	Aplastic anemia (22)
Devitt et al.[19]	USA	2014	132	AML 26)	MDS (17)	Unremarkable (14)
Govindraj et al[20]	India	2015	50	Megaloblastic (44)	Combined nutritional anemia (20)	Hypersplenism (12)
Raina R et al.[21]	India	2016	69	Megaloblastic (36.2)	Dimorphic anemia (18.8)	Hematological malignancies (17.4)
Present study	India		140	Dimorphic anemia (49.3)	Megaloblastic (35.0)	Iron deficiency anemia (5.7)

AML: Acute myeloid leukemia; MDS: Myelodysplastic syndrome.

Table 5: Comparison of MCV in different studies.

| S. No.	Authors	Mean MCV(fl)	MCV in MA	MCV in DA	MCV in IDA
1	Priya P et al[24]	94.6±21.1	119.9±5.5	87.9±7.5	-
2	Hamid et al[9]	84.7±11.9	101.2±11.9	-	66.9±00
3	Present study	100.8±19.6	114.4±13.7	96.8±18.4	77.0±15.7

MCV: Mean corpuscular Volume, MA: Megaloblastic anemia, DA: Dimorphic anemia, IDA: Iron deficiency anemia

**Table 6: Bone marrow iron store in pancytopenia patients**

Causes of Pancytopenia		IRON store grades							Total
		0 (↓)	1 (↓)	2 (N)	3 (↑)	4 (↑)	5 (↑)	6 (↑)	
	DA	15(21.7%)	35(50.7%)	17(24.6%)	2(2.8%)	0	0	0	69
	MA	1(2.0%)	19(38.7%)	20(40.8)	8(16.3%)	1(2.0)	0	0	49
	IDA	6(75%)	2(25%)	0	0	0	0	0	8
	HS	1(25%)	1(25%)	2(50%)	0	0	0	0	4
	NM	0	1(25%)	2(50%)	1(25%)	0	0	0	4
	LYM	0	1(50%)	1(50%)	0	0	0	0	2
	MM	0	1(100%)	0	0	0	0	0	1

|								
ALL	1	0	0	0	0	0	0	1
ACD	0	0	0	1(100%)	0	0	0	1
AA	0	1(100%)	0	0	0	0	0	1
Total	24(17.1%)	61(43.5%)	42(30%)	12(8.5%)	1(0.7%)	0	0	140

(↓) – Decreased iron store, (N) – Normal iron store, (↑) – Increased iron store
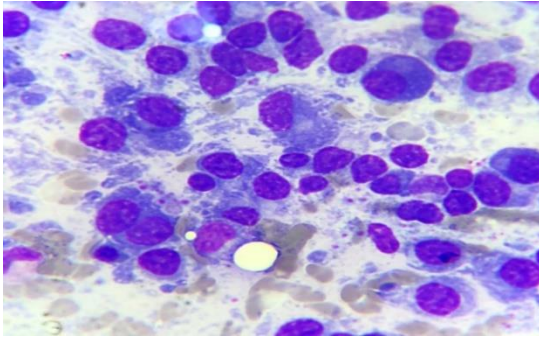
Fig. 1: Multiple myeloma: Hypercellular bone marrow, normal hemopoietic cells are replaced by plasma cells. (Leishman stain, x1000)
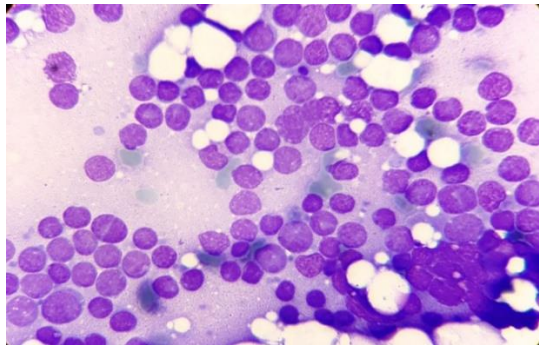

Fig. 2: Acute lymphoblastic Leukemia: Bone marrow imprints shows mostly lymphoblasts with high nuclear cytoplasmic ratio. (Leishman, x1000)
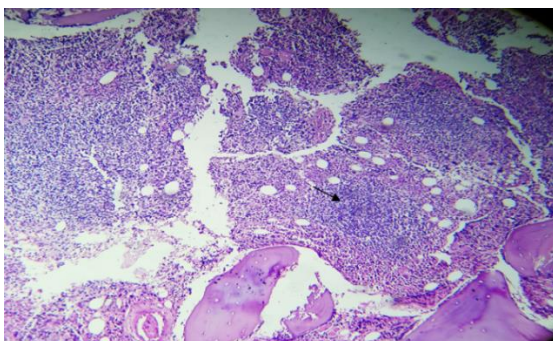
Fig. 3: Non-Hodgkin's lymphoma: trephine biopsy section shows hypercellular bone marrow, normal hemopoietic cells are infiltrated by the nodular aggregates of the lymphoma cells. (Arrow), (H & E stain, x100)
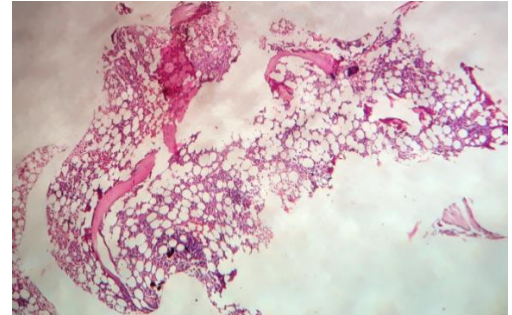
Fig. 4: Aplastic anemia: Bone marrow trephine biopsy shows hypocellular marrow, normal hemopoietic cells are replaced by the fat cells. (H & E, x100)
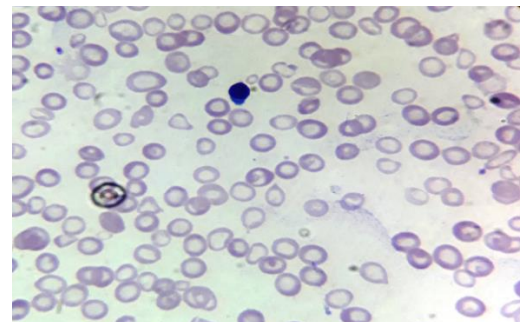
Fig. 5: Peripheral blood smear showing dimorphic red blood cells. (Leishman, x1000)

Discussion

Pancytopenia is a serious hematological problem, which makes the patient prone to anemic manifestations, infections and bleeding tendency. The causes are varied ranging from simple curable diseases to neoplastic conditions involving bone marrow. The exact diagnosis is necessary for patient's management. In this regard, the study of pancytopenic adults was undertaken.

In present study, patients in fourth decades of life were most commonly affected followed by third decade. Commonest age group affected by pancytopenia reported from various study ranges from 10 to 40 yrs.

Present study noted male preponderance with M: F ratio being 2.1:1. In most of the other the studies also male preponderance was noted except in the study by Dagdia et al.[8] (Table 3)

In the present study, most common clinical presentation was pallor (100%) followed by fatigue in 95.7%. Fever was present in 23% of patients. Almost similar pattern of presentations was noted in studies done by Khunger et al[9] Desalphine et al[11] and Santra et

al.[12] Other clinical manifestation like bleeding tendency was present in 13% of patients in present study. Desalphine et al[11] have noted bleeding tendency in 8% of their patients and Khodke et al.[6] noted in 20% of cases.

The significant findings on physical examination included hepatomegaly (10%), Splenomegaly (20%), and lymphadenopathy (3.6%) in our study. Khodke et al[6] noted hepatomegaly in 38% and splenomegaly in 40% of patients in his study. Gayathri et al[13] observed hepatomegaly in 26.9%, splenomegaly in 35.5% and lymphadenopathy in 0.96% of patients in his study. Santra et al[12] observed hepatomegaly in 24.3%, splenomegaly in 44.1% and lymphadenopathy in 6.1% of patients in his study. Hamid et al[9] observed hepatomegaly in 21.3%, splenomegaly in 48% and lymphadenopathy in 14.7% of patients in his study. The variation in clinical findings could be related to the spectrum of lesions in a particular set up.

On analyzing the causes of pancytopenia we have come across dimorphic anemia in 49.3% cases, megaloblastic anemia in 35.0%, and iron deficiency anemia in 5.7% cases. Also seen was hypersplenism in 2.9% cases. The bone marrow involvement by lymphoma, multiple myeloma and acute lymphoblastic leukemia was seen in 2.8% cases. Other rare causes were anemia of chronic disease and aplastic anemia in 0.7% cases each. Normal bone marrow study was observed in 2.9% cases.

In other similar studies the incidence of dimorphic anemia varies from 8.7% to 20% .Study had done by Vandana R et al[18] shows incidence of dimorphic anemia 8.7%, Govindraj et al[21] shows incidence 20% and Raina R et al.[22] shows incidence 18.8%.

The second commonest cause of pancytopenia in the present study was megaloblastic anemia (35%). In most of the Indian studies, megaloblastic anaemia is the commonest cause of pancytopenia.[13,15,17-19,21,22] while in western world the haematological malignant & premalignant conditions outnumber anaemia as a cause for pancytopenia.[19,20] (Table 4)

History of poor eating habits, poor quality of food, self-avoidance of necessary foods, fasts and also increasing trend of chronic alcoholism in younger population aggravates the nutritional deficiencies of vitamin B12, folate and iron and often lead to pancytopenia .This can be attributed to the high prevalence of combined nutritional anemia (dimorphic anemia) in present study.

We encountered 5.7% cases of Iron deficiency anemia. Various other studies have reported incidence of 3.7, 1.3, 2.0 and 4.3%[1,10,11,22] respectively, indicating that though rare, one has to think of iron deficiency anemia in pancytopenia.

In present study we found 2.9% of cases of Hypersplenism. Our study had concordance with the study of Khunger et al[8] which shows 3% of incidence of hypersplenism. Other studies like Dagdia et al.,[8]

Santra et al,[12] and Subrahmanyam et al.[1]shows 8, 13.5 and 24.5% of incidence of splenomegaly respectively which is higher than our study. This can be attributed to infective and neoplastic etiology in their cases.

We came across neoplastic etiology for pancytopenia in 2.8% of our cases. These were non-Hodgkin's lymphoma, acute lymphoblastic lymphoma and multiple myeloma. Similar observations were made by various other workers like Khunger et al,[9] Pathak R et al[23] who showed incidence of lymphoma 1% and 2.9% respectively. Other similar studies by Subrahmanyam et al.[1] and Desalphine et al[11] had incidence of lymphoma 3.7% and 4% respectively. While the indian studies done by Kale p et al,[14] and Kumar et al[16] show high incidence of acute leukemia as 14.5% and 18% respectively. Also USA based study by Weinzierl et al[19] and Devitt et al.[20] showed leukemia in 31 and 26% of their pancytopenic patients. This can be attributed to the type of hospital, geographic and socioeconomic status of study population.

The present study shows one case (0.7%) of Anemia of chronic disease, presented with fever and known case of rheumatoid arthritis. On analyzing various other studies the incidence of anemia of chronic disease was negligible, where in a study done by Subrahmanyam et al.[1] it was 7.5%.

A case of elderly male was presented with easy fatiquability and bleeding tendencies was diagnosed as aplastic anemia. Thus the incidence was 0.7%. Study done by Jain et al[24] had incidence of 4.8%. Other studies like Raina R et al.[22,] and Subrahmanyam et al.[1] had a incidence of Aplastic anemia 7.2% and 13.2% respectively which is comparatively higher than our study.

We observed 2.9% cases showing normal bone marrow study. This can result due to sequestration and /or destruction of cells by the action of antibodies or trapping of normal cells in a hypertrophied and over reactive reticuloendothelial system. Raina R et al.[22] showed 2.9% cases showing normal bone marrow study. While Jha et al[5] and Pathak R et al[23] had incidence of 3.38% and 5.8% respectively.

In present study mean MCV was 100.8±19.6 fl. It was 114.4±13.7 fl in megaloblastic anemia, 96.8±18.4 fl in dimorphic anemia, 77.0±15.7 fl in iron deficiency anemia. In a similar study by Priya P et al[25] mean MCV was 94.6±21.1 fl. It was 119.9±5.5 fl in megaloblastic anemia, 87.9±7.5 fl in dimorphic anemia. Another study by Hamid et al[10] showed mean MCV of 84.7±11.9 fl. It was 101.2±11.9 fl in megaloblastic anemia, 66.9±00 fl in iron deficiency anemia and 88.4±3.9 in aplastic anemia. (Table 5)

In these study patients with iron deficiency anemia had iron store grade in range of 0-1. Study done by Pujara et al[26] shows iron store grade in marrow in range of 0-1 in 92.7% of iron deficiency anemia patients, which is in concordance with our study. In our study patients with megaloblastic anemia had iron store grade

in marrow in range of 1-4. Study done by Pujara et al [26] also showed iron store grade in marrow in range of 1-4 in megaloblastic anemia patients. In present study patients with dimorphic anemia had iron store grade in range of 0-3. Study done by Pujara et al [26] shows iron store grade in marrow in range of 2-3 in dimorphic anemia patients.

In present study reticulocyte count was ranging from 0 to 4%. It was normal in 95% of patients. Reticulocytopenia was seen in two patients, one of aplastic anemia and another was dimorphic anemia. Reticulocytosis was seen in the 3.6% cases, four of dimorphic anemia and one case of megaloblastic anemia, which indicates bone marrow regeneration which could be due to ongoing therapy. Study done by Desalphine et al[10] had reticulocyte count varied from 0.5 to 3.2%. Reticulocytopenia is seen in 23% of patients and Reticulocytosis seen in 0.5% of patients.

Conclusion

Pancytopenia is a common hematological presentation encountered in day todays clinical practice. It should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever and tendency to bleed.

There is spectrum of diseases which can present as pancytopenia.

After routine hematological examination, Bone marrow aspiration/trephine bone biopsy is an important diagnostic tool in hematology which helps to evaluate various causes of pancytopenia.

Bone marrow examination gives accurate, reproducible, rapidly available information at an economical cost and with minimal discomfort to the patient. Bone marrow aspiration is sufficient to make a diagnosis ranging from anemia to malignancies.

In this study dimorphic anemia was diagnosed in 49% patients who constituted the commonest etiology of pancytopenia. This was followed by megaloblastic anemia in 35%, Iron deficiency anemia in 5.7%, hypersplenism in 2.9%, lymphoma in 1.4%, aplastic anemia, multiple myeloma, acute lymphoblastic anemia and anemia of chronic diseases in 0.7% of cases each.

This seems to reflect higher prevalence of nutritional anemia, predominantly in young adult males in this region. This group constitutes the main work force of the family and in turn our country. Not only the socioeconomic status but also defective food habits, ignorance regarding balanced nutrition are the contributing factors in getting nutritional anemia and eventually pancytopenia in younger population. As this is a preventable cause, population based awareness programs in this regard can be an effective measure to prevent morbidity.

Also one has to keep in mind the neoplastic etiology for pancytopenia.

Present study concludes that basic primary hematological investigations along with bone marrow aspiration/trephine bone biopsy and biochemical parameters in the pancytopenia patients are helpful in understanding the disease process. This plays a key role in planning the further management.

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