

Clinico-pathological Study of Pancytopenia: A Prospective Study

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Abstract

Background and Objectives: Pancytopenia is an important hematological entity. It is a disorder in which all three major formed elements of blood are decreased in number. The present study has been undertaken to find out various causes of pancytopenia by evaluation of bone marrow findings so that the data will help the clinician in better management of patients.

Materials and Methods: It was a prospective study conducted in the Department of Pathology in King George Hospital, Visakhapatnam, a teaching institute and tertiary hospital in over a period of 1 year. Patients were referred to pathology from the departments of medicine and pediatrics for investigations on suspicion of pancytopenia. The patients were evaluated clinically along with hematological parameters and bone marrow aspiration biopsy. It was carried out in 68 patients from November 2016 to December 2017. Hemogram was obtained using five-part automated analyzer. Bone marrow aspiration was performed using Salah needle from the posterior superior iliac crest and from the medial aspect of tibial tuberosity in children <4 years. Bone marrow aspiration smears were stained using Leishman's stain and Giemsa stain.

Results: Among the 68 patients studied, the age of the patients varied from 3 years to 76 years with a male predominance. Most of the patients presented with fever and generalized weakness. The most common physical finding was pallor. Dimorphic anemia was the predominant blood picture. The most common bone marrow finding was erythroid hyperplasia with megaloblastic maturation. The most common cause of pancytopenia was megaloblastic anemia (64.7% of cases) followed by hypersplenism (10.2% of cases). Other causes include aplastic anemia, leukemia, idiopathic thrombocytopenic purpura, tuberculosis, lymphoma, and multiple myeloma.

Conclusion: Detailed clinical history and physical examination along with hematological investigations and bone marrow aspiration biopsy are helpful for understanding the disease process and to diagnose the cause of pancytopenia. Identification of correct cause will help in implementing appropriate therapy. This study helps in identifying the incidence of various causes of pancytopenia.

Key words: Megaloblastic anemia, pancytopenia, bone marrow

INTRODUCTION

Pancytopenia is a disorder in which all three major formed elements of blood (red blood cell, white blood cell, and platelets) are decreased in number.^[1] There are various trends in its clinical patterns, treatment modalities, and outcome.^[2] It may be the manifestation of numerous disorders which primarily or secondarily affect the bone marrow.^[3] The severity of pancytopenia and the underlying pathology determine the management and

prognosis.^[4] Thus, identifying the correct cause will help in implementing appropriate therapy.

MATERIALS AND METHODS

The present study was conducted in the Department of Pathology in King George Hospital, Visakhapatnam, a teaching institute and tertiary hospital in over a period of 1 year from November 2016 to December 2017. It was a prospective study during which 68 cases were studied based on clinical evidence and hematological parameters. Patients were referred to pathology from the departments of medicine and pediatrics for investigations. Patients of all age groups and both genders were included. All of them underwent bone marrow aspiration biopsy.

Inclusion criteria were the presence of all three of the following:

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- Hb level <10 g/dL.
- TLC <3.5 × 10⁹/L.
- Platelet count <100 × 10⁹/L.

Exclusion criteria were the presence of the following:

- Patients who received blood and blood products.
- Patients on radiotherapy and chemotherapy.

Hematological parameters were obtained using five-part automated analyzer. Peripheral blood smears (PBS) were stained using methylene blue and examined under a microscope. Bone marrow aspiration biopsy was done by taking informed consent in a conventional manner. Bone marrow aspiration was performed using Salah needle from the posterior superior iliac crest and from the medial aspect of tibial tuberosity in children <4 years. Bone marrow aspiration smears were stained using Leishman's stain and Giemsa stain.

RESULTS

Among the 68 patients studied, 41 were male and 27 were female. A male preponderance was observed with a male to female ratio of 1.5:1. The age of the patients varied between 3 years and 76 years. There were a total of 12 pediatric cases among which 7 were males and 5 were females.

The following Table 1 demonstrates the age distribution of the patients in the study.

Patients presented with a wide variety of symptoms among which fever was most frequently observed.

Generalized weakness/fatigue was the second most common symptom. Pallor was seen in all the patients.

Presenting complaints and physical findings are presented in Table 2.

The causes of pancytopenia were ascertained after evaluating complete blood cell, PBS, and bone marrow aspiration findings.

Table 1: Age distribution of patients

Age group	Cases	Total (%)
≤10	6	8.9
11–20	17	25.3
21–30	9	13.4
31–40	12	17.9
41–50	10	14.9
51–60	8	10.4
61–70	5	7.4
71–80	1	1.4

The diseases diagnosed are mentioned in Table 3.

The following Graph 1 demonstrates the case distribution between males and females for each cause of pancytopenia.

Dimorphic anemia was the most common finding on PBS as was seen in 58.4% of the patients. Macrocytic anemia was observed in 13.8% of the patients with normocytic anemia and microcytic anemia observed in 13.3% and 12.3% of the cases, respectively.

Hematological parameters noted are mentioned in Table 4.

Megaloblastic anemia was the most common etiology of pancytopenia in this study. It was seen in 44 (64.7%) patients with a male to female ratio of 1.7:1. The age of the patients ranged from 15 to 65 years. Fever, generalized weakness, and fatigue were the common symptoms. Shortness of breath was seen in few cases. Bleeding p/v, malena, loss of weight, diarrhea, and vomiting were the other presenting complaints. Bone marrow aspiration showed erythroid hyperplasia with megaloblastic maturation in 86% of the cases. 14% of the cases showed dimorphic erythroid hyperplasia predominantly megaloblasts, and normoblasts. Vitamin B12 deficiency was proved to be the cause in 56.8% of the cases with low B12 levels. In 5% of the patients, alcoholism was the cause. No cause was established in the remaining cases.

Hypersplenism was the second most common cause of pancytopenia in this study. It was seen in 7 patients (10.2%) with a male to female ratio of 1.3:1. Patients were in the age group of 8 years to 45 years. The causes of hypersplenism were thalassemia (3 patients), sickle cell anemia (2 patients), and malaria (2 patients). Erythroid hyperplasia with both micronormoblastic and megaloblastic maturation was seen on bone marrow aspiration biopsy. Ring forms of Plasmodium were also seen in the bone marrow of a patient with malaria.

Aplastic anemia was diagnosed in 6 (8.8%) patients. Male to female ratio was 2:1. The age of the patients varied between 7 and 40 years. Bone marrow was hypocellular with an increase in adipose tissue. The causes were viral hepatitis, tuberculosis (TB), and idiopathic aplastic anemia. Viral hepatitis was observed in two patients. Extrapulmonary TB was seen in one patient. The patient presented with TB ascites, hepatosplenomegaly, mild pleural effusion, and retroperitoneal lymphadenopathy. In the remaining four cases, no cause was established hence diagnosed as idiopathic aplastic anemia. Fever, diarrhea, vomiting, and generalized weakness were the clinical complaints in idiopathic cases. Splenomegaly, fatigue, and shortness of breath were seen in another patient with idiopathic aplastic anemia.

Table 2: Presenting complaints and physical findings

Presenting complaints and physical findings	Percentage of cases (%)	Presenting complaints and physical findings	Percentage of cases (%)
Fever	40.2	Vomiting	11.9
Generalized weakness/fatigue	29.2	Lymphadenopathy	4.4
Abdominal pain	8.9	Loss of appetite	4.4
Pallor	100	Burning micturition	1.4
Splenomegaly	11.9	Ascites	1.4
Hepatomegaly	7.4	Weight loss	4.4
Jaundice	8.9	Gum bleeds	1.4
Body pains	5.9	Purpura	2.9
Pedal edema	10.4	Cough	5.9
Bleeding p/v	2.9	Chills and rigor	7.4
Diarrhea	2.9	Ulcer foot	1.4
Generalized edema	4.4	Malena	1.4

Table 3: Causes of pancytopenia

Causes of pancytopenia	Cases (% of total)
Megaloblastic anemia	64.7
Hypersplenism	10.2
Hemoglobinopathies	
Malaria	
Aplastic anemia	8.8
Idiopathic aplastic anemia	
Viral hepatitis	
Tuberculosis	
Leukemia	8.8
AML	
ALL	
CML	
Idiopathic thrombocytopenic purpura	4.4
Lymphoma	1.4
Multiple myeloma	1.4

CML: Chronic myelogenous leukemia, ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia

Leukemia was seen in 6 (8.8%) patients, among which 3 patients in the age range of 14–65 years were diagnosed with acute myeloid leukemia (AML), 2 male children aged 3 and 4 years with acute lymphoblastic leukemia (ALL), and one female patient aged 28 years with chronic myelogenous leukemia (CML). Male to female ratio was 2:1. Fever, shortness of breath, jaundice, loss of weight, HSM, purpura, and bleeding gums were the clinical findings in AML. The children with ALL had abdominal distension, generalized edema, and fever. On bone marrow aspiration, marked an increase in myeloid series with myeloblasts forming 70% of the differential count, male:female ratio of 20:1, with erythropoiesis suppression was observed in AML. In ALL, the bone marrow was infiltrated with lymphoid series predominantly lymphoblasts. CML showed a marked increase in myelopoiesis with the shift to left, myelocytes, and metamyelocytes forming 48% of the differential count and myeloblasts forming 4%. Male:female ratio was 20:1 with normoblastic erythropoiesis suppression.

The present study revealed idiopathic thrombocytopenic purpura as a cause of pancytopenia in 3 cases. Fever with

chills and rigors, bleeding, and splenomegaly were the clinical findings. Megakaryoblasts were increased with premature forms - mono/bi/multinucleated seen in the bone marrow.

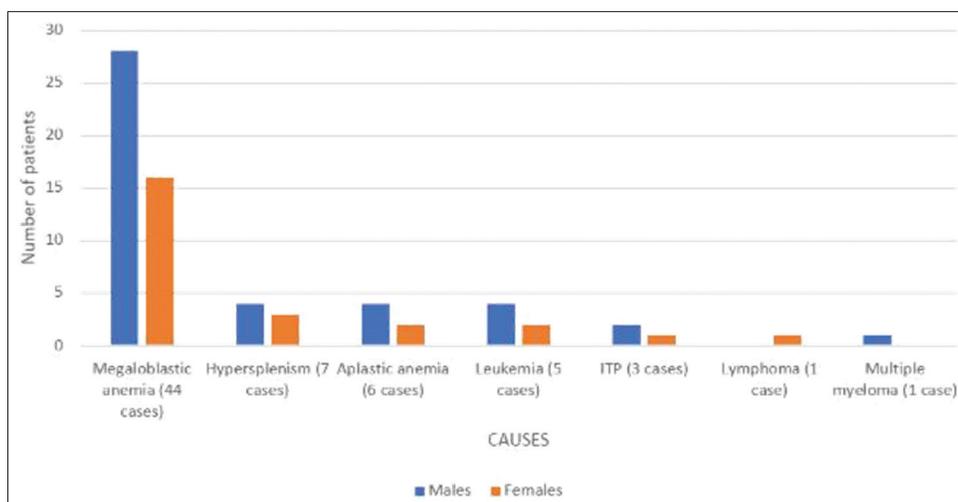
Lymphoma was encountered in a 16-year-old female. Atypical lymphocytes, myelocytes, and metamyelocytes were seen in the PBS. Bone marrow examination showed a marked increase in lymphopoiesis with immature cells of lymphoid series, showing large cells with cleaved, indented and folded nuclei, irregular clumping of chromatin, and few blast cells with uniformly distributed chromatin.

Multiple myeloma was the cause of pancytopenia in a 76-year-old male. The patient presented with an ulcer over left foot, fever, cough with expectoration, and shortness of breath and diffuses joint pains. Bone marrow showed both typical and atypical plasma cells, binucleated and multinucleated forms with intranuclear and cytoplasmic inclusions.

DISCUSSION

Decrease in hematopoietic cell production as a result of the destruction of bone marrow or replacement by abnormal tissue leads to pancytopenia.^[5] In this study of 68 patients, the age of patients ranged from 3 years to 76 years with a male to female ratio of 1.5:1. The following Table 5 compares the gender ratio and the number of cases in various studies.

Fever was the most common presenting complaint and was observed in 40.2% of the patients followed by generalized weakness/fatigue which was seen in 29.2% of the patients. Similar findings were seen in a study by Khodke *et al.*,^[15] where fever was seen in 40% followed by weakness (30%). In another study by Graham *et al.*,^[22] fever was the most common symptom (37% of the cases) and generalized weakness was seen in 20% of the cases.



Graph 1: Sex distribution of patients

Table 4: Hematological parameters

Hematological	Megaloblastic	Hypersplenism	Aplastic	Leukemia	ITP
Parameters	Anemia		Anemia		
Hb (g/dL)	2.4–6.5	2.9–4.7	3.6–7.1	4.4–6.7	3.4–7
WBC (μ L)	1200–3400	1100–3100	1400–3000	1400–2800	1300–3300
PC (μ L)	21,000–98,000	14,000–90,000	10,000–94,000	40,000–98,000	10,000–40,000

WBC: White blood cell, ITP: Idiopathic thrombocytopenic purpura

Table 5: Age and gender comparison

Study	Number of cases	Age range	Male to female
			Ratio
Tilak and Jain, 1999	77	5–70	1.14:1
Khodke <i>et al.</i> , 2000	50	3–69	1.3:1
Kumar <i>et al.</i> , 2001	166	12–73	2.1:1
Khunger <i>et al.</i> , 2002	200	2–70	1.2:1
Santra and Das, 2010	111	13–65	1.47:1
Subramanyam and Padma, 2015	106	4–75	1.12:1
Anjana <i>et al.</i> , 2016	132	2.5–76	1.5:1
Present study	68	3–76	1.5:1

On PBS examination, dimorphic anemia (58.4%) was followed by macrocytic anemia (13.8%). In a study by Gayathri *et al.*, predominant blood picture was dimorphic anemia (37.5%) followed by macrocytic anemia (31.7%). Hypersegmented neutrophils were seen in 42.4% of the patients in this study. Graham *et al.* reported a much higher percentage of hypersegmented neutrophils (51.35%) whereas Khunger *et al.* demonstrated an absence of hypersegmented neutrophils on PBS in his study.

The most common cause of pancytopenia in this study was megaloblastic anemia followed by hypersplenism. The following Table 6 compares the important causes of pancytopenia in various studies.

The most common cause of pancytopenia reported in the majority of studies from various parts of the world has

been megaloblastic anemia.^[6] It is a rapidly correctable disorder and should be promptly notified.^[7] Megaloblastic anemia has the highest incidence in this study and was seen in 64.7% of the patients. Similarly, Tilak *et al.* reported an incidence of 68% and the study by Gayathri *et al.*^[14] revealed an incidence of 74%.

In hypersplenism, there is peripheral pooling or trapping and destruction in an enlarged spleen resulting in cytopenias.^[8] A second most common cause, in this study, was hypersplenism, and its incidence was 10.2%. Much alike, in the study by Sharma *et al.*, the incidence of hypersplenism stood at 10.6%. The causes of hypersplenism were thalassemia (3 patients), sickle cell anemia (2 patients), and malaria (2 patients) in this study. Pereira *et al.*^[18] reported one case each of paroxysmal nocturnal hemoglobinuria, malaria, and mastocytosis causing hypersplenism whose incidence was 6.25% in their study.

Malaria, especially *Plasmodium Falciparum*, may cause pancytopenia as a result of hypersplenism, immune hemolysis, disseminated intravascular coagulation, hemophagocytosis, impairment of marrow function or direct marrow invasion by the parasite.^[9] 2.9% of the cases were due to malaria in this study compared to 1.93% in the study by Gayathri *et al.* and 1% in that of Khunger *et al.*

The incidence of aplastic anemia in this study was 8.8%. Tilak and Jain *et al.* revealed a comparable incidence of aplastic

Table 6: Comparison of important causes of pancytopenia

Study	Most common etiology (% of cases)	Second most common cause (% of cases)
Tilak and Jain, 1999	Megaloblastic anemia (68)	Aplastic anemia (7.7)
Khodke <i>et al.</i> , 2000	Megaloblastic anemia (44)	Aplastic anemia (14)
Khunger <i>et al.</i> , 2002	Megaloblastic anemia (72)	Aplastic anemia (29.51)
Kumar <i>et al.</i> , 2001	Aplastic anemia (29.51)	Megaloblastic anemia (22.28)
Santra and Das, 2010 ^[17]	Aplastic anemia (20)	Hypersplenism (11.7)
Subramanyam and Padma, 2015 ^[23]	Megaloblastic anemia (26.42)	Hypersplenism (24.53)
Anjana <i>et al.</i> , 2016 ^[19]	Megaloblastic anemia (50.7)	Hypersplenism (10.6)
Present study	Megaloblastic anemia (64.7)	Hypersplenism (10.2)

anemia (7.7%) in their study. However, Khodke *et al.* disclosed a much larger incidence which stood at 14%. The causes of aplastic anemia in this study were viral hepatitis, disseminated TB, and idiopathic aplastic anemia. Viral hepatitis as a cause of aplastic anemia was observed in 2 patients in this study. Jain *et al.* described one case of viral hepatitis as a cause of pancytopenia. The incidence of idiopathic aplastic anemia was identified at 4.4% whereas Jain *et al.* reported an incidence of 3.2% for idiopathic aplastic anemia.

The pathogenesis of pancytopenia in TB has intrigued both physicians and pathologists for years, the exact pathology being not known.^[10] TB constituted 2.9% of the cases in this study. Likewise, Khunger *et al.*^[6] and Kumar *et al.* described only one case of TB in their studies each, making TB one of the rare causes of pancytopenia.

In leukemia, the pathophysiology is related to a combination of suppression of the normal hematopoiesis and replacement of bone marrow by leukemic cells resulting in pancytopenia and immunosuppression.^[11] We encountered 3 cases of AML (4.4%), 2 cases of ALL (2.9%), and 1 case of CML (1.4%), totaling 8.8%. Only 3.4% of the cases had subleukemic leukemia in a study by Para *et al.*, however, Graham *et al.*, reported a much higher incidence of AML (13.3%) and 3.3% was that of ALL.

Present study divulged idiopathic thrombocytopenic purpura (ITP) as a cause of pancytopenia in 3 cases (4.4%). In a study by Rajesh Para *et al.*,^[21] 1.7% of the patients had ITP, and its incidence was observed at 10.5% in the study by Pudasaini *et al.*^[20]

One case of non-Hodgkin's lymphoma was encountered in this study (1.4%). Non-Hodgkin lymphoma (NHL) is known to infiltrate bone marrow more commonly than Hodgkin's and thus leading to pancytopenia.^[12] Jain *et al.* found NHL to be a cause of pancytopenia in 0.8% of the cases in their study making it a less common cause of pancytopenia.

Patients with multiple myeloma develop pancytopenia due to the replacement of bone marrow by immunoproliferative

cells.^[13] Multiple myeloma was diagnosed in a single case (1.4% of the cases) in this study. In a similar way, Tilak and Jain *et al.* disclosed a single case of multiple myeloma as a cause of pancytopenia. 3.5% of the patients showed pancytopenia in the study by Pudasaini *et al.*

CONCLUSION

Pancytopenia is a very important hematological problem and should be kept in mind when diagnosing a patient with unexplained fever, generalized weakness, and fatigue. There are numerous causes most frequent of which is B12/folate deficiency which can achieve spontaneous remission on treatment. It should be remembered that idiopathic thrombocytopenic purpura can also present with pancytopenia. The prognosis can be bad if the diagnosis of pancytopenia is missed and untreated and hence all the causes of pancytopenia, even those uncommon, are equally important. Detailed clinical history and physical examination along with hematological investigations and bone marrow aspiration biopsy are needed to evaluate and assess the cause of pancytopenia. Identification of correct cause will help in implementing appropriate therapy. This study has helped us to identify the incidence of different causes of pancytopenia in a tertiary hospital in South India.

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