



An observational study on the common causes leading to pancytopenia in patients presenting to tertiary care hospital in south India

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Abstract

Background & Objective: Pancytopenia is a striking feature of many serious and life threatening illnesses and may be caused by several disorders ranging from simple drug-induced bone marrow hypoplasia and megaloblastic anemia to fatal aplastic anemia and leukemia's. The present observational study was conducted to find out the causes leading to pancytopenia, their distribution among the study cohort and their clinico-pathologic features. The primary outcome was to analyze the clinico-haematological parameters including bone marrow aspiration and finding out the common disease entities leading to pancytopenia.

Methods: A hospital based prospective observational study was undertaken among the adult patients diagnosed/presented with Pancytopenia at SDM College of Medical Sciences & Hospital, Dharwad, Karnataka, India. A detailed meticulous physical examination as well as history of recent viral infections, fever, and weight loss, bleeding from various sites (gums, nose, mouth and vagina) were noted. And laboratory analysis, Peripheral blood smear examination, Bone marrow aspiration were recommended.

Results: Out of total 105 patients, about 51.4% of the study subjects were males while remaining 48.6% were females. Our maximum study population were > 60 years (42.9%) with mean age 72.3 ± 7.7 years, followed by patients between 50 – 59 years (20%) with mean age 54.1 ± 2.5 years. Megaloblastic anemia (36.2%) was found to be the commonest cause of pancytopenia whereas aplastic anemia (26.7%) was the second most common etiology. 6.7% of the total cases were diagnosed as MDS while Acute Promyelocytic Leukemia was recorded in 9.5%. Five cases of Acute Lymphocytic Leukemia were also recorded with marked hypercellular bone marrow.

Conclusion: The present study concludes that detailed primary investigations of hematological parameters along with bone marrow aspiration in cytopenic patients are helpful for understanding the underlying etiology; to diagnose, or to rule out the causes of cytopenia; and in planning further investigations and management of such patients. Megaloblastic anemia followed by Aplastic anemia still remains the major etiology related to pancytopenia as far as Indian setting is concerned.

Keywords: pancytopenia; bone marrow biopsy; megaloblastic anemia; bone marrow aspiration; aplastic anemia

Introduction

Pancytopenia is regarded as an important clinico-hematological entity encountered in day-to-day clinical practice. It is not a disease entity but a triad of findings as it involves all three major formed elements of blood i.e. red blood cells, white blood cells and platelets are decreased in number^[1]. It may result from a number of disease processes – primarily or secondarily involving the bone marrow. Amongst the investigations, the examination of blood and bone marrow play a vital role in the establishment of diagnosis. In understanding the pathogenesis behind pancytopenia in a particular case, routine hematological investigations help in great aspects as well as detailed etiology can be verified with the help of bone marrow aspiration and biopsy. Studies from North and South India have implicated megaloblastic anemia as the most common cause of pancytopenia, whereas a study conducted in Maharashtra has found hypersplenism and infections to be the most frequently responsible diseases^[2, 3]. Aplastic anemia and erythroid hyperplasia were found to be the most common cause of pancytopenia in a study was undertaken in Nepal^[4]. Aplastic anemia followed by infections such as

malaria and leishmaniasis were the major causes of pancytopenia reported from Bangladesh^[5]. In contrast, neoplastic diseases and radiation have been reported as the most common cause of pancytopenia, in Europe and Israel^[6]. In India, the causes of pancytopenia are not well defined, so the present study has been undertaken to diagnose the patients with pancytopenia by analyzing the clinico-haematological parameters including bone marrow aspiration and finding out the common disease entities responsible for it. Thereby, this data would help in planning the diagnostic and therapeutic approach in patients with pancytopenia.

Methods

A hospital based prospective observational study was undertaken among the adult patients diagnosed/presented with Pancytopenia at SDM College of Medical Sciences & Hospital, Dharwad, Karnataka, India. The study included patients presented/referred to Department of General Medicine in the hospital; fulfilling the below mentioned inclusion and exclusion criteria. This study comprised of 105 patients and was conducted from October 2018 to

March 2020 after taking ethical clearance from committee.

Inclusion Criteria

Patients with age ≥18 years of either sex with pancytopenia.

Exclusion Criteria

1. Chemotherapy and radiation induced pancytopenia cases.
2. Patients already treated at other centres and referred to our centre for further management with no details available at the time of first presentation.
3. Patient who did not gave valid consent or refused to be a part of the study.

History of recent viral infections, fever, and weight loss, bleeding from various sites (gums, nose, mouth and vagina) were noted. A detailed meticulous physical examination of every patient was done for pallor, icterus, pedal oedema, mouth ulcers, hepatosplenomegaly, lymphadenopathy, sternal tenderness and gum hypertrophy was also done. Evidence of hypersplenism and primary malignancy was searched for wherever necessary.

The laboratory analysis includes Complete Blood Count (CBC) with absolute values which were conducted on an automated blood analyzer. All hematological parameters were obtained. Values of hemoglobin, red blood cell count, total leucocyte count, differential leucocyte count, platelet count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration, Packed Cell Volume (PCV) and reticulocyte count were noted and analyzed. Bone marrow aspiration studies along with trephine biopsy were done where ever indicated from anterior superior iliac spine using standard methods and under all aseptic precautions. All the patients thus selected were investigated in a systematic manner and cause of pancytopenia was ascertained. The data were recorded, tabulated and analyzed on the basis of etiology, clinical and haematological findings. Clinico-pathological evaluation was done in all cases before reaching a definitive diagnosis. The outcome data was descriptively analysed. The collected data variables obtained was compiled by using an excel spreadsheet. The patient characteristics are presented as frequencies for the categorical variables and as the means and standard deviations. All care and caution were exercised while utilizing the patient data for current research as outlined in the hospital guidelines pertaining to the usage of patient’s data for this study and confidentiality was maintained throughout. Informed consent process was initiated prior to the individual agreeing to participate in the study and continuing throughout the individual’s study participation.

Observations

Out of total 105 patients, about 51.4% of the study subjects were males with mean age 51.8 ± 19.4 years and 48.6% were females with mean age 56.2 ± 19.4 years. THE maximum study population were > 60 years (42.9%) with

mean age 72.3 ± 7.7 years, followed by patients between 50 – 59 years (20%) with mean age 54.1 ± 2.5 years and 18 – 29 years (17.1%) with mean age 23.0 ± 3.7 years. Small numbers of cases were also observed in age group 40 – 49 years and 30 – 39 years with 11.4% and 8.6% respectively. Total mean age of entire study population was 53.9 ± 19.4 years. Most reported symptom was easy fatigability, which was present in 72 (68.6%) patients followed by breathlessness (43.8%). Fever was presenting feature in 30 (28.5%) patients while palpitation was reported by 18.1% patients. Bleeding manifestation in one form or other was reported in 14.2% patients. On examination, pallor was the commonest sign present in all the cases followed by splenomegaly (33.3%), hepatomegaly (28.5%), raised JVP (22.9%), edema (21.9%), icterus (18.1%). While small number of findings that were recorded were purpura (4.8%), clubbing (3.8%) and lymphadenopathy (2.9%). The Hemoglobin level in our study ranges from 3.0 gm/dl to 10.4 gm/dl. In this study, 1.9% (n=2) patients were mild anemic, 33.4% (n=34) patients were moderate anemic and 65.7% (n=69) patients were severely anemic. The leucocyte counts in our study ranges from 130/cmm to 3480/cmm. Out of them 12.4% (n=13) patients had leucocyte counts between >3000 to <4000/cmm and 79.1% (n=83) patients had leucocyte counts between <1000 to <3000/cmm, and 8.5% (n=9) patients had leucocyte counts below 1000/cmm. In this study, the platelet count ranges from 4000/cmm to 1, 47, 000/cmm. Maximum number of patients (60%) had platelet count range between 50,000/cmm to 1, 40, 000/cmm. 25.7% (n=27) patients had moderate thrombocytopenia and their platelet count were between >20,000/cmm to <50,000/cmm. Only 14.3% (n=15) patients in our study were severely thrombocytopenic and had platelet count were less than 20,000/ cmm. In our series, 36.2% of cases of pancytopenia were found to be due to megaloblastic anaemia and 26.7% had aplastic anaemia. Myelodysplastic syndrome was diagnosed in seven cases (6.7%) while Myelofibrosis in five cases (4.8%). Acute Lymphocytic Leukemia and Acute Promyelocytic Leukemia were diagnosed in 4.7% & 9.5% respectively. Burkitt – ALL & Trilineage Hematopoiesis were diagnosed in 2.9% cases each. Single cases were recorded for Metastatic bone marrow disease as well as Chronic Myeloid Leukemia.

Table 1: Baseline characteristics with their respective frequency distribution.

Variables	Patient (n)	Percentage (%)	Mean Age ± SD
Gender			
Male	54	51.4	51.8 ± 19.4
Female	51	48.6	56.2 ± 19.2
Age (years)			
18 - 29 Yrs	18	17.1	23.0 ± 3.7
30 – 39 Yrs	9	8.6	36.2 ± 1.9
40 – 49 Yrs	12	11.4	44.6 ± 2.2
50 – 59 Yrs	21	20.0	54.1 ± 2.5
≥ 60 Yrs	45	42.9	72.3 ± 7.7

Table 2: Clinical characteristics with their respective frequency distribution

Variables	Patient (n)	Percentage (%)
Signs and Symptoms		
Breathlessness	46	43.8
Palpitation	19	18.1
Easy Fatigability	72	68.6
Fever	30	28.5

Epistaxis	3	2.8
Gum Bleeding	2	1.9
Menorrhagia	3	2.8
Hematuria	7	6.7
Physical findings		
Pallor	105	100
Icterus	19	18.1
Clubbing	4	3.8
Edema	23	21.9
Lymphadenopathy	3	2.9
Hepatomegaly	30	28.5
Splenomegaly	35	33.3
Purpura	5	4.8
Raised JVP	24	22.9
Diagnosis		
Acute Lymphocytic Leukemia	5	4.7
Acute Promyelocytic Leukemia	10	9.5
Aplastic anemia	28	26.7
Burkitt - ALL	3	2.9
Chronic Lymphocytic Leukemia	2	1.9
Chronic Myeloid Leukemia	1	0.9
Megaloblastic Anemia	38	36.2
Myelodysplastic Syndrome	7	6.7
Metastatic bone marrow disease	1	0.9
Myelofibrosis	5	4.8
Sepsis induced bone marrow suppression	2	1.9
Trilineage Hematopoiesis	3	2.9

Table 3: Comparison of hematological parameters among leading causes of pancytopenia.

Diagnosis	Hemoglobin (gm %)	TLC (cells/mm ³)	Platelets (lakh/mm ³)
Acute Lymphocytic Leukemia	7.3 ± 2.2	1661.8 ± 1398.7	0.40 ± 0.20
Acute Promyelocytic Leukemia	6.5 ± 1.9	1808.4 ± 931.5	0.70 ± 0.37
Aplastic anemia	6.9 ± 1.8	1975.1 ± 887.9	0.54 ± 0.43
Megaloblastic Anemia	7.1 ± 1.9	2039.6 ± 671.8	0.77 ± 0.38
Myelodysplastic Syndrome	6.6 ± 1.7	1974 ± 745.9	0.73 ± 0.47
Myelofibrosis	7.0 ± 1.7	2065 ± 891.9	0.75 ± 0.46

Discussion

To identify the root cause or the etiology, thorough physical examination with meticulous history, hematological investigations, extensive use of investigative procedures, and constant reevaluation of the clinical evidence remains the base of any disease entity. However in India, the causes of pancytopenia are not well defined and there is a paucity of data in this regard. This data, if available, would help in planning the diagnostic and therapeutic approach in patients with pancytopenia as well as it will also guide the physician in monitoring the patients, ordering timely tests (eg. blood culture and peripheral smears at height of fever), and ruling out factitious etiologies. A total of 105 cases of pancytopenia were studied. Age, gender-wise incidence, presenting complaints, peripheral blood picture, bone

marrow aspiration smears and various causes of pancytopenia were studied in all cases, and observations were compared with those in studies published in the literature. Variations in the frequency of various underlying entities of pancytopenia have been attributed to difference in methodology and stringency of diagnostic criteria, geographic area, period of observation, genetic differences, etc. The age of the patients ranged from 18 to 88 years, with a mean age of 53.9 ± 19.4 years. Cytopenias were observed more in males (51.4%) than females (48.6%), with male-to-female (M: F) ratio of 1.1:1. Age and sex distribution was compared with other studies as shown in Table 4. Our maximum study population were > 60 years (42.9%) with mean age 72.3 ± 7.7 years, followed by patients between 50 – 59 years (20%) with mean age 54.1 ± 2.5 years.

Table 4: Age and sex comparison with the other studies of pancytopenia

Author	Year of study	No. of cases	Age range	M:F ratio
Khunger JM <i>et al.</i> [2]	2002	200	2 – 70	1.2:1
Kumar R <i>et al.</i> [7]	2001	166	12 - 73	2.1:1
Gayathri and Rao, <i>et al.</i> [8]	2011	104	2 – 80	1.2:1
Tilak V <i>et al.</i> [9]	1999	77	5 – 70	1.14:1
Khodke K <i>et al.</i> [10]	2001	50	3 – 69	1.3:1
Present study	2020	105	18 – 88	1.1:1

The most common presenting complaint in our study was easy fatigability (68.6%), followed by difficulty in breathing (43.8%), fever seen in 28.5% of the cases, palpitation in 18.1% cases and bleeding manifestations in 14.2% cases.

On examination, pallor was the commonest sign present in all the cases followed by splenomegaly (33.3%), hepatomegaly (28.5%), raised JVP (22.9%), pedal edema (21.9%), icterus (18.1%). Small number of cases also

reported with lymphadenopathy (2.9%), clubbing (3.8%) and purpura (4.8%). The presenting symptoms were usually attributed to anemia or thrombocytopenia. Leucopenia was an uncommon cause of the initial presentation of the patient but can become the most serious threat to life during the course of the disorder. In a study done by Khodake *et al.*, fever (40%), was most common presenting symptom followed by weakness (30%), and bleeding manifestation in 20% cases studied [10]. Yadav *et al.* found in their study

generalized weakness and easy fatigability as most common presenting complaints [11]. In a study by Santra G, Das BK most common presenting complaints was weakness (68.2%), followed by fever in 47.7% of cases and bleeding manifestation was presenting complaints in 33.7% of cases.¹² The frequencies of other clinical features were variable and different from these studies probably due to broad spectrum of etiologies behind pancytopenia.

Table 5: Comparison of common presentation & physical findings with other Indian studies of pancytopenia.

Study	M: F ratio	Most common presentation	Physical findings
Khodke K <i>et al.</i> [10] (n=50)	1.3:1	Fever (40%), Weakness (30%)	Pallor (100%), Splenomegaly (40%), Hepatomegaly (38%)
Tilak and Jain <i>et al.</i> [9] (n=77)	1.14:1	---	Pallor (100%), Splenomegaly (49.3%), Hepatomegaly (41.5%)
Alam <i>et al.</i> [13] (n=50)	1.08:1	Fever (72%), Weakness (38%), Increasing paleness (32%)	Pallor (100%), Splenomegaly (28%), Hepatomegaly (20%)
Present study (n=105)	1.1:1	Fever (28.5%), Breathlessness (43.8%), Fatigability (68.6%)	Pallor (100%), Splenomegaly (33.3%), Hepatomegaly (28.5%)

After analysing our data, we feel that the presenting symptoms in pancytopenia patients are usually attributable to anemia or thrombocytopenia. Haematological parameters revealed, as expected, a depression in all the cell counts. On comparing the haematological parameters among leading causes of pancytopenia, anemia appeared to be more severe in cases of Acute Promyelocytic Leukemia, Myelodysplastic Syndrome, Aplastic anemia and Megaloblastic Anemia. Leukocyte count was most severely depressed in cases of patients of Acute Lymphocytic Leukemia, Aplastic Anemia, Myelodysplastic Syndrome and Megaloblastic Anemia. Similarly, platelet count, although it showed wide variation, it was most severely depressed in patients of Acute Lymphocytic Leukemia and Aplastic anemia (Refer table 3).

Megaloblastic anemia is a group of disorder characterized by defective nuclear maturation caused by impaired DNA synthesis. This was the most common cause of pancytopenia in the present study that was observed in 36.2% of the total cases. This was similar in the study by Bijaya *et al.* which accounted 44% of the cases of Megaloblastic anaemia [14]. Also, incidence of 72% was reported by Khunger JM *et al.*; and 68% by Tilak V *et al.* [9, 10]. Many studies in the past especially from Indian subcontinent have shown megaloblastic anemia to be a common cause of pancytopenia in this region. Prevalence of megaloblastic anaemia was as high as 74% reported by Gayathri in 2011 [8]. Kumar *et al.* and Jalbani *et al.* study in 2009 documented aplastic anaemia as the commonest cause in their series which is in contrast to our series [7, 15]. In this study, 31.6% cases of megaloblastic anemia, presented with splenomegaly and hepatomegaly each. Erythroid hyperplasias with predominance of precursors were also noted in the bone marrow aspiration of the megaloblastic anemia. Bone marrow was hypercellular with megaloblastic erythropoiesis and giant metamyelocytes. Ishtiaq *et al.* in their study found 15.4% and 17.9% of megaloblastic anemia with splenomegaly and hepatomegaly respectively [1]. Sweta *et al.* reported 29% case and 11% cases of megaloblastic anemia, presented with splenomegaly and hepatomegaly.¹⁶ Likewise, hepatomegaly (66%) and splenomegaly (21%) were seen in the study done by Gomber *et al.* in patients with megaloblastic anemia [17].

Megaloblastic anaemia was found to be the commonest cause of pancytopenia in most of the studies whereas aplastic anemia is the second most common etiology. Same scenario was also encountered in the present study as aplastic anemia was the second most common etiology with 26.7% of the total cases diagnosed with it. There was slightly female preponderance with male to female ratio of 0.87:1. Majority of patients had hypoblastic bone marrow while some showed decreased trilineage hematopoiesis.

In the present study, 6.7% (n=7) of the total case were diagnosed as MDS. Three cases were diagnosed as refractory cytopenia with multilineage dysplasia. Bone marrow aspiration showed hypercellular in all the three cell lines. While lone case of Myelodysplastic Syndrome RAEB 2 was also diagnosed showing hypercellular with few hypocellular fragments in bone marrow aspiration. The incidence of MDS as reported in other similar studies varies from 0 to 18%. Khunger *et al.* reported 2% of MDS causing pancytopenia while Santra G *et al.* with 2.7% cases in 111 adult pancytopenia patients [2, 12]. Jain A *et al.* just reported 0.4% case of pancytopenia due to MDS of RAEB type.¹⁸ However, Bijaya *et al.* reported 8% MDS of the total cases [14]. MDS are most common in the elderly as also observed in the current study with mean age of 63.1 years in this diagnosed group.

In the present study, Leukemia constituted about 20% of the total subjects which was comparatively higher to the study done by Savage DG *et al.* recorded eleven cases (8.2%) of AL from the 134 patients with pancytopenia [19]. Further differentiating the type of leukemia in the current study, Acute Promyelocytic Leukemia was recorded in 9.5% (n=10) of the total subjects whose peripheral blood showed atypical mononuclear cells and bone marrow showed an increase in atypical promyelocytes and decreased trilineage hematopoiesis. Three cases of Burkitt – ALL were also recorded who had cellular bone marrow with decreased to absent trilineage hematopoiesis. “Starry Sky” appearance was also evident in the results. Further, two cases of sepsis induced bone marrow suppression was also encountered that showed reactive bone marrow with presence of granulomas. Five cases of Acute Lymphocytic Leukemia were also recorded with marked hypercellular bone marrow. Biopsies results of two subjects showed the extensive necrosis of

bone marrow as well in these cases. 4.8% of the cases were diagnosed of Myelofibrosis with hypercellular bone marrow. Even this disease is of older adults (mean age 60 years) and mean age of this diagnosed group in this study was 60.4 years. Splenomegaly which is often considered a hallmark of this disorder was present in all five cases of myelofibrosis. Constitutional symptoms such as fatigue, dyspnea and low grade fever was consistent in this group. All the patients of pancytopenia in our study made complete hematological and clinical recovery after appropriate treatment. As with the majority of studies, the design of the current study is also subject to limitations, and findings of this study have to be seen in light of some of the factors.

- This is a hospital based small study of a short duration. A prospective study with large sample size and follow up evaluation would have helped to evaluate the various causes better.
- Specifically, in this research, we accepted only data from adults aged 18 or older. Therefore, our results may not be applicable to children or adolescents.
- We also did not correlate its occurrence with diet and socioeconomic profile.

Conclusion

Pancytopenia is not an uncommon hematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient present with unexplained anemia. The present study concludes that detailed primary investigations of hematological parameters along with bone marrow aspiration in cytopenic patients are helpful for understanding the underlying etiology; to diagnose, or to rule out the causes of cytopenia; and in planning further investigations and management of such patients. Megaloblastic anemia followed by Aplastic anemia still remains the major etiology related to pancytopenia as far as Indian setting is concerned as same statistics were also observed in the current study. Accurate diagnoses and timely intervention still remains the cornerstone to manage the pancytopenia patients.

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