

## Original Research Article

# A prospective clinico-hematological study in 100 cases of Pancytopenia in a tertiary care teaching hospital

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**Received:** 18 April 2019

**Accepted:** 30 May 2019

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### ABSTRACT

**Background:** Pancytopenia is encountered regularly in haematology practice, yet there exist only few published assessments of the frequencies of various aetiologies and this exhibit substantial geographic variation. Pancytopenia is a manifestation of many life-threatening diseases with a wide range of differential diagnosis. Haematological investigation forms the bedrock in the detection and management of patients with pancytopenia.

**Methods:** This study is a prospective study conducted in the Institute of pathology and haematology, Madras medical college and Rajiv Gandhi Government General Hospital, Chennai during the period from August 2015 to August 2016 on 100 cases. Case selection is based on clinical features and supported by laboratory evidence. Peripheral smear was obtained and stained by Leishman stain for all cases and examined in detail. Bone marrow aspiration /biopsy was subsequently carried out under aseptic precautions.

**Results:** Among the 100 cases studied, age of the patients ranged from 13 to 80 years with a slight male predominance. Most of the patients presented with generalized weakness and fever. The commonest cause for pancytopenia was aplastic anaemia followed by megaloblastic anaemia. The other causes include acute myeloid leukaemia, myelodysplastic syndrome, myelofibrosis, multiple myeloma, malarial parasite, miliary tuberculosis and osteopetrosis.

**Conclusions:** Pancytopenia can be diagnosed, and its etiological profile can be ascertained with the help of detailed clinical history, meticulous physical examination and haematological investigations. Every attempt should be done to establish the underlying cause so that treatable conditions are diagnosed without delay and prognosis is improved.

**Keywords:** Aplastic anaemia, Megaloblastic anaemia, Pancytopenia

### INTRODUCTION

Pancytopenia is a condition in which there is decrease in the number of red blood cells, white blood cells, and platelets. The word pancytopenia was coined in 1940 and has the literal meaning as, pan -all; cyte – cell, penia - poverty, lack. Pancytopenia exhibits varying trends in its clinical pattern, haematological change, treatment modalities and outcome. It should be suspected clinically when a patient presents with pallor, prolonged fever and a tendency to bleed.<sup>1</sup> It is not a disease but a triad of

findings that may result from various disease processes which primarily or secondarily involves the bone marrow. The workup of new-onset pancytopenia is extensive and should include a detailed clinical history and haematological investigations.<sup>2</sup> Bone marrow examination although reveals an underlying pathology causing pancytopenia, is not always conclusive.

This study was carried out with the aim to obtain detailed clinical and haematological spectrum of the common disorders producing pancytopenia its causes and

diagnostic approaches and thereby enhance the management process.

**METHODS**

This study is a prospective study conducted in the Institute of Pathology and Haematology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India during the period from August 2015 to August 2016. Patients of all age groups and both sexes are included. Case selection is based on clinical features and supported by laboratory evidence, which included peripheral blood counts for haemoglobin, leukocytes and platelets. A total of 100 cases were selected based on the following criteria.

**Inclusion criteria**

Presence of all 3 of the following:

- Haemoglobin, <9 g/dL
- Total leukocyte count (TLC), <4,000 / μL
- Platelet count, <100,000/ μL.<sup>3</sup>

**Exclusion criteria**

- Patients on myelotoxic chemotherapy were excluded.

In all patients, a complete relevant medical history including age, sex, history of any treatment, intake of or exposure to potentially toxic chemicals, agents or drugs, radiation exposure, history of symptoms such as bone pain, fever, malaise, weight loss etc. was obtained. A detailed meticulous physical examination of every patient was done for pallor, jaundice, hepatosplenomegaly, lymphadenopathy, sternal tenderness and gum hypertrophy.

Two millilitres of EDTA (ethylene diamine tetra-acetic acid) anticoagulated blood was collected and processed through automated haematology analyser. Peripheral smear was obtained and stained by Leishman stain for all cases and examined in detail. Bone marrow aspiration /biopsy was subsequently carried out under aseptic precautions after obtaining written consent.

The statistical analysis was performed using statistical package for IBM SPSS version 20 which consisted computing the frequency counts and percentages for qualitative variables and mean for the quantitative variables

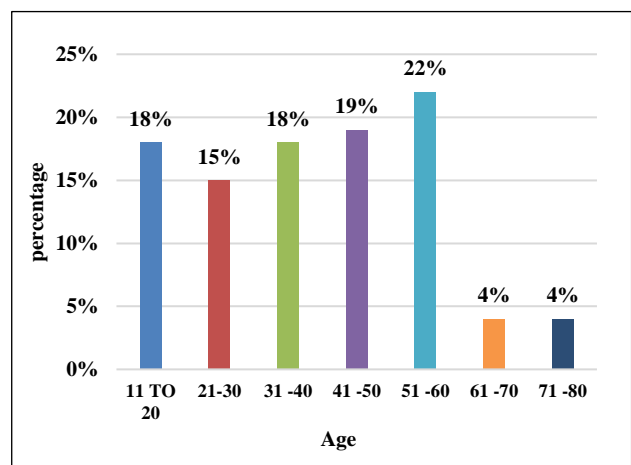
**RESULTS**

In the study period from August 2015 to August 2016, a total of 1,47,661 samples were received for complete blood count. Among these, 100 successive patients who met the inclusion and exclusion criteria were selected and subjected for the study to evaluate etiological profile of

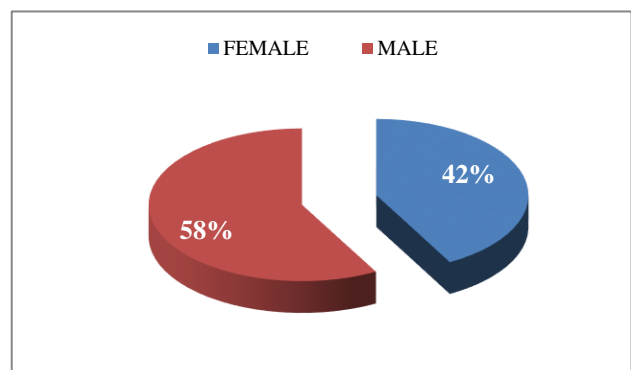
pancytopenia. The clinical and haematological examination, including bone marrow examination were done.

**Age distribution**

In this study there was a wide age range with the youngest patient being 13 years of age and the maximum being 80 years of age. The peak incidence was found in the age group of 51-60 years contributing to 22 % of cases. The least incidence was recorded in the age group of 61-80 years contributing to 8 % of cases in the one year study period (Figure 1). Among the total 100 cases of pancytopenia there were 42 female patients and 58 male patients and the male to female ratio was 1.38:1 (Figure 2).



**Figure 1: Age wise distribution of Pancytopenia.**

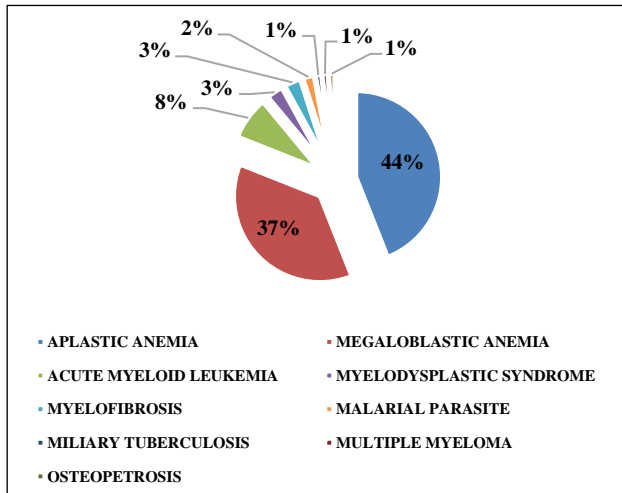


**Figure 2: Gender wise distribution of Pancytopenia.**

**Distribution of causes of Pancytopenia**

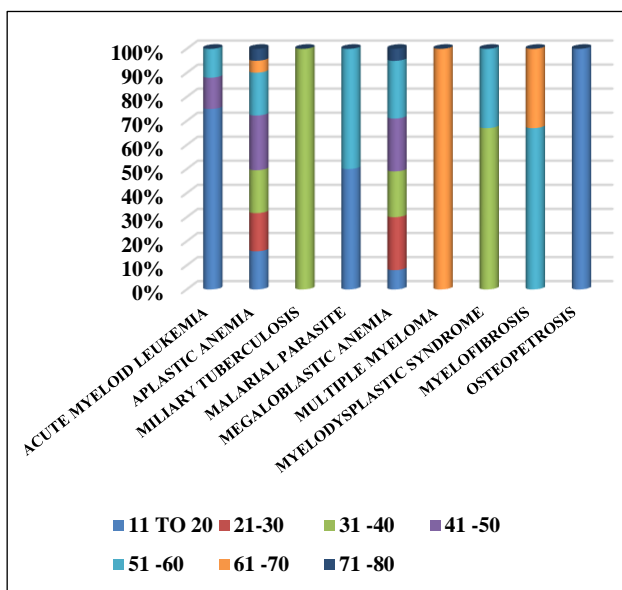
In this study the most common cause of pancytopenia was aplastic anaemia seen in 44 % of cases. The second most common cause was megaloblastic anaemia which was observed in 37% of cases. This was followed by acute myeloid Leukaemia seen in 8% of cases, myelodysplastic syndrome, myelofibrosis each contributing to 3% of cases, malarial parasite in 2%,

miliary tuberculosis, multiple myeloma and osteopetrosis each contributing to 1% of cases (Figure 3).



**Figure 3: Distribution of causes of Pancytopenia.**

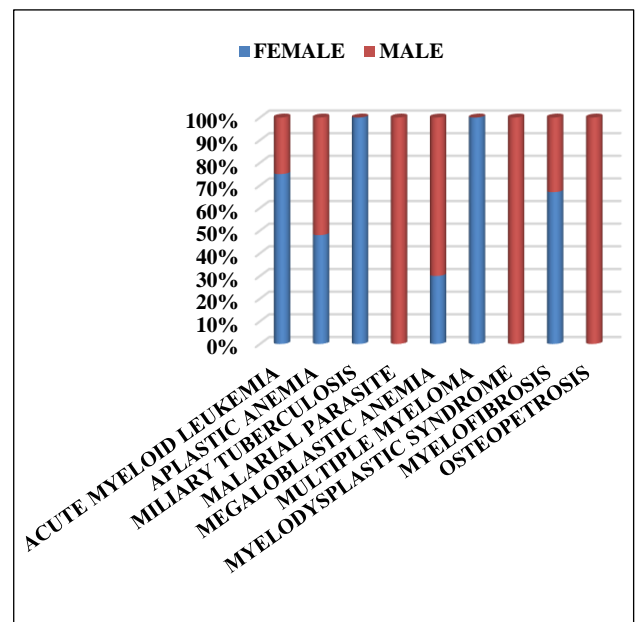
The incidence of pancytopenia showed peak incidence in the age group of 51-60 years. Of the total 44 cases of aplastic anaemia peak incidence was seen in the age group of 41-50 years, accounting 22.7% of cases likewise in megaloblastic anaemia the peak incidence was seen in the age group of 51-60 years, which accounts 24.3% of cases. Out of the 8 cases of acute myeloid leukaemia the peak incidence was seen in 11-20 years contributing to 75 % of cases, in myelodysplastic syndrome out of 3 cases 2 were seen in the age group of 31-40 years accounting 66.7% of cases. Out of 3 cases of myelofibrosis, 2 cases occurred in the age group of 51-60 years, accounting for 66.7% of cases. One case of osteopetrosis and one case of miliary tuberculosis were seen in the age group of 11-20 years and 31-40 years of age respectively (Figure 4).



**Figure 4: Age distribution of various causes of Pancytopenia.**

The incidence of pancytopenia showed preponderance among males. The male to female ratio was 1.38:1. Of the total 44 cases of aplastic anaemia, 23 (52.3%) were males and 21 (47.7%) were females, likewise in megaloblastic anaemia, among the total 37 cases, 26 (70.3%) were males and 11 (29.7%) were females.

Out of the 8 cases of acute myeloid Leukaemia, 6 (75%) were females and 2 (25%) were males, in myelodysplastic syndrome all the 3 (100%) cases were seen among males, in myelofibrosis among 3 cases 2 (66.7%) were females and 1 (33.3%) was male, in malarial parasitic infection both the cases 2 (100%) were males, in multiple myeloma and miliary tuberculosis each of which contributed one case (100%) were seen in females only. Similarly, the one case of osteopetrosis was male (Figure 5).

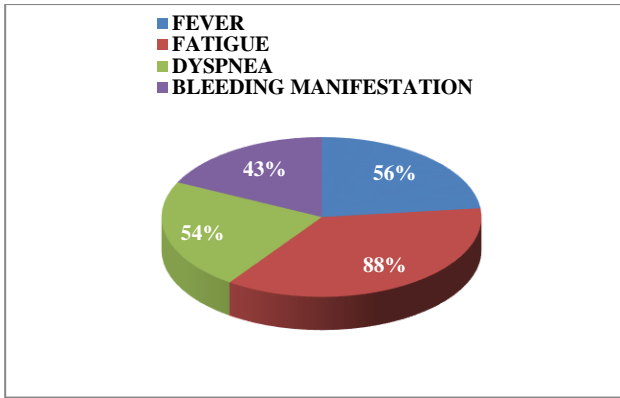


**Figure 5: Sex distribution of various causes of Pancytopenia.**

**Clinical features**

Fatigue was the most common clinical feature which constituted 88% followed by fever in 56% of cases, dyspnoea in 54% and bleeding manifestations in 43% of cases (Figure 6). Other less common presenting symptoms were headache, vomiting, low back ache, pedal oedema, facial puffiness, blurring of vision, loss of appetite, loss of weight.

Most common physical finding observed was pallor. Pallor was present in all the cases. The other physical finding includes hepatomegaly, splenomegaly, lymphadenopathy and sternal tenderness. Sternal tenderness was observed in all patients with acute myeloid leukaemia and multiple myeloma.

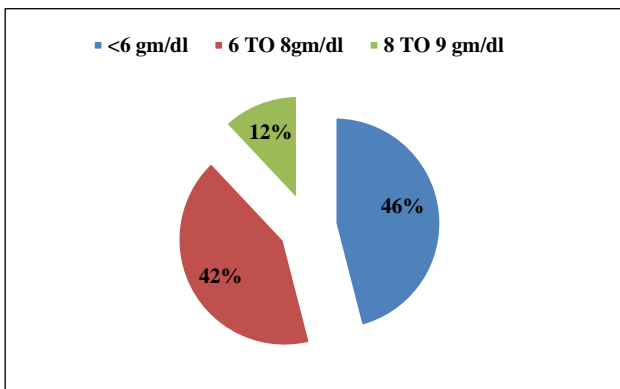


**Figure 6: Clinical features in various causes of Pancytopenia.**

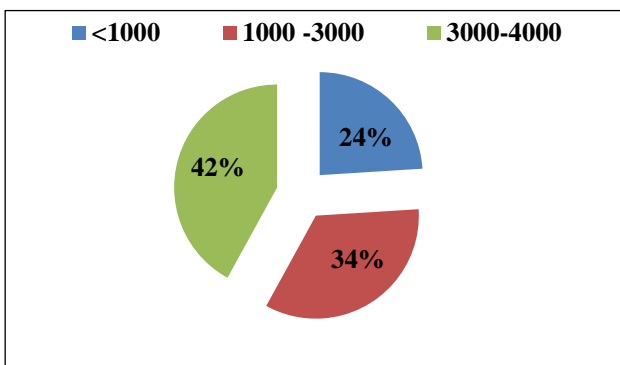
**Peripheral blood findings**

**Haemoglobin distribution**

Among the 100 cases of pancytopenia analysed maximum cases had haemoglobin concentration less than 6 gm/dl. This was seen in 46% of cases which formed the major group of patients. In 42% of the cases it was between 6 and 8 g/dl, 12% of the cases had haemoglobin between 8 and 9 g/dl, which formed the least group of patients (Figure 7).



**Figure 7: Hemoglobin distribution (gm/dl).**



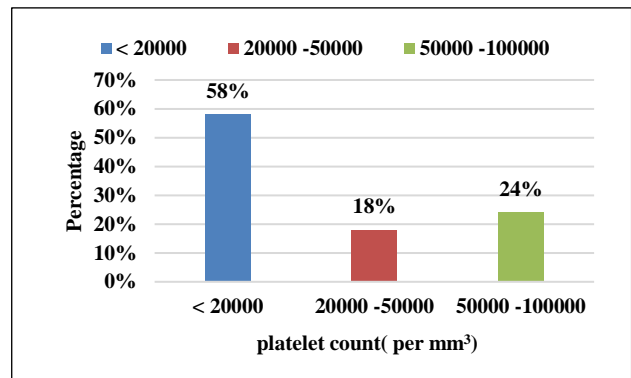
**Figure 8: Distribution of total WBC count-per mm<sup>3</sup>.**

**Total leukocyte count**

Total leukocyte count was between 3000 and 4000/mm<sup>3</sup> in 42% of cases. In 34 % of the cases, the leukocyte count was between 1000 and 3000/mm<sup>3</sup>. In 24% of the cases it was <1000/mm<sup>3</sup> (Figure 8).

**Platelet count**

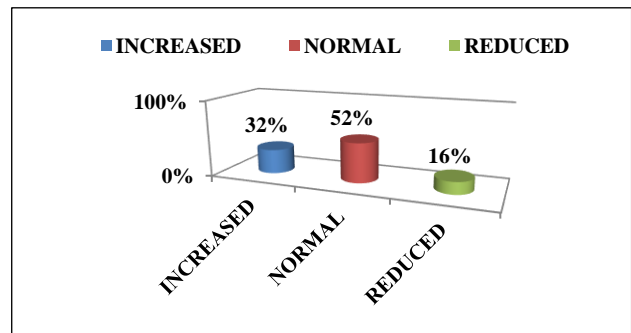
The platelet count was less than 20000/mm<sup>3</sup> in 58% of cases. In 24% of cases the platelet count was between 50000 and 100000/mm<sup>3</sup>. In 18% of the cases it was between 20000/mm<sup>3</sup> to 50000/mm<sup>3</sup> (Figure 9).



**Figure 9: Distribution of platelet count (per mm<sup>3</sup>).**

**Mean corpuscular volume (MCV)**

Among the total cases of pancytopenia, the mean corpuscular volume (mcv) was increased in 32% and the most common cause was megaloblastic anaemia. It was decreased in 16 % of cases and was found to be within the normal range in 52 % of the cases (Figure 10).



**Figure 10: Distribution of mean corpuscular volume (MCV).**

**Reticulocyte count**

The reticulocyte count was within normal range in 7 % of the cases of pancytopenia. 91 % of the cases showed a decreased reticulocyte count. An increased count was seen in 2 % of cases and these were those cases with malaria (Figure 11).

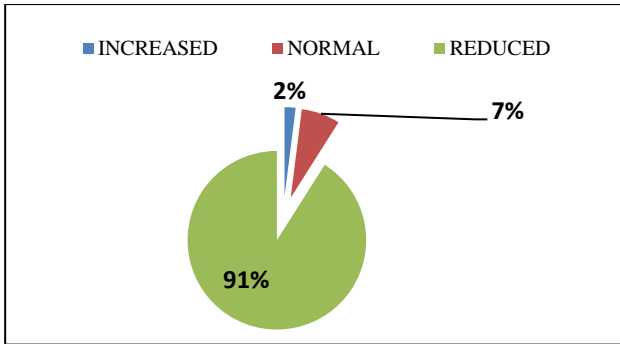


Figure 11: Distribution of reticulocyte count.

Peripheral smear findings

The predominant blood picture was normocytic anaemia which constituted 46 % of cases, followed by macrocytic anaemia seen in 32 %. Dimorphic picture was seen in 14 % of cases. Microcytic blood picture was seen in 8% of cases (Figure 12).

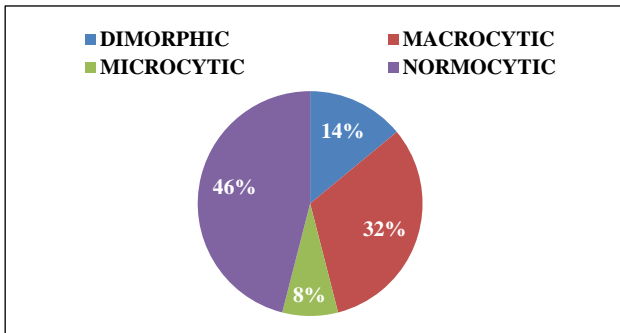


Figure 12: Morphological pattern of red blood cells in peripheral smear.

Table 1: Peripheral smear findings in Pancytopenia.

Causes	Total cases	A	B	C	D	E	F
Aplastic anemia	44	-	-	-	40	-	-
Megaloblastic anemia	37	37	-	-	11	-	-
Acute myeloid leukemia	8	-	3	8	-	-	-
Myelodysplastic syndrome	3	2	3	3	-	2	-
Myelofibrosis	3	-	3	3	-	3	-
Mutiple myeloma	1	-	-	-	-	-	-
Miliary tuberculosis	1	-	1	1	-	-	-
Malarial parasite	2	-	-	-	-	-	2
Osteopetrosis	1	-	-	-	-	-	-

A- Hypersegmented neutrophils, B- Nucleated RBCs, C- Immature WBCs, D- Relative lymphocytosis, E- Tear drop cells, F- Malarial parasites.

Hypersegmented neutrophils were seen in 39% cases and the commonest cause revealed megaloblastic anaemia followed by myelodysplastic syndrome. Nucleated red blood cells were seen in 10% and immature white blood cells observed in 13% of cases. Myeloblasts were seen in all cases of sub leukemic Leukaemia. Relative lymphocytosis was seen in 55 % patients and was seen predominantly in patients with aplastic anaemia. Tear drop cells were seen in 5% of cases of which 3% constituted myelofibrosis and 2% of myelodysplastic syndrome. Increased rouleaux formation was seen in multiple myeloma. Malarial parasites were seen in 2% of the total cases (Table 1).

Bone marrow examination

Bone marrow examination was required in 98 cases only. Two cases of malaria were diagnosed based on peripheral blood examination. Bone marrow was hypercellular in 40% cases, which included 37 cases of megaloblastic anaemia. Hypercellular marrow was also seen in acute myeloid leukaemia and multiple myeloma. Marrow was hypocellular in 55 % cases, which included 44 cases of aplastic anaemia and 3 cases of myelofibrosis and one case of osteopetrosis. Normal marrow cellularity was seen in 3% cases which is observed in myelodysplastic syndrome and miliary tuberculosis. Megaloblastic maturation, presence of myeloblasts, dysplastic features in all three lineages, abnormal plasma cells were salient diagnostic features in bone marrow examination. (figure 13).

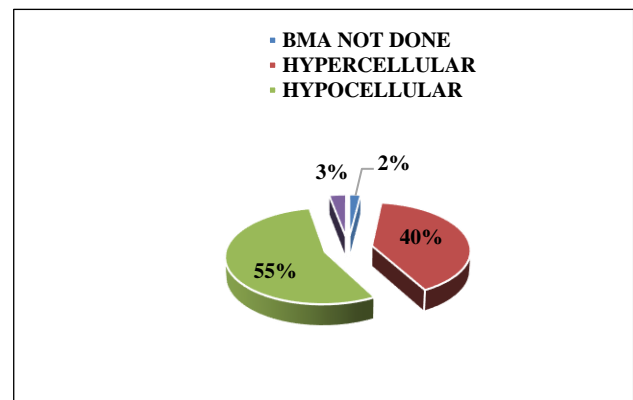


Figure 13: Bone marrow aspiration in Pancytopenia.

DISCUSSION

The present study concludes that meticulous primary haematological investigations along with thorough bone marrow examination in pancytopenia patients is of utmost importance to analyse and evaluate the different causes of pancytopenia and in understanding It is also helpful in planning further investigations to be carried out for effective and appropriate management and in understanding disease process. Though pancytopenia by itself is not a disease, it is a striking feature of many life-threatening and serious illness.

### **Comparison of age and sex distribution with other studies**

In this study, the age of patients ranged from 13-80 years with the highest incidence in 51-60 years of age group. Males (58%) had a higher incidence when compared to females (42%) with the ratio of 1.38: 1. The age range is similar to Kumar et al, and the male to female ratio is similar to that of Khodke et al.<sup>4,5</sup>

Similarly, Khodke et al, found the maximum number of pancytopenia in the age group of 12-30 years.<sup>5</sup> about 10% of the cases were above 50 years of age. Niazi and Raziq in their study found most common age group of pancytopenia was in the range from 21 to 30 years.<sup>6</sup> the present study showed that maximum number of pancytopenia in a higher age range when compared to other studies.

### **Causes of pancytopenia**

The most common aetiology of pancytopenia in the present study was aplastic anaemia which is similar with that reported by Kumar et al, Jha et al, Tariq et al, Santra and das, Qamar and Aijaz, Bajracharya et al. In their study of 166, 148, 50, 111, 150 and 10 cases respectively.<sup>4,7-11</sup> The second most common cause was megaloblastic anaemia which is similar with the studies listed above.

The current study showed that fatigue (88%) was the most common symptom followed by fever (56%). This is similar to the studies done by prashanth b gandhi et al which also showed fatigue (81%) as the most common symptom followed by fever (46%), dyspnoea (52%), bleeding manifestation (48%).<sup>12</sup>

### **Aplastic anaemia**

Among pancytopenia patients the incidence of aplastic anaemia in this study was 44% (44/100 cases) which is higher than the studies done by Khodke et al, and the Khunger et al, in which the incidence was 14%.<sup>5,13</sup> Kumar et al, reported a higher incidence viz 29.5%.<sup>4</sup>

### **Megaloblastic anaemia**

Megaloblastic anaemia constituted 37% of cases in the present study which was the second common cause of pancytopenia. The incidence is less when compared to 72% reported by Khunger et al, and 68% by Tilak et al.<sup>13,14</sup> both the studies have reported megaloblastic anaemia as the major cause of pancytopenia.

The study done by Qamar and Aijaz reported the incidence to be 36.6% which was similar to the present study.<sup>10</sup>

### **Acute myeloid leukemia**

In the present study, 8 (8%) patients with pancytopenia had acute myeloid Leukemia. Among the 8 % of cases, 7% had sub leukemic leukemia and 1% had aleukemic Leukemia. All the 8 cases were diagnosed as acute myeloid Leukemia after bone marrow examination and cytochemical staining by myeloperoxidase. In the studies done by Khodke et al, and Tilak et al, only 1.3% cases presented with subleukemic leukemia.<sup>5,14</sup> this was higher in the study conducted by Jha et al. Accounting for 21.4%.<sup>7</sup> Khunger et al. Reported 5 % of cases.<sup>13</sup> Kumar et al. Reported 1 % of cases of subleukemic leukemia.<sup>4</sup>

### **Myelodysplastic syndrome**

In the present study 3% of cases were diagnosed to have myelodysplastic syndrome. The peak age group in which myelodysplastic syndrome occurs is 51-60 years. All the three cases were seen in males. In the study done by prashanth et al the incidence was 5.97%.<sup>12</sup> it was diagnosed as multilineage dysplasia with refractory cytopenia. Bone marrow aspiration showed dysplasia in all the three cell lineages.

### **Malaria**

In the present study 2 cases of malaria were reported. One case was reported in the age of 54 years and the other in the age of 18 years. Both the cases were reported in males. Trophozoites and gametocytes of plasmodium vivax were seen in both cases. Gayathri and Rao reported an incidence of 1.9% in their study.<sup>15</sup> malaria related cytopenia was also noted in studies done by Santra and das, Cannard et al, Albaker in 2%, 2% and 1% of cases respectively.<sup>9,16,17</sup> in the above studies both plasmodium vivax and plasmodium falciparum were observed. Since the trophozoites were seen in peripheral smear bone marrow aspiration was not done.

### **Myelofibrosis**

Among the 100 cases three cases were reported as myelofibrosis. The present study had a lesser incidence when compared to the study done by Tejeswini et al, with reported incidence of myelofibrosis in 5.2% of cases.<sup>18</sup> Peripheral smear showed leucoerythroblastic blood picture with nucleated RBCs and tear drop cells. Bone marrow aspiration was diluted with peripheral blood. No marrow elements were seen. Trephine biopsy revealed the presence of dysplastic megakaryocytes which is seen clustering around the marrow sinusoids. Reticulin stain was done to demonstrate marrow fibrosis.

### **Miliary tuberculosis**

One case was reported as miliary tuberculosis causing pancytopenia. This was similar to the studies done by sweta et al. And fauzia shafi khan et al in which one percent cases in each were reported.<sup>19,20</sup> in these cases, granulomas were seen in the marrow. But this patient died despite treatment given. Studies done by Khunger et

al, and Tilak et al, have revealed that pancytopenia can be seen in miliary tuberculosis.<sup>13,14</sup> The mechanism of pancytopenia in these patients is unknown but could be due to multifactorial causes including increased histiocytic phagocytosis, hypersplenism, and bone marrow infiltration by tubercular granulomas.

### Osteopetrosis

Osteopetrosis is a rare cause of Pancytopenia. One case of osteopetrosis was reported in this study. The patient was a male and the age of the patient was 20 years. Bone marrow aspiration showed clusters of osteoblasts and biopsy showed increased thickening of the bony trabeculae with reduction in the medullary cavity. Medullary space showed increase in connective tissue. Osteopathies due to vitamin d dependent rickets had been reported in the literature but osteopetrosis as a cause of pancytopenia is not reported in the literature reviewed thus far.<sup>2</sup>

### CONCLUSION

Pancytopenia can be diagnosed, and its etiological profile can be ascertained with the help of detailed clinical history, meticulous physical examination and haematological investigations. In this study aplastic anaemia was the most common cause followed by megaloblastic anaemia. Other causes were acute myeloid leukemia, myelodysplastic syndrome, myelofibrosis, multiple myeloma, malarial parasite, miliary tuberculosis and osteopetrosis. Early diagnosis and intervention especially in conditions like megaloblastic anaemia will lead to disease remission and better quality of life.<sup>21</sup> Time and again, the investigation of choice to diagnose the aetiology of unexplained pancytopenia has been bone marrow aspiration/biopsy. Every attempt should be done to establish the underlying cause so that treatable conditions are diagnosed without delay and prognosis is improved.

### ACKNOWLEDGEMENTS

Author would like to thank all the patients, teaching and non-teaching staff of Institute of Pathology and Haematology in Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Regis DM, Padmavathi R. A prospective clinico-hematological study in 100 cases of Pancytopenia in a tertiary care teaching hospital. Int J Res Med Sci 2019;7:2610-6.