

Hemorrhagic manifestation in different etiologies of pancytopenia: A prospective, cross-sectional study

Mridu Singh¹, Vikram Singh¹, Durga Prasad Singh¹, Gopal Krishna Bohra², Arup Kumar Misra³

¹Department of Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, ²Department of Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan, ³Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Mangalagiri, Andhra Pradesh, India

ABSTRACT

Background: Pancytopenia is a triage of anemia, leukopenia, and thrombocytopenia. The etiology causing pancytopenia varies depending upon factors such as age, sex, occupation, and geographical distribution. Unfortunately, the major treatises of hematology have not given emphasis on the hemorrhagic manifestation of different etiologies causing pancytopenia. **Objective:** This observational study was carried out with the aim to identify hemorrhagic manifestation in patients with pancytopenia in eastern India. **Design:** This study was conducted over a period of two years at the Department of Medicine of a tertiary care teaching institute in eastern India. All the patients with features of anemia, thrombocytopenia, or leukopenia were screened for pancytopenia and a total of 214 cases were selected. Patients were divided into two groups as patients with age more than 14 years constitute group one and the patients less than 14 years constitute the second group. A detailed physical examination, hematological, and biochemical investigation was done to ascertain the hemorrhagic manifestations in pancytopenia patients. **Results:** In the groups, the most common cause of hemorrhagic manifestation in patients with pancytopenia was aplastic anemia, leukemia, myelodysplastic syndrome, and myelofibrosis. No bleeding manifestation was seen in patients with megaloblastic anemia, kala-azar, hypersplenism, and other causes of pancytopenia. **Conclusions:** Patients with pancytopenia caused by aplastic anemia, acute leukemia, and myelodysplastic syndrome have more chances of bleeding manifestation as compared with pancytopenia caused by megaloblastic anemia, kala-azar, or hypersplenism.

Keywords: Aplastic anemia, hemorrhagic manifestation, kala-azar, megaloblastic anemia, pancytopenia

Introduction

Pancytopenia is the triad of anemia, leukopenia, and thrombocytopenia.^[1] It is a concerning laboratory abnormality that requires urgent evaluation for its various etiologies.^[2] It exists when the hemoglobin (Hb) level (less than 13.5 g/dL in males or 11.5 g/dL in females), the leucocytes count (less than $4 \times 10^3/L$)

and the platelets count (less than $150 \times 10^3/L$).^[3] are below the specified level. The clinical course of pancytopenia may go unnoticed in the initial stages due to mild impairment in the marrow function. At the time of stress, infection, or bleeding disorders, it may become more apparent.^[4] There are multiple hematopoietic and nonhematopoietic conditions that manifest as prominent features of pancytopenia. The underlying mechanisms responsible for pancytopenia are decrease in hematopoietic cell production due to the destruction of marrow tissue, marrow replacement by abnormal or malignant cells, suppression, and uneven differentiation of marrow growth,

Address for correspondence: Dr. Vikram Singh, Department of Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. E-mail: vikramrpsingh@gmail.com

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and ineffective hematopoiesis.^[5,6] Major treatises of hematology have not given emphasis to etiologies that cause hemorrhagic manifestation in a pancytopenia patient. The severity of hemorrhagic and other manifestations of pancytopenia along with underlying pathology determine the management and prognosis of these patients.^[7] This study was conducted at a tertiary care teaching institute in the eastern part of the country mainly with the aim to evaluate the hemorrhagic manifestation in the patients with pancytopenia.

Methods

Study design

A prospective, cross-sectional study was conducted at the Department of General Medicine at a tertiary care teaching hospital catering to the population of eastern Uttar Pradesh and Bihar. The study took overall 2 years for recruitment and follow-up. Patients with the age group of 3–73 years with hemorrhagic manifestation attending medicine outpatient department (OPD) were included in the study based on the following criteria:

Inclusion criteria

1. Hemoglobin (Hb) level – below 8.5 g/L for both males and females.
2. Total Leukocyte Count (TLC) – below $3.5 \times 10^9/L$.
3. Platelet count – below $100 \times 10^9/L$.

Exclusion criteria

1. A patient on myelotoxic chemotherapy or receiving therapy for cytopenia was excluded.

Sample size

In view of the availability of patients, time constraint, and resources, no formal sample size calculation was done. It was decided to include a reasonable number of patients to have meaningful, valid, and credible results. Two hundred and sixty-one patients (age between 3 and 73 years) attending medicine OPD were selected based on the inclusion criteria for the study. Informed consent was taken from all patients. Patient's demographic data were collected at the time of the visit to the medicine OPD.

Subjects eligible for the study were divided into two (2) groups based on age. The hemorrhagic manifestation due to various diseases causing pancytopenia were divided into above and less than 14 years of age. The group with the hemorrhagic manifestations above 14 years of age consisted of 153 subjects. The second group with the hemorrhagic manifestations less than 14 years of age consisted of 108 subjects.

In all patients, a relevant medical history which consisted of age, sex, alcohol intake, treatment history, intake of or exposure to toxic chemical agents, radiation exposure was taken. The patients were also asked about symptoms such as bone pains, fever, night sweats, malaise, weight loss, and pruritus.

On examination, general and systematic examinations were done for pallor, hepatosplenomegaly, lymphadenopathy, sternal tenderness, gum hypertrophy, mucocutaneous bleed, and retinal bleed. Fundoscopy was done for retinal bleed.

The basic hematological investigations like complete blood count (CBC), reticulocyte count, and peripheral smear examination were performed for each patient. Bone marrow aspiration was done for all the patients except in cases of failed aspiration due to dry or bloody tap. A bone marrow trephine biopsy was done from the anterior superior iliac spine using standard methods.

The patients were also investigated for biochemical parameters like erythrocyte sedimentation rate (ESR), vitamin B12 and folate estimation, serum lactate dehydrogenase (LDH), stool examination, liver and renal function tests. Serological investigations for kala-azar, HAM test, and blood culture were also done. Chest and bone radiographs and abdominal ultrasonography were also done for patients. K-39 dipstick test was done in all cases of kala-azar.

All the patients selected were investigated in a systematic manner, cause of pancytopenia was ascertained, and the data were analyzed on the basis of etiology, hemorrhagic manifestation, and hematological findings.

Ethical consideration

Ethical clearance was taken from the Institutional Ethical Committee.

Statistical analysis

Data were compiled using Microsoft Excel and analyzed using SPSS software (IBM-SPSS statistics 20.0; SPSS Inc., Chicago, IL, USA). Quantitative variables were analyzed using frequency, mean, and standard deviation.

Result

As the study was aimed to know various hemorrhagic manifestations in pancytopenia patients (adult population as well in the pediatric population). All the pancytopenia patients with hemorrhagic manifestations were selected from the Department of Medicine with age more than 14 years and Department of Pediatrics with age less than 14 years.

The bleeding manifestation and etiology of pancytopenia in the age group greater than 14 years is given in Table 1. In this group, there were 51 patients of aplastic anemia with the mean age of 32 years and age range of 15–73 years. Nearly 26 patients were examined to have fundal bleed and 15 patients had a mucocutaneous bleed. The number of patients suffering from myelodysplastic syndrome was 14 with the mean age of 31.5 years and the age range was 16–65 years. In this subgroup, it was found that only one patient had fundal bleed and mucocutaneous bleed,

respectively. In the subgroup of leukemia, the number of patients were 11 with a mean age was 45.5 years and the age range of 18–70. Only seven patients had a fundal and mucocutaneous bleed, respectively in the subgroup of leukemia.

The remaining pancytopenia patients did not have any bleeding manifestation in the group, and they were mostly suffering from megaloblastic anemia (37), kala-azar (21), hypersplenism (9), *P. falciparum* malaria (4), and one patient of multiple myeloma, systemic lupus erythematosus (SLE), and *P. vivax* malaria, respectively.

In the age group less than 14 years [Table 2], 28 children had aplastic anemia with the mean age of 9.07 years and the age range of 2–13 years. Fundal bleed was found in 18 children, whereas mucocutaneous bleed was seen in 15 children. Myelodysplastic syndrome was diagnosed in nearly 28 children in the sample with the mean age of 12.11 years and age range of 10–14 years. In this subgroup, two children were examined to have fundal bleed and only one child had mucocutaneous bleed. Leukemia was diagnosed in six children in the sample with the mean age of 7.5 years with the age range of 3–14 years. In this subgroup, only one child had a fundal bleed and two children were examined to have mucocutaneous bleed. No children with pancytopenia were found to have hemorrhagic manifestation with the diagnosis of kala-azar, malaria, megaloblastic anemia, enteric fever, and celiac disease with tropical splenomegaly syndrome.

In both the groups, irrespective of age, aplastic anemia, acute leukemia, and myelodysplastic syndrome the patients were found to have an increased bleeding manifestation in the . [Table 3 and 4] No other causes of pancytopenia in our study showed such a high incidence of hemorrhagic manifestation.

Discussion

Pancytopenia patients with severe thrombocytopenia have a major risk for hemorrhage, but platelet function and bleeding risk at low platelet counts are poorly understood. There are multiple reports on the underlying etiology of pancytopenia in the literature from all over the world. The most common cause of pancytopenia in patients above 14 years of age in our study was aplastic anemia with an incidence of about 37%, which was comparable with the studies by Varma *et al.* (40.6%) and Kumar *et al.* (29.5%).^[8,9] On the other hand, studies by Tilak *et al.* and Khunger *et al.* found that megaloblastic anemia to be the most prevalent cause of pancytopenia in adults in India.^[4,7] Megaloblastic anemia in addition to severe B12 deficiency in some cases causes pancytopenia and hemolysis.^[10] The incidence of aplastic anemia varies from 10% to 52.7% of all pancytopenia patients in different studies from all over the world.^[11,12] It was found that the incidence of bleeding manifestation in patients of aplastic anemia having platelet count less than 20,000/cu mm was statistically significant than the patient with platelet count more than 20,000/cu mm (*P*-value < 0.001). The bleeding manifestation was significantly higher in leukemia

Table 1: Hemorrhagic manifestation in diseases causing pancytopenia in age group >14 years

Diagnosis	Mean age (years)	Age range (years)	No. of cases with fundal bleed (n) (%)	No. of cases with mucocutaneous bleed (n) (%)
Aplastic anemia (n=51)	32	15-73	26 (51%)	15 (29.4%)
Megaloblastic anemia (n=37)	31.97	15-72	0 (0%)	0 (0%)
Kalazar (n=21)	40.46	18-70	0 (0%)	0 (0%)
MDS (n=14)	31.5	16-65	1 (7.14%)	1 (7.14%)
Leukemia (n=11)	45.5	18-70	7 (63.6%)	7 (63.6%)
Hypersplenism (n=9)	39.33	16-65	0 (0%)	0 (0%)
Malaria (n=4)	44	20-65	0 (0%)	0 (0%)
Myelofibrosis (n=2)	50.5	45-56	1 (50%)	0 (0%)
Multiple Myeloma (n=2)	57	53-65	0 (0%)	0 (0%)
SLE (n=1)	26	NA	0 (0%)	0 (0%)
Malaria (P Vivax) (n=1)	17	NA	0 (0%)	0 (0%)

n=Number, % = Percentage, MDS= Myelodysplastic Syndrome, Systemic lupus erythematosus

Table 2: Bleeding manifestation in various disease-causing Pancytopenia patients <14 years

Diagnosis	Mean age (years)	Age range (years)	No. of cases with fundal bleed (n) (%)	No. of cases with mucocutaneous bleed (n) (%)
Aplastic anemia (n=28)	9.07	2-13	18 (72.22%)	15 (53.57%)
Kalazar (n=4)	9.5	5-14	0 (0%)	0 (0%)
MDS (n=28)	12.11	10-13	2 (7%)	1 (3.57%)
Leukemia (n=6)	7.5	3-14	1 (16.6%)	2 (33.33%)
Malaria (n=1)	4	NA	0 (0%)	0 (0%)
Enteric Fever (n=2)	11	NA	0 (0%)	0 (0%)
Tropical Splenomegaly Syndrome (n=1)	6	NA	0 (0%)	0 (0%)
Celiac Disease with Tropical Splenomegaly Syndrome (n=1)	13	NA	0 (0%)	0 (0%)

n=Number, % = Percentage, MDS=myelodysplastic syndrome

Table 3: Platelet counts and hemoglobin in various diseases causing pancytopenia in age group >14 years

Diagnosis	Hb (gm%)	Platelet Count (/μL)
Aplastic anemia (n=51)	4.68±1.64	45901±27004
Megaloblastic anemia (n=37)	4.63±1.79	67108±28759
Kalazar (n=21)	6.32±1.52	67142±27249
MDS (n=14)	5.21±1.9	54928±24084
Leukemia (n=11)	4.3±1.38	42909±24229
Hypersplenism (n=9)	6.68±1.75	79111±17359
Malaria (n=4)	6.65±1.8	56000±26770
Myelofibrosis (n=2)	5.65±0.91	65142±24249
Multiple Myeloma (n=2)	5.1±1.27	76111±15359
SLE (n=1)	7.5	57108
Malaria (P Vivax) (n=1)	5	47888

n=Number, Mean±SD=Mean plus minus Standard Deviation, MDS=myelodysplastic syndrome, SLE=systemic lupus erythematosus

Table 4: Platelet counts and Hemoglobin in various diseases causing pancytopenia in age group <14 years

Diagnosis	Hb (gm%)	Platelet Count (/μL)
Aplastic anemia (n=28)	4.42±2.11	33500±22852
Megaloblastic anemia (n=37)	6.5±1.32	76666±18929
Kalazar (n=4)	6.47±1.33	58500±19824
MDS (n=28)	3.88±2.26	48888±26026
Leukemia (n=6)	6.08±1.38	63000±27770
Malaria (n=1)	8.3	80000
Enteric Fever (n=2)	7	50000
Tropical Splenomegaly Syndrome (n=1)	4.3	98000
Celiac Disease with Tropical Splenomegaly Syndrome (n=1)	5.3	46000

n=Number, Mean±SD=Mean plus minus Standard Deviation, MDS=myelodysplastic syndrome

group in patients above 14 years of age with a prevalence of 63.6%. ($P < 0.001$).

The comparison of incidence of bleeding in patients with platelet count less than 20,000/cu mm between the aplastic anemia group and leukemia group was statistically insignificant (P value = 3.421), but this comparison was significant in a patient having a platelet count more 20,000 (P value < 0.001). Bleeding manifestation in aplastic anemia is usually seen late in the course of the disease, while hemorrhagic sign and symptoms including petechia and easy bruising may be found in up to one-half of patients of acute leukemia at the time of diagnosis.

Megaloblastic anemia was the second common cause of the pancytopenia in the subjects who were above 14 years of age in the study with an incidence of 18.7%. However, there were no bleeding manifestations in the patients with megaloblastic anemia. There are two Indian studies namely, Verma *et al.* and Kumar *et al.* which also reported megaloblastic anemia as the second leading cause of pancytopenia in adult population.^[8,9]

Megaloblastic anemia was found to be statistically significant ($P < 0.01$) between the two groups with a prevalence of 23.4% in the group with age more than 14 years as compared

to 5.4% in the age group less than 14 years. The incidence of megaloblastic anemia between the two groups is found to have a similar observation in the studies reported by Tilak *et al.* and Dasgupta *et al.*^[7,13] It can be observed from our study that megaloblastic anemia is a rare cause of pancytopenia in the pediatric age group, which is quite contrary to the study done by Zeeshan *et al.*^[14] The incidence of kala-azar was 11.7% in the pediatric group in the study which makes it as the third leading cause of pancytopenia. The incidence of kala-azar is slightly higher than the study done by Naseem *et al.* which has an incidence of 2.9% among the nonmalignant causes of pancytopenia.^[15]

The incidence of myelodysplastic syndrome (MDS) in the present study is 10.7% with a male to female ratio of 3:1, and it correlates well with the studies done by studies by Keisu *et al.*^[11] Other studies show that the incidence of MDS varies from 0% to 14% of all pancytopenia patients.^[4,16,17] The increased risk of bleeding in patients with MDS is typically attributed to both low platelet counts and abnormalities of platelet morphology and function (i.e., platelet aggregation defects).^[18] Patients with pancytopenia with MDS having low platelet levels are at an increased risk of hemorrhagic manifestations but the mechanism is not well defined.^[19,20] The incidence of bleeding complications reported in the literature, in patients with MDS, range from 3% to 53%.^[21]

Retinal hemorrhage was reported in 24% of patients in a retrospective study of ocular complications associated with MDS and was associated with significantly reduced platelet count ($P = 0.006$).^[22] The incidence of leukemia in the adult groups was found to be 7.9% which correlates well with a study by Kramer *et al.* wherein the incidence of leukemia in the pancytopenia patients worldwide varies between 2.3% and 40%.^[4,7,9,23-25] It constitutes nearly 2%–19% of all pancytopenia patients in India with incidence higher in the adult group of patients, which is well correlated with our study.^[4,9,26]

The incidence of pancytopenia caused by malaria in our study is only 2%, which is comparable with the other studies such as Khunger *et al.* reported an incidence of only 1%; whereas Tilak V *et al.* and Kumar R *et al.* reported an incidence of 3.9% and 3%, which are higher than our finding in the present study.^[4,7,9] Multiple myeloma is a rare cause of pancytopenia. Its incidence varies from 0% to 4% in Indian studies conducted on pancytopenia. In our study, its incidence is only 0.93%, which correlated well with other similar studies on pancytopenia.^[4,7,9]

Conclusion

In the present study, megaloblastic anemia was found to be the second most common cause of pancytopenia in the age group of greater than 14 years with an incidence of nearly 23%. Contrary to this finding in the adult population, it was an uncommon cause of pancytopenia in the pediatric age group. This type of study is quite relevant to the primary care physicians,

hematologists, and pathologists as it will help them to diagnose the cases of the hemorrhagic manifestation in different etiologies of pancytopenia and manage accordingly. In the end, it can be summarized that patients with pancytopenia having the etiologies of aplastic anemia, acute leukemia, and myelodysplastic syndrome have more chances of bleeding manifestation as compared to pancytopenia caused by megaloblastic anemia, kala-azar, or hypersplenism.

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Conflicts of interest

There are no conflicts of interest.

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