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Original Research Article

Pancytopenia: etiologies and manifestation in eastern India

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ABSTRACT

Background: Pancytopenia is the simultaneous presence of anemia, leucopenia and thrombocytopenia. The aetiologies causing pancytopenia varies depending upon factors e.g. age, sex, occupation, and geographical distribution. Unfortunately, the major treatises of haematology give more emphasis to Aplastic anaemia; while Megaloblastic anaemia is more common in developing countries than western world. Therefore, this Observational study was carried out over a period of two years in the Department of Medicine of Institute of Medical Sciences (IMS), BHU with the aim to identify etiologies of pancytopenia and its manifestation in eastern India.
Methods: All the patients with features of anemia, thrombocytopenia or leukopenia were screened for pancytopenia and a total 214 cases were selected. A detailed physical examination, hematological and biochemical investigation was done.
Results: The most common cause of pancytopenia in our study was Aplastic anemic (36.9%) followed by Megaloblastic anaemia (18.7%), Kala-azar (11.7%) and Myelodysplastic syndrome (10.5%).
Conclusions: Megaloblastic anemia should be considered as important cause of Pancytopenia, especially when serum LDH level of patient is raised.

Keywords: Aplastic anemia, Kala-Azar, Magaloblastic anemia, Pancytopenia, Serum LDH

INTRODUCTION

Pancytopenia is the simultaneous presence of anemia, leucopenia and thrombocytopenia. It is not disease entity, but a triad of finding that may result from number of disease.[1]

Mechanism responsible for pancytopenia result from destruction of marrow tissue, replacement by abnormal or malignant cell, or suppression of marrow growth and differentiation.[2] The frequency of underlying aetiologies causing pancytopenia varies depending upon several factors e.g. age, sex, occupation, and geographical distribution.

Despite of this the major treatises of haematology gives major emphasis to aplastic anaemia with little description about other important causes of pancytopenia. Some causes of pancytopenia such as megaloblastic anemia is more common in developing countries than western world.

As the severity of pancytopenia and the underlying pathology determines the management and prognosis of these patients identifying the correct etiopathology in a given case is crucial and helps in timely and appropriate treatment.[3] Thus, this study was conducted at Institute of medical sciences, Banaras Hindu University, India mainly with the aims to diagnose the patients with pancytopenia and finding out the common disease entities responsible for pancytopenia.

METHODS

This Observation study was carried out over a period of two years in the Department of Medicine of Institute of

Medical Sciences (IMS), BHU which is a teaching institute and a tertiary care hospital catering to the population of Eastern Uttar Pradesh and Bihar. Approval from Institute ethical committee was obtained to conduct this study.

All the patients who attended the out-patient's department and in patient's department of Department of Medicine and Pediatrics with features of anemia, thrombocytopenia or leukopenia were screened for pancytopenia and a total number of 214 cases were selected, based on the criteria's that include.[4]

- Hemoglobin (Hb) level-below 8.5 g/L for both males and females,
- Total Leucocyte Count (TLC)-below 3.5 × 109/L,
- Platelet count-below 100 × 109/L.

Patient on myelotoxic chemotherapy or receiving therapy for cytopenia were excluded. In all patient's relevant medical history including age, sex, alcohol intake, history of treatment, intake of or exposure to toxic chemicals, agents or drugs, radiation exposure, history of symptoms such as bone pains, fever, night sweats, malaise, weight loss and pruritus was taken.

A detailed physical examination was done for pallor, jaundice, hepatosplenomegaly, lymphadenopathy, sternal tenderness and gum hypertrophy and fundal bleed. Basic hematological investigations like CBC, reticulocyte count, peripheral smear examination was performed in each case. Bone marrow aspiration and in cases of failed aspiration due to dry / bloody tap a bone marrow trephine biopsy was done from anterior superior iliac spine using standard methods.

Wherever indicated, other investigations were performed that included erythrocyte sedimentation rate (ESR), Vitamin B12 and folate estimation, Serum lactate dehydrogenase level, stool examination, liver and renal function tests, serological investigations for Kala-azar, HAM test, blood culture, chest and bone radiographs, abdominal ultrasonography, urinary Bence Jones proteins and serum electrophoresis. K-39 dipstick test was done in all cases of Kala-azar which is a qualitative membrane based immunoassay for the detection of antibodies to visceral leishmania (VL) in serum of patients.

All the patients selected were investigated in a systematic manner, cause of pancytopenia was ascertained, and the data was analyzed on the basis of etiology, clinical and hematological findings before reaching a definitive diagnosis.

RESULTS

Out of 214 Pancytopenic patients highest number of patients 79 (37%) were of Aplastic anemia, followed by Megaloblastic anemia 40 (18.7 %), Kalazar 25 (11.7 %), MDS 23 (10.7%), Leukemia 17(7.9%), Hypersplenism 9 (4.2%) and Malaria (P falciparum) 5 (4.2%). In 7 patients no diagnosis was made. One case, each of Systemic lupus erythematous, *P. Vivax* malaria, Enteric fever, Tropical Splenomegaly Syndrome, Celiac disease with Splenomegaly and two cases, each of Myelofibrosis and Multiple myeloma (Table 1).

Table 1: Incidence of various diseases and male to female ratio.

Diagnosis	Number of patients	Incidence (%)	Male female ratio
Aplastic anemia	79	36.9	4.64:1
Megaloblastic anemia	40	18.7	1.5:1
Kalazar	25	11.7	5.25:1
Myelodysplastic syndrome	23	10.7	1.3:1
Leukemia	17	7.9	2.4:1
Hyperplenism	9	4.2	2:1
Malaria (*P. falciparum*)	5	2.3	4:1
No diagnosis	7	3.7	3:1
Myelofibrosis	2	0.93	2:0
Multiple myeloma	2	0.93	1:1
SLE (systemic lupus erythematosus)	1	0.46	0:1
Malaria (*P. vivax*)	1	0.46	1:0
Enteric fever	1	0.46	1:0
Celiac disease with tropical splenomegaly syndrome	1	0.46	0:1
Tropical splenomegaly syndrome	1	0.46	1:0

All patients were divided into two groups age more than 14 years and age less than 14 years because patients were selected from the Department of Medicine with age more than 14 years and Department of Pediatrics with age less than 14 years.

Age distribution and physical finding of diseases causing Pancytopenia in Age >14 years (Table 2). Age distribution and physical finding of diseases causing Pancytopenia in Age <14 years (Table 3).

Table 2: Age distribution and physical finding in various diseases causing pancytopenia in patients >14 years.

Diagnosis	Mean age (years)	Age range (years)	No. of cases with palpable liver	No. of cases with palpable spleen	No. of cases with palpable lymphnode
Aplastic anaemia (n=51)	32	15-73	9 (17.64%)	4 (7.84%)	6 (11.76%)
Megaloblastic anaemia (n=31)	31.97	15-72	23 (62.16%)	24 (64.86%)	1 (2.7%)
Kalazar (n=21)	40.46	18-70	16 (76.19%)	19 (90.5%)	0
MDS (n=14)	31.5	16-65	5 (35.7%)	4 (28.57%)	2 (14.28%)
Leukemia (n=11)	45.5	18-70	6 (54.54%)	4 (36.36%)	5 (45.45%)
Hypersplenism(n=9)	39.33	16-65	8 (88.88%)	9 (100%)	0
Malaria (n=4)	44	20-65	3 (75%)	3 (75%)	0
Myelofibrosis (n=2)	50.5	45-56	2 (100%)	2 (100%)	0
Multiple myeloma(n=1)	59	53-65	-	-	-
SLE (n=1)	26		1	1	-
Malaria (n=1) (*p. Vivax*)	17		1	1	-

Table 3: Age distribution and physical finding in various diseases causing pancytopenia patients <14 years.

Diagnosis	Mean age (years)	Age range (years)	No. of cases with palpable liver	No. of cases with palpable spleen	No. of cases with palpable lymphnode
Aplastic anaemia (n=28)	9.07±3	2-13	10 (35.7%)	5 (17.9%)	4 (14.3%)
Mds (n=9)	12.11±1.26	10-14	1 (11.11%)	2 (22.22%)	0
Leukemia (n=6)	7.5±5.08	3-14	4 (66.66%)	4 (66.66%)	5 (83.33%)
Kala-azar (n=4)	9.5±3.87	5-14	3 (75.0%)	3 (75.0%)	0
Malaria (n=1)	4	-	1	-	0
Enteric fever (n=1)	11	-	1	1	0
Celiac disease with tropical splenomegaly syndrome (n=1)	6	-	1	1	0
Tropical splenomegaly syndrome (n=1)	13	-	1	1	0
Megaloblastic anemia (n=3)	12	10-14	1	1	0
No diagnosis(n=2)	37	47-57	1	0	
Total (n=56)					

Table 4: Blood counts in various diseases causing pancytopenia in age group >14 years.

Diagnosis	HB (GM%)	Range (GM%)	TLC/µL	Platelet Count /µL
Aplastic anemia (N=51)	4.68±1.64	2.2-8.2	2501±770	45901±27004
Megaloblastic anemia (N=37)	4.63±1.79	2.5-8	2663±851	67108±28759
kala-azar (N=21)	6.32±1.52	3.7-8.2	2261±767	67142±27249
Myelodysplastic syndrome (N=14)	5.21±1.9	2.2-8.2	2440±824	54928±24084
Leukemia (N=11)	4.3±1.38	2-7	2377±787	52909±23229
Hyperplenism (N=9)	6.68±1.75	3.13-8.5	2485±638	79111±17359
Malaria (N=4)	6.65±1.8	4.1-8.3	2437±654	56000±26770
Myelofibrosis (N=2)	5.65±0.91	3.2-4.5	1600±141	42909±24229
Multiple myeloma (N=2)	5.1±1.27	4.2-6	2500±565	62142±24249
SLE (N=1)	7.5	7.5	2100	69142±27249
Malaria (*P. vivax*) (N=1)	5	5	3100	61142±21249

There were two patients of multiple myeloma with mean age of 59 years without any significant physical finding.

There was one female aged 26 years diagnosed to be a case of systemic lupus erythematosus.

Table 5: Hemoglobin in various diseases causing pancytopenia in age group <14 years.

Diagnosis	HB (GM %)	Range (GM %)	TLC/µL	Platelet count /µL (MEAN: SD)	Mean RC in (MEAN:SD)
Aplastic anaemia	4.42±2.11	1.3-8.5	2457±667.76	33500±22852	0.43±0.51
MDS	3.88±2.26	1.5-7.9	2864±717.2	48888±26026	0.42±0.35
Leukemia	6.08±1.38	4-7.8	2416±640.0	63000±27770	0.69±0.28
kalazar	6.47±1.33	4.9-8	2095±450.3	58500±19824	2.1±0.67
Megaloblastic anaemia	6.5±1.32	5.5-8	2433±321.0	76666±18929	1.3±0.92
Malaria	8.3		3500	80000	3.68
Enteric fever	7		2500	50000	2.07
Celiac disease with tropical splenomegaly syndrome	4.3		3200	98000	1.59
Tropical splenomegaly syndrome	5.3		1550	46000	2.17

The patient with malaria caused by *P. vivax* was male aged 17 years with palpable hepatosplenomegaly. The mean hemoglobin in age more than 14 years was lowest in leukemia followed by aplastic anaemia. The mean hemoglobin in age group less than 14 years was lowest in the patients of myelodysplastic syndrome (3.88 gm%) followed by aplastic anaemia (4.42 gm%) and in same group the mean hemoglobin was highest in megaloblastic anemia group (6.5gm%) followed by kala-azar group (6.47gm%). The mean hemoglobin in age less than 14 years was highest in megaloblastic anemia group (6.5 gm%) followed by kala-azar group (6.47 gm%). The mean hemoglobin was lowest in the patient of myelodysplatic syndrome (3.88 gm%) followed by aplastic anaemia (4.42 gm%).

Serum LDH in megaloblastic anaemia and in myelodysplastic syndrome

An important observation from this study is the difference in Serum LDH level between megaloblastic anemia and myelodysplastic syndrome. The serum LDH in myelodysplatic syndrome in none of the patients was more than 410 IU/L while the lowest level of S. LDH in Megaloblastic anemia was 1330 IU/L with mean of 2250 IU/L (range 1330-6550). Puline. M. Emeson et al. have also found similar results regarding S LDH levels in Patients with MDS and Megaloblastic anemia.

Out of 37 patients who were diagnosed as having Megaloblastic anemia (on the basis of peripheral blood and bone marrow picture), in 35 patients S. LDH >1330 (IU/L) and those patients who had serum LDH 340 IU/L and 550 IU/L respectively did not respond to the vitamin B12 and folic acid supplementation. In the MDS group none of the patients had serum LDH value >410 IU/L and none of them responded to the treatment. In the Megaloblastic anemia group a negative correlation between hemoglobin gm% and Serum LDH (IU/L) was also observed.

DISCUSSION

Out of 214 Pancytopenic patients, highest number of patients 79 (37%) caused by Aplastic anemia, followed by Megaloblastic anemia 40 (18.7 %), Kalazar 25 (11.7 %), MDS 23 (10.7%), Leukemia 17 (7.9%), hypersplenism 9 (4.2%) and Malaria 5 (4.2%). In 7 patients no diagnosis was made.

The most common cause of pancytopenia in our study was aplastic anemia with incidence of 36.9%. The incidence of aplastic anemia varies from 10% to 52.7% of all Pancytopenic patients in different studies.[5]

Our incidence of 36.9% correlated with the other studies. Our result is in accordance with three major Indian studies namely Verma et al Kumar et al and Sarode et al who have also found Aplastic anemia to be the commonest cause of pancytopenia in their study.[6-8]

Presence of palpable spleen is not an expected feature of Aplastic anemia and it is surprising that 7.8% of our patients of age group more than 14 years and 17.9% in age group less than 14 years have just palpable spleen. This can be accounted for by high incidence of asymptomatic splenomegaly in areas endemic for malaria.[9]

Megaloblastic anemia was the second common cause of the pancytopenia in our study with incidence of 18.7%. The mean age of presentation was 30.1±16.83 with range of (6-72 year). Our incidence of 18.7% correlates with other studies. Out of the six Indian studies two studies Verma et al and Kumar et al have similarly reported Megaloblastic anemia to be the second most common cause of pancytopenia.[6,7] Our results are in disagreement with the other two Indian studies Tilak et al and Kishore et al, which have found Megaloblastic anemia to be the most common cause of pancytopenia.[3,10]

In age group more than 14 year the incidence of Megaloblastic anemia was 23.4%, while it incidence in age group less than 14 years was 5.4%. The incidence of Megaloblastic anemia between the two groups is statistically significant with P<0.01. Similar observation has also been reported by David et al and Tilak et al.[3,11] Thus, in contrast to the age group more than 14 years Megaloblastic anemia is a rare cause of pancytopenia in the pediatric age group.

The incidence of Kala-azar was 11.7% making it 3rd most common cause of pancytopenia with male: female ratio was 5.25:1. The incidence of kala-azar varies from 0 to 14% of all pancytopenic patients. The high incidence of kala-azar in our study is due to the fact that our center is located in the endemic zone of Kala-azar, Eastern Uttar Pradesh situated adjacent to north west region of Bihar. Hussain et al from Bangladesh have shown Kala-azar along with chronic malaria to be the second most common cause of pancytopenia.[12]

The incidence of MDS in present study is 10.7% with male to female ratio of 3:1, and correlates with that of other studies. Its incidence in age group >14 years is 8.9% with male to female ratio 1:1 and in age group less than 14 years is 16.1% with male to female ratio 2:1. The incidence of MDS in present study is 10.7% with male to female ratio of 3:1, and correlates with that of other studies by Keisu M and Ost A et al which shows incidence of MDS varies from 0% to 14% of all pancytopenic patients in various studies.[5]

The mean age of presentation is 23.9+14.43 years with range of 10-65 years. Usually MDS is considered to be disease of elderly, but in our study as well another Indian series by Tejinder and Sudha Rani et al over all 75.5% of individual (20/33) were of <50 years of age, 8 (21.6%) of 33 patients were less than 20 years of age.[13]

Incidence of Leukemia in our study was 7.9% correlates with other studies wherein the incidence of leukemia varies from 2.3-19% of all pancytopenic patients.[5,14] It incidence in India varies from 2-19% of all pancytopenic patients. Its incidence in age group more than 14 years is 7% and in age group <14 years is 11.53%. High incidence in less than 14years of age group is also reported by different studies.[15,14,12,8,7,5]

The incidence of Pancytopenia caused by hypersplenism was 4.2% which was within the range 0% to 19% reported by various studies [5]. The overall incidence was 4.2 % with M:F ratio was 2:1. The mean age of presentation was 39.33+16.63 yrs. with range of 16-65 years. The incidence in age group >14 years is 5.7% with M:F ratio was 2:1. All cases were caused by portal hypertension secondary to liver cirrhosis. While in age group <14 yrs, not a single case of hypersplenism occurred due to chronic liver disease but 2 cases of tropical splenomegaly syndrome were seen. In one patient this syndrome was associated with celiac disease.

Incidence of pancytopenia caused by malaria, in various studies throughout the world, ranges from 0 % to 3.89%. In our study its incidence is 2 % which is correlating with other studies. In all these cases, pancytopenia was caused by acute malarial infection and not by the hpersplenism due to tropical splenomegaly syndrome.

Multiple myeloma is a rare cause of pancytopenia. Its incidence varies from 0% to 4% in Indian studies conducted on pancytopenia.[8,10,13] Our incidence of 0.93% correlated with other studies on pancytopenia. Hence, multiple myeloma should be considered in any order patients presenting with generalized bony pain and pancytopenia.

CONCLUSION

The study was an observational study and involved all the pancytopenic patients who were either admitted to Department of Medicine or Department of Pediatrics or whose peripheral blood smears and bone marrow aspirate smears were received in the Department of Pathology of Institute of Medical Sciences, BHU. The salient features of our study were

- Megalolastic anemia was the second most common cause of pancytopenia in age group of >14 years with incidence of 23.4 %, on the contrary it was an uncommon cause of pancytopenia in pediatric population. The difference in incidence is statistically significant compared to its incidence in age group >14 years (p <0. 01),
- Aplastic anemia emerges as the most important cause of pancytopenia in pediatric age group and its incidence was significantly more than that in the adult population (50.5% Vs 37.2%),
- Visceral leishmaniasis account for substantial number of pancytopenia patients 11.7%. The diagnosis was particularly difficult in elderly patients with visceral leishmaniasis, who had non-palpable or just palpable spleen. Consequently, it should always have kept in the differential diagnosis of pancytopenia in area endemic or the area which are adjacent to the endemic area,
- Megaloblastic anemia (52.72%), Aplastic anemia (34.54%) and Myelodysplastic syndrome (12.72%) were the most important cause of macrocytosis in

pancytopenia patients. 42.85% of patients of MDS have macrocytosis which is unusual finding as compared to western data. Thus, MDS should be put high on the differential diagnosis while evaluating the causes of macrocytic anemia in Indian setup,

- Serum LDH was found to be a very important diagnostic test to differentiate between the megaloblastic of vitamin B12 and folate deficiency from the megaloblastosis seen in some cases of myelodysplastic syndrome. A value more than thousand was present in all cases of megaloblastic anaemia while it was less than 400IU in all the cases of myelodysplastic syndrome with megaloblastosis. None of the patients who had macrocytosis and megaloblastic bone marrow aspirate with LDH <400 IU responded to the vitamin B12 and folic acid supplement. While all such patients with LDH >1000 IU respond to their supplement.

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