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Original Research Article

Study of etiological spectrum and clinical profile of patients admitted in tertiary care hospital of South Gujarat, India

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ABSTRACT

Background: Pancytopenia is defined as reduction of all three formed elements of blood below normal reference range. The symptoms are fatigue, fever, dizziness and weight loss. Evaluation was done using complete hemogram and peripheral smear. The presenting marrow biopsy is most useful and accurate in evaluation of pancytopenia.
Methods: Two ml of anticoagulated blood was collected for complete hemogram. The peripheral blood smear was stained with Leishman's stain and studied. Bone marrow biopsy and aspiration was done in all the patients to identify etiology.
Results: Predominance was seen in the age group of 31-60 years. Most common cause of pancytopenia was megaloblastic anaemia in this study compared to other studies all over the world where most common cause was aplastic anaemia. This reflects higher prevalence of megaloblastic anaemia in the Indian subjects.
Conclusions: A comprehensive clinical, haematological land bone marrow study of patients with pancytopenia usually helps in identification of the underlying cause.

Keywords: Aplastic anaemia, Fatigue, Megaloblastic anaemia, Pancytopenia

INTRODUCTION

The different diseases primarily or secondarily affecting the bone marrow may manifest with peripheral pancytopenia.[1] Pancytopenia is defined as reduction of all the three formed elements of blood below the normal reference range. The presenting symptoms are often attributable to the anaemia or thrombocytopenia. Leucopenia is often seen in the subsequent course of the disorder. Features of pancytopenia may be present in varieties of hematopoietic and non-hematopoietic conditions. The pathophysiology leading to Pancytopenia in different diseases include, decrease in hematopoietic cell production, marrow replacement by abnormal cells, suppression of marrow growth and differentiation, ineffective hematopoiesis with cell death, defective cell formation, antibody mediated sequestration or destruction of cells in a hypertrophied and overactive reticuloendothelial system.[2]

The most common causes leading to Pancytopenia on bone marrow examination are hypoplastic (aplastic anaemia) bone marrow (29.05%), Megaloblastic anaemia (MA) (23.64%), Hematological malignancies i.e. Acute Myeloid Leukemia (AML) (21.62%), and Erythroid hyperplasia (EH) (19.6%). Other rare causes that are easily treatable and may not require bone marrow

examination for diagnosis include SLE, Malaria, Dengue, Enteric fever, etc.[3]

The commonest clinical manifestations of Pancytopenia are usually Fever (86.7%), fatigue (76%), dizziness (64%), weight loss (45.3%), anorexia (37.3%), night sweats (28%), pallor (100%), bleeding (38.7%), splenomegaly (48%), hepatomegaly (21.3%), and lymphadenopathy (14.7%).[4]

Bone marrow examination is the most useful and accurate in evaluation of Pancytopenia.[5] This allows complete assessment of marrow architecture and the pattern of distribution of any abnormal infiltrate and for the detection of focal bone marrow lesions.[6,7] While bone marrow failure syndromes and malignancies are important causes, certain non-malignant conditions such as infections and nutritional anaemia are equally important causes.[5]

Various factors encompassing geographic distribution and genetic disturbances may cause variation in the incidence of disorders causing Pancytopenia.[8-10] A few similar studies are available in literature. Although it is a common clinical pattern with an extensive differential diagnosis, there is a little discussion of this abnormality in major textbooks of internal medicine and hematology. Since the underlying pathology of Pancytopenia determines the management and prognosis of patients, there is definite need to study about Pancytopenia.[11]

METHODS

This is a hospital based cross-sectional study of indoor patients of the Medicine department of tertiary care hospital of South Gujarat over a period of 8 months (January 2016 - August 2016) including 80 patients. Patients who fulfilled the following inclusion criteria were enrolled in the study after their consent.

Inclusion criteria

- Age >18 years
- Anemia (Hemoglobin<10gm/dl)
- Leucopenia (total count < 4000 cells/cumm.)
- Thrombocytopenia (platelet count <150000 cells/cumm.)

Exclusion criteria

- Patients on cytotoxic drugs
- Patients on Radiotherapy
- Pregnant female

Study was approved by Human Research Ethics Committee of tertiary care hospital of South Gujarat. Two ml of anticoagulated blood was collected for complete hemogram. The peripheral smear was studied after staining with Leishman's stain. Bone marrow aspiration and biopsy was done in all the patients to identify the etiology. An informed consent was obtained.

Statistical analysis done by software MS Excel 2007 and Open Epi version 2.3. Percentage, mean, standard deviation, chi-square and 'p' values were calculated wherever applicable.

RESULTS

In the present study, Megaloblastic anemia (37.5%) was the commonest cause of Pancytopenia, followed by nutritional anemia (16.25%), aplastic anemia (11.25%), hypersplenism (10%), malignant diseases (10%), myelodysplastic syndromes (2.5%) and others (12.5%). Others included uncommon causes like Dengue fever (5%), Malaria (2.5%), Multiple myeloma (2.5%), Hemophagocytosis (1.25%) and SLE (1.25%) (Table 1). The commonest cause of Pancytopenia reported from various studies throughout the world has been aplastic anemia. This is in sharp contrast with the results of present study where the commonest cause of Pancytopenia was Megaloblastic anemia. This seems to reflect the higher prevalence of nutritional anemia in Indian subjects as well as in developing countries. However similar results have been reported in studies from other Indian centres (Table 2).

Most of the patients were in the age group of 31-60 years (60%) and the least occurrence was seen in the age group of 61-70 years (3.75%). The sex distribution of Pancytopenia showed a male preponderance. The male to female ratio was 1.35:1 (Table 3). In present study, anemia, generalized weakness and fever were the most common clinical features in pancytopenic patients comprising of (100%), (46.25%) and (31.25%) respectively. Similar results have been reported in studies by Aziz T, Ishtiaq O and Niazi M.[12-14] The frequencies of other clinical features were variable and different from these studies probably due to broad spectrum of etiologies behind pancytopenia (Table 4).

Table 1: Etiology of pancytopenia in present study.

Diseases	No. of patients	Percentage (%)
Megaloblastic anaemia	30	37.5%
Nutritional anaemia	13	16.25%
Aplastic anaemia	9	11.25%
Hypersplenism	8	10%
Malignant diseases	8	10%
Dengue fever	4	5%
Myelodysplastic syndrome	2	2.5%
Malaria	2	2.5%
Multiple myeloma	2	2.5%
Hemophagocytosis	1	1.25%
Sle	1	1.25%
Total	80	100%

Table 2: Causes of pancytopenia in various studies.

Study	Country	Year	No. of cases	Commonest cause	Second most common cause
Retief FP, Heyns AD	South Africa	1976	195	Bone marrow failure (67.7%)	Severe infection (9.7%)
International agranulocytosis and aplastic anemia study	Europe	1987	389	Aplastic anemia (52.7%)	MDS (10.5%)
Imbert M et al	Europe	1989	213	Malignant myeloid disorders (42%)	Malignant lymphoid disorders (18%)
Tilak V, Jain R	India	1998	77	Megaloblastic anemia (68%)	Aplastic anemia (7.7%)
Khodke et al	India	2000	166	Hypoplastic anemia (29.51%)	Megaloblastic anaemia (22.3%)
Kumar R et al	India	2001	166	Aplastic anemia (29.5%)	Megaloblastic anemia (22.3%)
Khunger et al	India	2002	200	Megaloblastic anaemia (72%)	Aplastic anaemia (22.1%)
Jha et al	Nepal	2008	148	Hypoplastic anemia (29.5%)	Megaloblastic anemia (23.64%)
P. M. Devi et al	India	2008	50	Hypoplastic anaemia (22%)	Megaloblastic anaemia (18%)
Vandana R et al	India	2012	80	Megaloblastic anaemia (41.2%)	Nutritional anaemia (8.7%)
Present study	India	2016	80	Megaloblastic anemia (37.5%)	Nutritional anemia (16.25%)

Table 3: Comparison of age and sex in patients with Pancytopenia among different studies.

	Hayat AS et al (N=85)	Gayathri BN et al (N=104)	Present study (2016) (N=80)
Mean age for males	30.20±15.42	37.22±16.23	38.12±14.93
Mean age for females	35.12±16.31	39.45±15.89	38.4±14.79
M:F ratio	2.69:1	1.2:1	1.35:1
95% Confidence interval	26.9-33.5	34.1-40.4	34.8-41.4

Table 4: Clinical features of patients having Pancytopenia in present study.

Clinical features	No. of cases	Percentage
Pallor	80	100
Generalized weakness	37	46.25
Fever	25	31.25
Hepatosplenomegaly	14	17.5
Pedal edema	10	12.5
Easy fatigability	10	12.5
Abdominal distention	8	10
Bleeding	6	7.5
Pain in abdomen	5	6.25
Icterus	5	6.25
Giddiness	4	5
Difficulty in breathing	3	3.75
Lymphadenopathy	2	2.5
Joint pain	2	2.5

Bone marrow aspirate in the present study of Pancytopenia showed the following types of cellularity: Hypocellularity (11.25%), Hypercellularity (58.75%), Normocellularity (30%) (Figure 1).

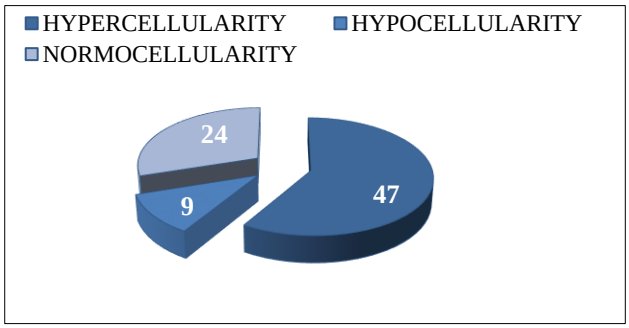

Figure 1: Marrow cellularity of patients with Pancytopenia.

DISCUSSION

Megaloblastic anemia

This was the most common cause of Pancytopenia in the present study. There was a male preponderance with male

to female ratio 2.3:1. It was most common in the age group of 41-60 years. In the study of Pancytopenia cases by Jha et al, the age range was 10-79 years (31years).[2] There was a male preponderance and male to female ratio was 1.5:1. In the study by Kumar et al, the ages ranged from 14-73 years (39.5%).[15] There was a male preponderance and the male to female ratio was 2:1. Hemoglobin varied from 1g% to 10g%. The total leukocyte count ranged from 500-4000 cells/cumm. Platelet count ranged from 25000-1.5 lakh cells/cumm. Reticulocytes count ranged from 0.1% to 2%. MCV was more than 100 fl in 57.5% of cases. Majority of the patients had macro ovalocytes with a considerable degree of anisopoikilocytosis. Hyper segmented neutrophils were present in all the patients. In the study by Kishore Khodke et al, 120/22 cases showed anisocytosis, 10/22 cases showed dimorphic blood picture and 20/22 cases showed hyper segmented neutrophils. In the study by Tilak et al, 51/53 cases showed anisocytosis, 45/53case showed hyper segmented neutrophils, 13/53 showed circulating erythroblasts.[4] Reticulocytes were seen in 5/53 and relative lymphocytosis was seen in 7/53 cases. Bone marrow was hypercellular. Megaloblastic erythropoiesis with giant metamyelocytes and band forms were seen. Megakaryocytes were normal.

Mixed nutritional anemia

This was the second most common cause of Pancytopenia in the present study. The nutritional deficiency of either B12 or folate results in Megaloblastic anemia. Other causes include mixed deficiency anemia (macrocytes and macrocytic). In the study by Shazia Memon mixed deficiency was seen in 20 cases (8.69%).[16] Mobina et al, in their study of 392 cases of Pancytopenia found 11.2% cases of mixed deficiency anemia.[4]

There was a female preponderance with a male to female ratio 0.8:1. It was most common in age group of 41-50 years. Hemoglobin varied from 2.8 gm% to 7.5gm%. The total leukocyte count ranged from 1900-4000 cells/cumm. Platelet count ranged from 59000-1.5 lakh cells/cumm. Reticulocytes count tanged from 0.1-8%. Majority of the patients had normochromic normocyticanemia. Two patients had microcytic hypochromic anemia. Bone marrow was hypercellular with a reversal of M:E ratio in 93.8% of cases.

Aplastic anemia

This was next common cause of Pancytopenia in the present study. There was a female preponderance with a male to female ratio of 0.8:1. It was most common in the age group of 21-30 years. In the study by Kumar et al, the ages ranged from 12-63years (29 years).[15] There was a male preponderance and male to female ratio was 1.4:1. In the study by Jha et al, the ages ranged from 1.5-70 years (17 years).[2] There was a male preponderance with male to female ratio of 1.3:1. Hemoglobin varied from 3.1-10 g%. The total leukocyte count ranged from 400-4000 cell/cumm. Platelet count ranged from 4000-1 lakh cells/cumm. Reticulocytes count ranged from 0.1-1.5%. Majority of the patients had normochromic normocytic anemia (44.45%). Some (33.33%) showed macrocytosis. There was relative lymphocytosis. In the study by Kishore Khodke, 3/7 patients showed anisocytosis and 1/7 patients showed relative lymphocytosis.[1] In the study by Tilak et al, 2/6 patients and by Daniel NM et al, found normocytic normochromic erythrocytes in 64% of the patients, macrocytic normochromic blood picture in 20% of the patients.[4,17] Bone marrow was hypocellular with an increase in marrow fat. Lymphocytes and plasma cells were prominent.

Hypersplenism

This was the next common cause of Pancytopenia in the present study. There was a male preponderance with a male to female ratio of 3:1. It was most common in the age group of 51-60 years. Kumar et al, reported on incidence of hypersplenism in 19/166 cases in which ages ranged from 14-49 years.[15] There was a male preponderance with male to female ratio being 2:1. Shazia Memon et al, in their study of 230 cases found hypersplenism in 10 patients (4.34%).[16] Hemoglobin varied from 3.5 g% to 8.6g%. The total leukocyte count ranged from 2000-4000 cells/cumm. Platelet count ranged from 50000-1.5 lakh cells/cumm. Reticulocytes count ranged from 0.6-2%. Majority of the patients had normochromic normocytic anemia (60%), 40% of patients had microcytic hypochromic anemia. Bone marrow was hypercellular with a reversal of M:E ratio in 75% of cases. In the study by Kumar et al, the Hemoglobin% ranged from 3.5-8.6 gm%.[15] The TLC ranged from 1100-3600 cells/cumm. The platelets ranged from 40000-125000 cells/cumm. Most of the patients (60%) had normocytic normochromic anemia. 40% of them had microcytic hypochromic anemia. In the study by Osama et al, macrocytosis was seen in 63.1% cases and microcytosis in 36.8% cases.[18]

Leukemia

The male to female was 1:1. It was most common in the age group of 18-20 years. In the study by Jha et al, acute leukemia alone constituted 90.62%. of all the hematological malignancies. It accounted for 19.59% of total cases of Pancytopenia. Age ranged from 2-75 years with a male to female ratio of 1.9:1. Khodke et al, and Tilak et al, reported one case of AML causing Pancytopenia.[1,4] Acute leukemia was the third common cause of Pancytopenia in the study of Varma and Dash which is similar to the study by Savage et al, Hemoglobin varied from 3.3-9.8%.[19] The total leukocyte count ranged from 800-4000 cells/cumm. Platelet count ranged from 10000-150000 cells/cumm. Reticulocytes count ranged from 0.6-2%. Majority of the patients had normochromic normocytic anemia. Leukocytes were reduced in number and immature cells including myeloblasts were seen. Bone marrow was hypercellular with a reversal of M:E

ratio in 80%. In the study by Tilak Jain et al, one case of acute myeloid leukemia with anisocytosis, circulating erythroblasts and immature cells was reported.[4] Kishore Khodke et al, found one case of acute myeloid leukemia with immature cells in the peripheral blood.

CONCLUSION

Pancytopenia is a common entity. However, it has received inadequate attention in the Indian subcontinent. A study of Pancytopenia using easily available diagnostic techniques is therefore important.

Age and sex distribution of patients with Pancytopenia in this study was consistent with the findings in other studies. Megaloblastic anemia was the commonest cause of Pancytopenia in the present study. Most other studies have reported aplastic anemia as the commonest cause. This seems to reflect higher prevalence of nutritional anemia in the Indian subjects. The hematological parameters and bone marrow morphological features in patients with Megaloblastic anemia, aplastic anemia and malignant diseases including MDS in the present study were comparable to the findings by other authors.

Uncommon etiological factors like dengue fever, malaria, hemophagocytosis, SLE and multiple myeloma were identified in this study. A comprehensive clinical, haematological and bone marrow study of patients with Pancytopenia usually helps in identification of the underlying cause. However, in view of a wide array of etiological factors, Pancytopenia continues to be a challenge for haematologists.

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