Original Article

Etiological and clinical spectrum of pancytopenia based on bone marrow examination and case records: A retrospective study

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ABSTRACT

Background: Pancytopenia is a common entity seen in clinical practice. This study aims to determine the spectrum of etiology and clinical presentation of pancytopenia by conducting a retrospective study of case records, peripheral blood smears and bone marrow aspiration/biopsy findings of patients admitted to M S Ramaiah Medical Teaching Hospital, Bangalore, India.

Methods: Case records, blood smear reports and bone marrow aspiration/biopsy findings of patients presenting with pancytopenia who fit the inclusion criteria during the period of January 2010 to May 2015 were analyzed. Relevant history, physical and systemic examination and hematological parameters at presentation were recorded using a standard proforma.

Results: Among 134 cases of pancytopenia at presentation mean age was 28 years. Male to female ratio was 1.16. The etiological break up was according to the following order – megaloblastic anemia (46.27%), leukemia (20.15%), aplastic anemia (9.7%), hypersplenism (7.46%), infections (6.72%), myelodysplastic syndrome (5.97%) and HIV (3.37%). The clinical spectrum in patients with each of these etiologies has been elucidated.

Conclusion: The commonest cause of pancytopenia in this part of the India is megaloblastic anemia which is a curable deficiency. This is followed by leukemia, where an early diagnosis and intervention will improve their quality of life dramatically.

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Introduction

Pancytopenia is a common entity seen in clinical practice. It is a condition where all the three formed blood elements (red blood cells, white blood cells and platelets) are reduced below the normal reference range. It has numerous causes. The pattern of diseases leading to pancytopenia may vary with differences in age and geographic distribution, nutritional status and prevalence of infection. The etiology ranges from simple treatable ones like infections and megaloblastic anaemia to serious conditions like leukemia. Studies conducted during various timeline have given variable results about its proportional distribution .This study is aimed at understanding the etiological spectrum of pancytopenia in the southern part of India.

Although all the cell-lines of the blood are depleted, the clinical manifestations are varied and mutually different from one another. This calls for a need to identify a pattern in the symptoms so as to pick up the clues to the etiology. A correlation between the clinical features of individual patients and the blood picture, bone marrow examination is being reviewed in this study in order to achieve the same. Such a correlation will help the clinicians to gauge the diagnosis early and easily. Importance of the study lies in the timely intervention for the causes of pancytopenia which can either bring about a complete cure or at least a remission from the disease.

In a nutshell, this study is aimed at obtaining a key symptoms and signs, which, when coupled with Peripheral blood smear of pancytopenia; can help the clinician to arrive at a diagnosis. This can be confirmed with a bone marrow examination. An early and an affordable method of diagnosis is the key to better prognosis.

The objective of this study is to determine the spectrum of etiology and clinical presentation of pancytopenia by conducting a retrospective study of case records, peripheral blood smear and bone marrow aspiration/biopsy findings.

Materials and Methods

Study design: retrospective record analysis

Study site: M. S. Ramaiah medical teaching hospital and Memorial Hospital, Bangalore.

Method: After obtaining institutional review board's approval, case records, blood smear reports and bone marrow aspiration/biopsy findings of patients presenting with pancytopenia who fit the inclusion criteria during the period of January 2011 to May 2015 were analyzed. Relevant history, physical and systemic examination and hematological parameters at presentation were recorded using a standard proforma.

Statistical analysis: From the data gathered, statistical analysis was done and results regarding the distribution of etiology and clinical presentation of pancytopenia were summarized using descriptive statistics like proportions. Quantitative data such as age and blood investigations will be summarized using descriptive statistics like mean, median and standard deviation.

Inclusion criteria: Pancytopenia as per the criteria (1):

1. Anemia
2. Leucopenia and Neutropenia
3. Thrombocytopenia: platelet count

Exclusion criteria:

1. Patients on chemotherapeutic agents
2. Patients on radiation therapy
3. Patients who did not undergo bone marrow analysis
4. Obvious causes of pancytopenia like Dengue fever, other viral fevers where bone marrow aspiration was not indicated and the changes were transient.

Result

There were 134 cases of pancytopenia at presentation for which bone marrow aspiration/biopsy was done to ascertain the diagnosis. Samples where the diagnosis could not be arrived at were excluded from study. Most common causes of pancytopenia where there was no clinical decision made to do a bone marrow analysis were Swine flu (n=76) and dengue fever (n=103). Here the improvement in count was expected in due course of the illness.

The mean age of presentation of pancytopenia was 28 years. Male to female ratio was 1.16. The etiological break up was in the following order of megaloblastic anemia (46.27%), leukemia (20.15%), aplastic anemia (9.7%), hypersplenism (7.46%), infections (6.72%), myelodysplastic syndrome (5.97%) and HIV (3.37%).

The descending order of symptom presentation was as follows: fatigue (80.6%), shortness of breath (52.24%), bleeding manifestation (48.51%), fever (45.52%), frequent infections (44.71%), palpitation (42.54%), headache (23.13%), dizziness (22.4%) and chronic diarrhea (11.19%).

Around 88.71% of megaloblastic anemia patients presenting as pancytopenia were lacto vegetarians. The most common presenting sign was pallor (99.25%), followed by tachycardia (61.94%), fever (52.99%), splenomegaly (44.03%), hepatomegaly (39.55%), petechiae (36.52%), bone tenderness (18.66%), lymphadenopathy (11.94%) and jaundice (6.72%).

The clinical features of individual etiologies are shown in table 1 and table 2. Based on analysis of peripheral smear report, the hematological parameters during presentation were as follows: hemoglobin (mean 5.5g/dL), WBC (mean $3.04x10^9$/L), neutrophils (mean $0.9x10^9$/L) and platelets ($48.85x10^9$/L).

Based on bone marrow cellularity, 67.91% of cases were associated with hypercellular causes and 14.92% each were associated with normocellular and hypocellular causes.

Discussion

Pancytopenia is a common clinical presentation. According to Bashawri (2), 11.9% is the frequency of bone marrow examination done as pancytopenia being the indication. From pathogenesis point of view, the causes of pancytopenia can be broadly categorized as follows:

1. Reduced formation in the marrow.
2. Cell death in marrow due to ineffective erythropoiesis.
3. Defective cell formation which is avidly removed by circulation.
4. Destruction of cells due to action of antibodies.
5. Trapping of normal cells due to overactive and hypertrophied reticulo-endothelial system.

The etiological break up of pancytopenia in this study is comparable with similar studies done in India. The following table compares the two most common causes according to few similar studies (Table 3).

Based on our analysis of peripheral smear reports, the hematological parameters during presentation were as follows: hemoglobin (mean 5.5g/dL), WBC (mean $3.04x10^9$/L), neutrophils (mean $0.9x10^9$/L) and platelets ($48.85x10^9$/L). These are comparable with the results produced by a study in Nepal (13).

The most common cause of pancytopenia in the present study was megaloblastic anemia (46.27%). The increased incidence of megaloblastic anemia can be correlated to the increased prevalence of nutritional deficiency in our country. The mean age of presentation was 38 years. The male to female ratio was 0.82. This was the only etiology

Table 1: Symptom presentation of individual etiology:

	Megaloblastic anemia [n, (%)]	Leukemia [n, (%)]	Aplastic anemia [n, (%)]	Hypersplenism [n, (%)]	Infection [n, (%)]	MDS [n, (%)]	HIV [n, (%)]
Fatigue	51(82.26)	22(81.48)	9(69.23)	8(80)	7(77.78)	6(75)	5(100)
Shortness of breath	37(59.68)	12(44.44)	5(38.46)	5(50)	4(44.44)	4(50)	3(60)
Dizziness	15(24.19)	3(11.11)	2(15.32)	4(40)	2(22.22)	1(12.5)	3(60)
Palpitation	29(46.77)	9(33.33)	6(46.15)	5(50)	1(11.11)	5(62.5)	2(40)
Headache	14(22.58)	7(25.93)	3(23.08)	1(10)	3(33.33)	0(0)	3(60)
Fever	19(30.65)	20(74.07)	5(38.46)	4(40)	8(88.89)	2(25)	3(60)
Frequent infections	26(41.93)	17(62.96)	4(30.77)	3(30)	2(22.22)	3(37.5)	5(100)
Bleeding manifestations	27(43.55)	14(51.85)	6(46.15)	7(70)	5(55.56)	2(25)	4(80)
chronic diarrhea	10(16.13)	0(0)	0(0)	0(0)	1(11.11)	1(12.5)	3(60)

Table 2: Signs in individual etiologies

	Megaloblastic anemia [n, (%)]	Leukemia [n, (%)]	Aplastic anemia [n, (%)]	Hypersplenism [n, (%)]	Infection [n, (%)]	MDS [n, (%)]	HIV [n, (%)]
Tachycardia	42(67.74)	16(59.26)	6(46.15)	6(60)	6(66.67)	5(62.5)	2(40)
Fever	23(37.1)	20(74.07)	5(53.85)	5(50)	8(88.89)	4(50)	4(80)
Pallor	62(100)	27(100)	13(100)	9(90)	9(100)	8(100)	5(100)
Jaundice	2(3.23)	0(0)	0(0)	4(40)	3(33.33)	0(0)	0(0)
Petechiae	21(33.87)	11(40.74)	4(30.77)	5(50)	4(44.44)	1(12.5)	3(60)
Lymphadenopathy	1(1.61)	9(33.33)	0(0)	0(0)	0(0)	1(12.5)	4(80)
Splenomegaly	34(54.84)	7(25.92)	0(0)	10(100)	3(33.33)	1(12.5)	3(60)
Hepatomegaly	34(54.84)	6(22.22)	0(0)	6(60)	1(11.11)	2(25)	2(40)
Bone tenderness	12(19.35)	8(29.63)	1(7.69)	0(0)	0(0)	2(25)	2(40)

Table 3: Other studies

Study	Country	Year	Number of cases	Commonest cause	2nd Most common cause
International agranulocytosis and aplastic anemia group(3)	Israel & Europe	1987	319	Hypoplastic anemia (52.7%)	MDS (4.5%)
Keisu and Ost(4)	Israel & Europe	1990	100	Neoplastic disease, radiation (32%)	Hypoplastic anemia(19%)
Verma and Dash(5)	India	1992	202	Hypoplastic anemia(40.6%)	Megaloblastic
Tilak and Jain(6)	India	1999	77	Megaloblastic	Hypoplastic anemia
Kumar et al(7)	India	1999	166	Hypoplastic anemia	Megaloblastic
khunger et al(8)	India	2002	200	Megaloblastic anaemia (72%)	Aplastic anaemia (14%)
Khodke et al(9)	India	2000	50	Megaloblastic	Hypoplastic anemia
Memom et al(10)	Pakistan	2008	230	Aplastic anemia (23.9%)	Megaloblastic anemia (13.04%), leukemia (13.05%)
Istiaq et al (11)	Pakistan	2004	100	Megaloblastic anemia (39%)	Hypersplenism (19%)
Savage et al(12)	Zimbawe	1999	134	Megaloblastic anemia	Aplastic anaemia
Jha et al(13)	Nepal	2008	148	Hypoplastic anemia (29.05%)	Megaloblastic anemia (23.64%)
Gamal and Safa	Yemen	2008	75	Hypersplenism (28%)	Malaria (17.3%)
Ramesh et al(14)	Nepal	2009	28	Megaloblastic anemia (42.855)	Aplastic anemia (35.71%)
present study	India	2011	134	Megaloblastic anemia (46.27%)	Leukemia (20.15%)

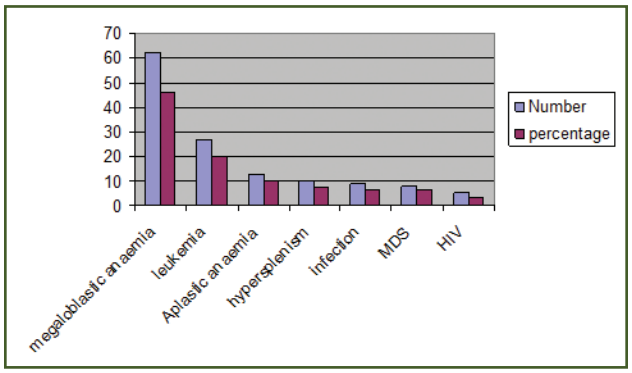

Fig. 1: Representation in bar graph:

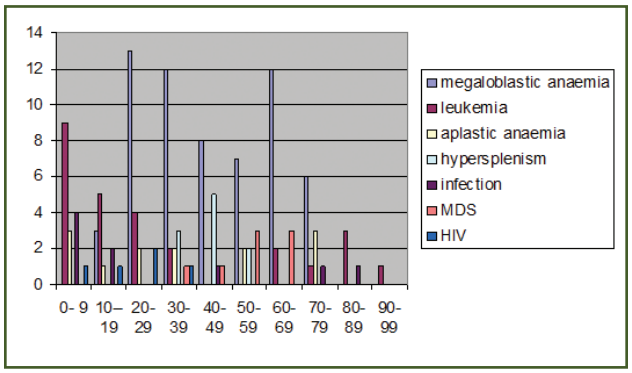

Fig. 2: Age distribution of individual etiologies

which affected females more than males. The overall sex ratio of pancytopenia was 1.16. Around 88.17% of these patients were lacto vegetarians, showing that dietary factor is an important contributing entity. 16.3% patients had chronic diarrhea which can be a cause for dietary losses. The only etiology where an even higher percentage of chronic diarrheas of 80% were seen was in case of HIV infection. Tropical sprue is endemic in southern India. It is readily corrected by folate and antibiotics. It primarily affects distal small intestine (15), therefore incriminated as the cause of cobalamine deficiency (16).

The most common symptom in patients with megaloblastic anemia was fatigue followed in descending order by shortness of breath, palpitation, bleeding manifestation, frequent infections, fever, dizziness, headache and chronic diarrhea. Due to gradual development of anemia in this condition, the symptoms of anemia are seen only when hematocrit is significantly low.

The most common presenting sign was pallor followed in descending order by tachycardia, splenomegaly, hepatomegaly, fever, petechiae, bone tenderness, jaundice and lymphadenopathy. On blood smear examination, significant parameters were hyper segmented neutrophils (82.26%), macrocytic hypochromic blood picture (80.64%) and anisopoikilocytosis (77.42%). Circulating normoblasts were seen in 22.58% patients. On bone marrow examination, 67.91 % of the cases demonstrated hypercellularity of which the predominant ones were of erythroid series. Findings of megaloblastosis clinch the diagnosis.

The second most common cause of pancytopenia was leukemia which constituted 20.15% of patients. Among these AML constituted 44.44% and ALL constituted 55.56%. The mean age of diagnosis of AML was 72 years in contrast to that of ALL which was 8 years. AML did not show any gender preponderance but the sex ratio of ALL was 1.5 in favor of male: female. The descending order of symptoms at presentation was fatigue, fever, recurrent infections, bleeding manifestations, shortness of breath, palpitation, headache and dizziness. The frequencies of clinical signs elicited were (in descending order): pallor, fever, tachycardia, petechiae, lymphadenopathy, bone tenderness, splenomegaly and hepatomegaly. On peripheral blood smear, 92.59% showed circulating immature cells, 74.07% showed normochromic normocytic anemia and 55.56% showed circulating normoblasts. On marrow examination, 85.18% showed hypercellular marrow. These findings correlate well with observations of other studies (17, 18, 19 and 20).

The third most common cause of pancytopenia was aplastic/ hypoplastic anemia of unknown cause which was seen in 9.7% patients. The mean age of presentation was 24 years. The male to female ratio was 2.25. The descending order of symptom presentation was as follows: fatigue, bleeding manifestations, palpitation, fever, shortness of breath, frequent infections, headache and dizziness. The descending orders of clinical signs were: pallor, fever, tachycardia, petechiae. No significant lymphadenopathy, splenomegaly and hepatomegaly were noted. Hence if any of the above mentioned finding is seen with pancytopenia, then it rules out aplastic anemia. On peripheral smear, 92.55% showed normocytic normochromic anemia with pancytopenia. On bone marrow examination, 100% showed hypocellular marrow.

The fourth most common cause of pancytopenia in this study was hypersplenism (7.46%). The mean age of presentation was 45 years. The male to female ratio was 2.33. Most of these patients were alcoholics and had decompensated liver disease, whose independent association with hypersplenism is shown by a study (21). In alcoholic liver cirrhosis, megaloblastic anemia is usually caused by folate deficiency (22 and 23). Alcohol acutely depresses serum folate levels and this accelerates megaloblastic anemia. Alcohol also causes marrow suppression of reticulocytes, granulocytes and platelets (24 and 25).

The next most common cause of pancytopenia in our study was infections (6.72%). One third of these patients had malaria, enteric fever and viral fever with sepsis each. These findings correlate well with studies done by Menon et al (10). Maximum infections occurred in the age group of 0 to 9 years. The male to female ratio was 2.

Myelodysplastic syndrome (MDS) was the next most common cause of pancytopenia seen in 5.97% of patients. In a study done in Israel and Europe, MDS was the second most common cause of pancytopenia (3). In this study, the mean age of presentation was 62 years and the male to female ratio was 1. Patients with multi-lineal cytopenia are a subset of MDS with increased morbidity and reduced life expectancy. Immune and inflammatory syndrome is seen in around 10% patients. A symptom complex which simulates systemic lupus erythematosus (fever, arthritis, pleurisy and pancytopenia with hypercellular marrow) may precede AML (26).

HIV accounted for 3.32% of cases presenting as pancytopenia. Of the 5 patients, two were in terminal stage of the disease. Pancytopenia in HIV has been attributed to many causes which include inflammatory cytokines or HIV virus itself, infiltration by lymphoma or infections, polypharmacy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, auto-antibodies and malnutrition (27 and 28).

Conclusion

The commonest cause in the southern part of India is megaloblastic anemia. It is a curable deficiency which if intervened at an early stage will prevent severe neurological and hematological sequelae. Adequate replenishment by vitamin B12 is enough to bring back the normal counts in these patients by which significant morbidity and mortality can be prevented. The second most common cause was leukemia, where it is needless to say the miracle that can be achieved on timely treatment. Early diagnosis and intervention will lead to remission of disease and better quality of life. Time and again, the investigation of choice to diagnose unexplained pancytopenia or to rule out grave conditions like neoplastic infiltration of bone marrow has been bone marrow aspiration/biopsy. Infective etiologies are easily diagnosable since it only needs a fairly good knowledge about the endemicity of an area like malaria and typhoid fever.

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Competing Interests

None declared

Reference

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