

Clinical Study of Pancytopenia

Vaidya M¹, Gupta V. A², Khandagale S.K³

¹Dr Meghna Vaidya, Associate Professor, ²Dr Vishal Anand Gupta, Assistant Professor, ³Dr Shrikrushna Khandagale, Resident, all authors are attached with Department of Medicine, Seth GS Medical College and KEM Hospital, Mumbai., India.

Address for Correspondence: Dr Meghna Vaidya, Email: meghnavaidya6@yahoo.com4

Abstract

Introduction: Pancytopenia is a common and alarming condition encountered by clinicians. We had studied the clinical presentation, laboratory investigations and various etiologies of Pancytopenia. **Material and Methods:** Study was carried out in a tertiary care centre in western India. A total of 102 patients fulfilling the criteria of pancytopenia were enrolled and studied. **Results and conclusion:** Megaloblastic anemia was commonest cause of pancytopenia. Easy fatigability and pallor were commonest symptoms and signs respectively. Maximum bleeding manifestations were seen in aplastic anemia and Myelodysplastic syndrome.

Keyword: Pancytopenia, Bone marrow, Megaloblastic anemia

Introduction

A wide spectrum of primary and secondary disorders affect the bone marrow and may manifest with pancytopenia [1]. Pancytopenia could present with normocellular, hypocellular or hypercellular marrow as seen in various conditions like infections, toxins, malignant infiltration, dysplasia, peripheral sequestration of blood cells, etc.

Pancytopenia can present with a wide spectrum of symptoms ranging from fatigue to life threatening bleeding manifestations depending on the underlying etiology and severity of pancytopenia. The study aims at describing the clinical signs and symptoms, lab investigation and etiologies in cases of pancytopenia.

Most of studies in India used following values for diagnosis of Pancytopenia [2,3]

- Hemoglobin <10 gm%
- Total leukocyte count less than 3500/cmm
- Platelet count less than 1,00,000/cmm

Above mentioned values of hemoglobin, total leukocyte count and platelet counts are used as diagnostic criteria for pancytopenia in our study.

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Study Design: The one year prospective observational study was done in a premier tertiary care teaching hospital.

Inclusion Criteria

- Indoor patients with pancytopenia (Hemoglobin <10 gm%, Total leukocyte count less than 3500/cmm, Platelet count less than 1,00,000/cmm)
- Age more than 12 years.
- Willing to give consent.

Exclusion Criteria

- Patients on Chemotherapy

Individual patients were asked detail history about symptoms, past history, personal habits. Detailed physical examination including general and systemic examination were carried out and entered in the proforma.

The routine and specific investigation done at discretion of treating physician was noted. Prognosis in terms of in-hospital mortality was assessed.

Unpaired T test and other relevant statistical tests were applied for statistical analysis.

Result and Analysis

Our study comprised of 102 patients ranging from 13 years to 65 years of age, youngest being 13 years and oldest 65 years old. Maximum patients of pancytopenia were in between 21 -30 years of age 33.3% (34/102) followed by 31-40 year 30.4% (31/102), 12- 20 year age group had 13.7% (14/102) and only 2.9% (3/102) were having age more than 60 year. Mean age in our study was 32.8 years.

Distribution of etiology for pancytopenia in our study is given in Table 01.

Table 1: Distribution of cases of pancytopenia according to etiology.

Disgnosis	No. of Cases	Percent
ALL	2	2.0
AML	9	8.8
Aplastic Anemia	20	19.6
CLD	3	2.9
Dengue	1	1.0
Enteric fever	1	1.0
HCV	1	1.0
Disseminated tuberculosis	1	1.0
Malaria	7	6.9
MDS	6	5.9
Megaloblastic anemia	44	43.1
Multiple myeloma	1	1.0
NHL	1	1.0
RA	1	1.0
SLE	4	3.9
Total	102	100.0

Megaloblastic anemia was the most common etiology of pancytopenia seen in 44 out of 102 patients (43.1%) in our study followed by aplastic anemia (19.6%),

Patients with Dengue with Hemophagocytic Lymphocytosis (HLH), Enteric fever, Hepatitis C Virus (HCV) related hepatitis, disseminated tuberculosis, multiple myeloma, Non Hodgkin Lymphoma (NHL), Rheumatoid Arthritis (RA) [Methotrexate induced] had pancytopenia in 1% of cases each.

In our study 3 patients had tuberculosis of which 2 had Ileocaecal tuberculosis who presented as megaloblastic anemia hence included in megaloblastic anemia, the third person had disseminated tuberculosis hence kept as a separate etiology. Amongst 3 Chronic Liver Disease (CLD) patients 2 had pancytopenia presumably due to hypersplenism and the third one had CLD secondary to hepatitis B and hepatitis C viral infections with chronic kidney disease.

Gender wise distribution of etiology is given in Table 2.

Male preponderance was seen in Megaloblastic anemia, Acute Myeloid Leukemia, CLD, Multiple myeloma, disseminated tuberculosis.

Female cases were more than males in aplastic anemia and Myelodysplastic syndrome (MDS). Acute Lymphoblastic Leukemia (ALL) was equally seen in male and female patients; one patient each. Enteric fever, HCV related hepatitis, NHL, RA, SLE were seen only in female patients in our study.

Table-2: Gender wise distribution of patient of pancytopenia as per etiology.

Diagnosis	Female	Male	Total No
ALL	1	1	2
AML	3	6	2
Aplastic Anemia	11	9	20
CLD	0	3	3
Dengue	0	1	1
Enteric fever	1	0	1
HCV	1	0	1
Disseminated tuberculosis	0	1	1
Malaria	2	5	7
MDS	5	1	6
Megaloblastic anemia	16	28	44
Multiple myeloma	0	1	1
NHL	1	0	1
RA	1	0	1
SLE	4	0	4
Total	46	56	102

Table-3: Distribution of cases pancytopenia according to symptoms.

Symptoms	Total	Percentage
Easy fatigability	100	98.0
Edema feet	6	5.9
Fever	34	33.3
Oral ulcer	10	9.8
Petechie bleeding gum other bleeding manifestation	15	14.7
Loss of appetite	65	63.7

Commonest symptom in our study was easy fatigability seen in 98%, followed by loss of appetite in 63.7%, fever in 33.3%, bleeding in 14.7%. Edema feet observed in least number of patients (5.9%).

Table-4: Distribution of cases pancytopenia according to signs.

Signs	Total	Percentage
Fever	36	35.29
Pallor	100	98
Bleeding manifestation	14	13.73
Knuckle pigmentation	11	10.78
Lymphadenopathy	5	4.90
Icterus	5	4.90
Oral Candidiasis	6	5.88
Sternal tenderness	6	5.88
Hepatomegaly	4	3.92
Splenomegaly	11	10.78
Edema feet	10	10.2

Commonest sign encountered in our study was pallor seen in 100 patients [98%]. This was followed by fever in 36 patients i.e., 35.29%, of these, 12 patients had an infectious disease, 9 patients had hematological malignancy, 7 had Aplastic anemia, 4 had an autoimmune disease, 3 had megaloblastic anemia and 1 had disseminated tuberculosis. Oral candidiasis was seen in 5.8% of patients, all of them had fever and had a hematological malignancy. Splenomegaly and knuckle pigmentation was seen in 10% of patients each. The least common sign was hepatomegaly seen in 3.9% patient [4/102]. Knuckle pigmentation was seen in 11 patients out of whom 10 patients had megaloblastic anemia.

Table-5: Distribution of number of patients according to laboratory parameters.

Hb (gm%)	<5	5-7.5	>7.5	Total
No of Cases	35 (34.3%)	53 (52%)	14 (13.7%)	102 (100%)
WBC (/cmm)	<1500	1500-2500	>2500	Total
No of Cases	27 (26.5%)	38 (37.2%)	37(36.3%)	102 (100%)
Platelet (/cmm)	<2000	20000-50000	>50000	Total
No of cases	26 (25.5%)	35(34.3%)	41(40.2%)	102(100%)

In our study maximum number of patients had Hemoglobin between 5 -7.5 gm% [52%], followed by Hb< 5 gm% [34.3%] and Hb>7.5 gm% in 13.7%. Maximum number of patients had WBC between 1500-2500/cmm [37.2%], followed by WBC > 2500/cmm [36.3%], WBC <1500/cmm in 26.5%. Maximum number of patients had platelet count > 50,000/cmm [40.2%], followed by platelet count between 20,000 to 50,000/cmm in 34.3% and platelet count< 20,000 in 25.5% of patients.

Patients with primary hematological spectrum of diseases [N=40, ALL -2, AML -9, Aplastic anemia-20, MDS-6, NHL-1, Multiple myeloma-1, HLH in dengue -1] 47.5% had Hemoglobin less than 5 gm% and 50% had Hemoglobin between 5-7.5 gm% and only one patient of AML had Hemoglobin more than 7.5 gm%.

In patients of Aplastic anemia hemoglobin <5 gm% was seen in 45% and between 5-7.5gm% was seen in 55% and none of them had Hb> 7.5 gm%. In megaloblastic anemia maximum number of patients, 54.4% had Hemoglobin between 5-7.5 gm%. Even though the number of patients of ALL and disseminated tuberculosis were low i.e. 2 and 1 respectively all had hemoglobin less than 5 gm%

All patients having mortality had Hb< 5gm%. On comparing mean Hb of expired group and survived group with mortality, there is significant mortality with low hemoglobin (p value<0.001 by unpaired t test).

Patients of MDS had lowest mean platelet count i .e. 25000/cmm, followed by aplastic anemia i.e. 25750/cmm, ALL 28000 and AML 38778/cmm. Maximum mean platelet count was seen in CLD i.e. 71000/cmm and megaloblastic anemia 58864/cmm.

Most common cause of megaloblastic anemia in our study was vegetarian diet [75%] leading to deficiency of vitamin B12 and/or Folic acid. chronic alcoholism [13%] was second common cause of megaloblastic anemia. Other causes were Ileocaecal tuberculosis 4.6% leading to Vitamin B12 malabsorption. Patients of pernicious anemia, HIV with megaloblastic anemia, HIV with alcoholic intake causing megaloblastic anemia formed 2.2% of the study group each. Mortality in patients with pancytopenia is shown in table 06.

Table-6: Mortality in cases of pancytopenia.

Outcome	No. of cases	Percentage (%)
Expired	6	5.9
Survived	96	94.1
Total	102	100.0

Table 06 Mortality in patients with pancytopenia: Out of 102 patients in our study 6 patients expired hence total mortality was 5.9%. Among the 6 patients 3 belonged to aplastic anemia [3 /6], followed by one each of patients having ALL, AML and MDS. Amongst patients with aplastic anemia mortality was seen in 15% of patients. Among patients ALL, AML and MDS mortality was seen in 50%, 11%, 16% of patients respectively.

Discussion

Pancytopenia is a common and serious hematological problem. The aetiology for pancytopenia varies widely depending on age and geographical distribution. Though extensive studies and guidelines are available for different etiologies like aplastic anemia and myelodysplastic anemia, guidelines and studies on pancytopenia are few.

The commonest cause of pancytopenia in our study was megaloblastic anemia. We found that megaloblastic anemia was also the commonest cause in many other Indian studies like Tilak et al [2], Khodke et al [3], Seema B et al [6], B N Gayathri et al [7], Doshi et al [8] Bhaskar B et al [9] as mentioned in table 07 below. In one study by Khanduri U, et al [10] out of 175 patients with megaloblastic anemia 62% of patients had pancytopenia. Megaloblastic anemia usually results from deficiency of Vitamin B12 or Folic acid or a deficiency in their metabolism [11].

Vitamin B12 is a water soluble vitamin with recommended daily requirement of 1-3 microgram (mcg) for adults [12]. Humans receive B12 exclusively from the diet. Meat is a good source of B12 with 10mcg/100 gm of weight. Other sources include egg yolk and fish. Dietary habits, taboos and poverty are responsible for majority of Vitamin B12 deficiency cases.

Vegetarians and vegans form a good number of Indian population reflecting high number of megaloblastic anemia in our study. Patients with severe B12 deficiency should receive parenteral 1mg of cobalamin daily for 1 week, 1mg twice weekly for one week thereafter followed by 1 mg every week for 4 weeks. This is to be followed by 1mg/month for life for malabsorption or lifelong 10 mg orally for nutritional deficiency. In other Indian study conducted by Santra G et al [13] in West Bengal the commonest cause was Aplastic anemia [20.7%] this could be explained by abundant sea food intake in West Bengal reducing the incidence of Vitamin B12 deficiency.

A Jain et al [14] reported hypersplenism as the commonest cause among 250 cases in southern Maharashtra owing to high cases of CLD in their study. In most studies conducted in western countries, aplastic anemia was the major cause of pancytopenia. On comparing international data: the International Agranulocytosis and Aplastic anemia study [4] aplastic anemia [52.7%] was the major etiology while in the study conducted by Keisu et al [5] neoplastic diseases and radiation [32%] were the commonest cause of pancytopenia, both studies were conducted in Israel and Europe.

Aplastic anemia seen in 19.6% of patients in our study was the second most common etiology. In other Indian studies like Santra G et al [13]. Doshi et al [8]. Bhaskar et al [9]. CLD [11.7%], infectious diseases [20%] and malaria [19%] were the second most common causes respectively. In our study CLD, infectious diseases including malaria were 2.9% and 8.5% respectively though malaria is endemic in Mumbai. Aplastic anemia is characterised by pancytopenia with a hypocellular marrow without any abnormal fibrosis or infiltrates.

Majority of the cases are idiopathic and the rest represent inherited or genetic bone marrow failure syndrome. It is important to rule out PNH and MDS in patients of aplastic anemia. Patients of aplastic anemia require supportive treatment like blood and platelet transfusion [15]. Immunosuppressive therapy is recommended for non-severe AA requiring treatment, treatment of severe or very severe AA not having matched hematopoietic stem cell donor or patients older than 50 years. Horse ATG and Cyclosporine are the preferred immunosuppressive drugs. Hematopoietic stem cell transplant should be considered in younger patients [15].

Hematological malignancies including AML, ALL, NHL and multiple myeloma were seen in 13 out of 102 cases. Infective etiologies were other important factors in our studies with malaria causing pancytopenia in 8 of the patients. Malaria can cause pancytopenia as a result of hemolysis, DIC, bone marrow necrosis, hemophagocytosis, impairment of marrow function, hypersplenism or direct bone marrow invasion by the parasite. Hamid et al. reported hypersplenism

(28%) and malaria (17.3%) to be the two most common causes of pancytopenia contributing for more than 45% of cases in his study of 75 pancytopenia patients. [16]. Leishmaniasis constituted about 13.58% of total cases of pancytopenia in study by Dasgupta [17], similar results were seen from other studies from other parts of India, [18] however none of our patients had leishmaniasis. Dengue fever is another common infection causing pancytopenia, though it was seen in only one patient during our study, it will be interesting to study leucopenia and thrombocytopenia (Bicytopenia) as hemoconcentration is commonly encountered in Dengue fever [19].

Table-7

Sr. No	Study / Year	Coun Try	No. of Cases	Commonest Cause	Second common cause	Most common presenting symptom	Most common sign	2nd most common sign
1	Keisu et al (1990)	Israel And Euro Pe	100	Neoplastic diseases and radiation [32%]	Aplastic anemia[19%]	-	-	-
2	Khodke et al (2002)	India	50	Megaloblastic Anemia [44%]	Aplastic anemia[14%]	-	-	-
3	Seema B et al (2006)	India	137	Megaloblastic Anemia [56.9 %]	Aplastic anemia[9.4%]	-	-	-
4	<i>B N Gayathri et a</i> (2005-07)	India	104	Megaloblastic Anemia [74%]	Aplastic Anemia [18.26%]	Generalised weakness [100%]	Pallor [100%]	Fever [38.46%]
5	<i>Santra B et al</i> (2010)	India	111	Aplastic anemia [20.7%]	CLD[11.7%]	Generalised Weakness [50%]	Generalised Weakness [50%]	Splenom egaly [44.14%]
6	<i>Doshi D et al</i> (2011)	India	100	Megaloblastic anemia [45%]	Infectious[20 %]	Lethargy [70%]	Pallor [100%]	Bleeding
7	Vandana Raphael et al (2007-09)	India	80	Megaloblastic anemia [41.2%]	Aplastic anemia [8.7%]	-	Pallor [100%]	Fever [42.5%]
8	<i>Bhaskar B et al</i> (2011)	India	100	Megaloblastic Anemia [37%]	Malaria [19%]	-	Pallor [100%]	Splenom egaly [70%]
9	<i>In our study</i> (2013)	India	102	Megaloblastic anemia [43.1%]	Aplastic Anemia [19.6%]	Easy fatiguability [98%]	Easy fatiguability [98%]	Fever [35.29%]

SLE is another important etiology in our study, seen in 4 out of 102 subjects and all of them were females. Bone marrow may be target organ in SLE [20]. Pereira et al studied 21 patients of SLE with peripheral cytopenia, on bone marrow biopsy they found global hypocellularity and increased reticulin proliferation as the commonest finding. [20] Drug induced pancytopenia should be considered and a detail drug history should be elicited.

Common over the counter drugs like ibuprofen can also cause pancytopenia. Organophosphorus exposure, cytotoxic drugs, chloramphenicol, methotrexate, phenytoin are commonly implicated [21].

Pancytopenia in Indian setting is mostly due to benign because mainly megaloblastic anemia secondary to B12 deficiency caused either by dietary deficiency or treatable condition for example tuberculosis. Emphasis on dietary awareness and supplements wherever required may thus reduce the incidence of pancytopenia and related problems.

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