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RESEARCH ARTICLE

TO STUDY THE CLINICO-HAEMATOLOGICAL SPECTRUM OF PANCYTOPENIA IN A TERTIARY CARE CENTRE OF NORTH INDIA

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ABSTRACT

The present prospective cross sectional study was conducted at Pt. B.D. Sharma PGIMS Rohtak, Haryana on 100 patients of pancytopenia of age group 14-65 years coming to OPD and admitted in hematology and medicine ward during year 2012-2013, over a period of 1 year. The patients were properly evaluated for their complete clinical profile & etiology of pancytopenia. Panctopenia was diagnosed in the presence of hemoglobin <12gm/dl, total leukocyte count (TLC) <4000/microL, platelet count <1,00,000/microL. Thorough relevant investigations were carried out. Most patients belong to young age group with mean age 42.87±15.54 years. Most common etiology of pancytopenia was megaloblastic anemia (39%) followed by aplastic anemia (29%), Aleukemic leukemia (15%) and other causes. Among megaloblastic anemia pure vitamin B12 deficiency was observed in 27 cases. On clinical examination pallor was present in 100% cases. 31% of patients had hepatomegaly, 27% of patients had splenomegaly. We compared the results of our study with other studies & concluded that clinico-hematological spectrum of pancytopenia varies from region to region.

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INTRODUCTION

Pancytopenia refers to a reduction in all the three formed elements of blood: red blood cells, white blood cells and platelets. The aetiology of pancytopenia varies in different populations depending on the differences in age patterns, nutritional status, climate and the prevalence of infections. The causes of pancytopenia can be due to ineffective hematopoiesis with cell death in the marrow; formation of defective cells which are rapidly removed from circulation; sequestration and/or destruction of cells by the action of antibodies or trapping of normal cells in a hypertrophied and over-reactive reticuloendothelial system (Khodke *et al.,* 2001). Till date there are a limited number of studies on the frequency of various causes of pancytopenia. There appears to be a changing spectrum of pancytopenia over the past two decades. Some of the diseases that exhibit pancytopenia include aleukemic leukemia, myeloma, lymphoma, myeloid metaplasia, storage reticulosis, pernicious anemia, paroxysmal nocturnal hemoglobinuria, and aplastic anemia (Simmons, 1996). Studies done in India recently revealed megaloblastic anemia, aplastic anemia, leukemia, leishmaniasis, myelodysplastic syndrome, paroxysmal nocturnal hemoglobinuria, overwhelming viral infections (HIV, viral hepatitis etc) and drug induced pancytopenia as the most commonly diagnosed causes of pancytopenia. However, there are a limited number of comprehensive studies on this subject (Tilak *et al.,* 1999; Khunger *et al.,* 2002). The incidence of aplastic anemia quoted from the west is 10-25%. However studies done in India show a lower proportion of aplastics in all cases of pancytopenia. The different studies have shown different causes of pancytopenia on geographic region. Therefore, the present studies has been planned to study the clinic-hematological spectrum of pancytopenia in the Indian subcontinent.

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MATERIALS AND METHODS

The present prospective cross sectional study was conducted at Pt. B.D. Sharma PGIMS Rohtak on 100 patients of pancytopenia of age group 14-65 years coming to OPD and admitted in hematology and medicine ward during year 2012-2013. Panctopenia was diagnosed in the presence of hemoglobin <12gm/dl, total leukocyte count (TLC) <4000/micro L, platelet count < 1,00,000/microL (Santra *et al.,* 2010). Patients on myelotoxic chemotherapy, age <14 yrs and

>65 yrs and patients who have received blood transfusions in last 3 weeks were excluded from the study. The written informed consent was taken prior to the enrollment in the study from each patient. All the patients were subjected to detailed history regarding symptoms of the patient like generalized weakness and fatigue, fever, shortness of breath, bleeding manifestations etc. This was followed by a detailed clinical examination including general physical examination and systemic examination. Presence or absence of pallor, icterus, lymphadenopathy, hepatomegaly and splenomegaly was particularly mentioned.

Complete hemogram; Red blood cell indices MCV(Mean corpuscular volume), MCH(Mean corpuscular hemoglobin) and MCHC(Mean corpuscular hemoglobin concentration); reticulocyte count; bone marrow examination (bone marrow aspiration and trephine biopsy) were performed in every case. Severity of pancytopenia was calculated as criteria defined by Santra G and Das BK (Santra *et al.,* 2010) according to which anaemia was defined as mild (Hb >9–12 gm%), moderate (Hb 5–9 gm%) and severe (Hb < 5 gm%).Leucopenia was defined as mild (leucocyte count > 3,000/mm^3), moderate (leucocyte count 1,000–3,000/mm^3) and severe (leucocyte count < 1,000/mm^3). Thrombocytopenia was defined as mild (platelet count > 50,000/mm^3), moderate (platelet count 20,000–50,000/mm^3) and severe (platelet count < 20,000/mm^3).

Some investigations were performed in selected cases to find out the cause of pancytopenia as warranted by the clinical context and the results of baseline investigations like USG abdomen and liver function tests (SGOT, SGPT, SAP, S. Bilirubin, S. Protein) for hepatitis and chronic liver disease, serum vitamin B12 and folic acid assays for megaloblastic anemia, anti-nuclear factor (immunofluorescent method) for SLE, viral serologies for HIV, hepatitis B virus, Hepatitis C virus and dengue; flow cytometry for CD55 and CD59 for PNH; chest X-ray, montoux test for disseminated TB; serum protein electrophoresis, urine for bence jones protein and X-ray skull for multiple myeloma. The data obtained was subjected to standard stastical analysis. The values were represented in number (%age) and mean±S.D.

Observations: The study included 100 adult patients (14-65 years) with pancytopenia who presented to Pt. B. D. Sharma, PGIMS Rohtak. The mean age of the study population was 42.87±15.54 years with range of 14 to 65 years. There were 57 males and 43 females in the study group with a male to female ratio (M:F) of 1.3:1.The most common symptom observed was generalized weakness/fatigue in 100% cases followed by fever (30%), shortness of breath (24%), palpitation(14%),bleeding manifestations in 19% of cases and pedal edema was documented in 9% cases (Table-1).

Table 1. Clinical symptomatology in pancytopenia

SYMPTOMS	% OF CASES
Generalised weakness / fatigue	100
Fever	30
Shortness of breath	24
Palpitation	14
Bleeding manifestations	19
Swelling on feet	9
Others	5

On examination, pallor was present in 100% cases, hepatomegaly in 31% of cases, splenomegaly in 27% of cases, icterus in 14%of cases, and lymphadenopathy was in 11 cases (Table-2).

Table 2. Clinical examination in pancytopenia

EXAMINATION	% OF CASES
Pallor	100
Icterus	14
Lymphadenopathy	11
Hepatomegaly	31
Splenomegaly	27

Mean hemoglobin in 100 patients was 5.66±1.94 g/dl. Anemia was moderate in 67% cases and severe in 33% cases. Mean total leukocyte count was 2470±974 cells/cumm. Leucopenia was mild in 26% cases, moderate in 67% cases and severe in 7% cases. Mean platelet count was 61, 626±24, 140 cells/cumm. Thrombocytopenia was mild in 68% cases, moderate in 28% cases and severe in 4% cases (Table-3). Mean MCV, MCH and MCHC were 97.55±13.18 fl, 25.49±3.30 pg/cell and 34.39±2.85 g/dl respectively. Mean reticulocyte count was 1.60±0.8 %. Peripheral blood picture was dimorphic in 54% of cases followed by macrocytic in 25% of cases, normocytic normochromic in 20% and microcytic hypochromic in 1 % of cases. Bone marrow examination corresponded with final diagnosis in 96 of cases. Bone marrow was hypercellular in 64% cases, hypocellular in 31% cases and normocellular in 5% cases

Table 3. Severity of pancytopenia

	Anemia (% of cases)	Leukopenia (% of cases)	Thrombocytopenia (% of cases)
Mild	0	26	68
Moderate	67	67	28
Severe	33	7	4

Table 4. Etiological spectrum of pancytopenia

S.no.	Diagnosis	Female N(%)	Male N(%)	Total/(%)
1.	Megaloblastic anemia	21(53.8)	18(46.2)	39
2.	Aplastic anemia	11(37.9)	18(62.1)	29
3.	Aleukemic Leukemia	5(33.3)	10(66.7)	15
4.	Lymphoma	0(0.0)	4(100)	4
5.	Multiple myeloma	2(50.0)	2(50.0)	4
6.	MDS	1(50.0)	1(50.0)	2
7.	Myelofibrosis	2(100)	0(0.0)	2
8.	Infection	0(0.0)	2(100)	2
9.	Hypersplenism	0(0.0)	2(100)	2
10.	SLE	1(100)	0(0.0)	1
Total		43	57	100

Megaloblastic anemia constituted 39 cases. Pure vitamin B_{12} deficiency was observed in 27 cases. Pure folic acid deficiency was observed in 5 cases and combined deficiency of B_{12} and folic acid was observed in 3 cases. Therefore, out of 39 cases of megaloblastic anemia, nutritional cause was found in 35 cases. Megaloblastic anemia was followed by Aplastic anemia constituting 29% of cases. Next in series were patients of aleukemic leukemia accounting for 15% of cases. Out of 15 cases of leukemia, 7 were of ALL, 7 of AML and 1 of CLL. Four cases each of non hodgkin's lymphoma and multiple

myeloma were diagnosed. Two cases of each myelodysplastic syndrome, myelofibrosis and hypersplenism were found. One case each of malaria and hepatitis B were found. One case of SLE was also there (Table-4).

DISCUSSION

Pancytopenia is diagnosed when there is reduction in all three hematopoetic cell lines. Conventionally reduction in hemaoglobin, total leukocyte count and platelet count has been used for defining pancytopenia (Tilak *et al.,* 1999). Young *et al.,* 2006 described panctopenia with hypocellular and cellular bone marrow. Common causes of hypocellular marrow were acquired aplastic anemia, constitutional aplastic anemia and some myelodysplastic syndromes while causes of cellular bone marrow were divided among primary bone marrow disease and secondary to systemic diseases. Common causes of pancytopenia because of primary bone marrow disease were myelodysplastic syndromes, PNH and myelofibrosis while causes secondary to systemic diseases were SLE, hypersplenism and vitamin B12 and folate deficiency.

The pathological mechanism of pancytopenia may be ineffective erythropoiesis/ dyshematopoiesis, aplastic/ hypoplastic marrow, bone marrow infiltrative disorders/myelopthisis, hypersplenism or immunological mechanisms (Khanduri *et al.,* 2007). In our study population of 100 patients with a mean age of 42.87±15.54 years with range of 14-65 years, the maximum number of cases (26%) belong to older age group 56-65 years. This was in contrast to other studies which reported pancytopenia more in younger population. Niazi *et al.,* 2004 have also reported the commonest age group between 21 and 30 years of age. In study by Jain *et al.* 2013 22.4% cases presented between 31 – 40 years of age making it the commonest age group for presentation. There were 57 males and 43 females in our study with a male to female ratio (M: F) of 1.3:1. Male preponderance was also reported in other studies. The most common symptom found in our study was generalized weakness / fatigue (100%) followed by fever (30%), shortness of breath (24%), palpitation (14%) and bleeding manifestations (19%) of cases. These findings were comparable with study by Gayathri *et al.,* 2011 in which most common presentation was generalized weakness in 100% cases followed by dyspnoea (43.26%) and fever (38.46%). In study by Santra *et al.,* 2010 where aplastic anemia was leading cause of pancytopenia, more number of patients presented with bleeding manifestations (41.44%) and fever (50.45%) as compared to our study.

In our study,anemia was severe enough in all patients to manifest as pallor. It was comparable with both Indian studies by Santra *et al.,* 2010 and Gayathri *et al.,* 2011 where pallor was observed in 84.68% and 100% respectively. Icterus was observed in 14% cases in our study. Gayathri *et al.,* 2011 also reported icterus in 3.82% cases. The cause for this could be attributed to more number of cases of megaloblastic anemia in our study. Lymphadenopathy was present in 11% patients in our study which is much higher than in study by Santra *et al.,* 2010 (6.31%) and Gayathri *et al.,* 2011 (0.96%). This could be explained by higher prevalence of leukemia and lymphoma cases in our study. Hepatomegaly was present in 31% and splenomegaly was present in 27% of cases in our study. These findings were comparable with other studies. Santra *et al.,* 2010 reported splenomegaly in 44.14% cases and hepatomegaly in 24.32% cases. Gayathri *et al.,* 2011 reported splenomegaly in 35.57% cases and hepatomegaly in 26.92% cases.

Mean hemoglobin in 100 patients was 5.66 ±1.94 g/dl in our study. Anemia was, moderate in 67% cases and severe in 33% cases. In study done by Santra *et al.,* 2010, mean hemoglobin was 5.9±1.90g/dl and anaemia was severe in 57.66%, moderate in 39.64% and mild in 2.70% of the cases. Mean total leukocyte count was 2470±974 cells/cumm. Leucopenia was mild in 26% cases, moderate in 67% cases and severe in 7% cases in our study. In study by Santra *et al.,* 2010, the leucocyte count was 850–3,800/cumm. Mean TLC was 2633/cumm. 54.95% of the patients had moderate leucopenia, while 40.55% and 4.50% had mild and severe leucopenia, respectively. Mean platelet count was 61, 626±24,140 cells/cumm. Thrombocytopenia was mild in 68% cases, moderate in 28% cases and severe in 4% cases. In study by Santra *et al.,* 2010, mean platelet count was $45.20\pm38.60\times10^3$/cumm. 60.36% of the patients had a mild degree of thrombocytopenia, 25.23% had moderate and 14.41% had severe thrombocytopenia

Most common type of peripheral blood picture reported was dimorphic in 54% of cases followed by macrocytic in 25% of cases, normocytic normochromic in 20% and microcytic hypochromic in 1 % of cases in our study. In study by Gayathri *et al.,* 2011, blood picture was dimorphic in 37.5% of cases, macrocytic in 31.7%, normocytic normochromic in 15.3% and normocytic hypochromic in 15.3% cases. Bone marrow cellularity was reported hypercellular in 64% cases, hypocellular in 31% cases and normocellular in 5% cases. In contrast, Santra *et al.,* 2010 reported hypocellular bone marrow 45.95% and 54.05% had cellular marrow including hypercellular 37.83% and normocellular 16.22%.This could be explained by higher prevalence of aplastic anemia in study by Santra *et al.,* 2010.

In 39 patients with megaloblastic anemia, pure vitamin B_{12} deficiency was observed in 27 cases (69.23%). Pure Folic acid deficiency was observed in 5 cases (12.82%) and combined deficiency of B_{12} and folic acid (7.69%) was observed in 3 cases. These results may be comparable with study of Khanduri *et al.,* 2007 on 107 patients of megaloblastic anemia which revealed cobalamin deficiency in 65% cases, combined cobalamin and folate deficiency in 12% cases and pure folate deficiency in 6% cases. Thus 35 out of 39 cases of megaloblastic anemia in our study had nutritional cause.

Etiological spectrum of our study was comparable with other Indian studies where megaloblastic anemia was the leading cause of pancytopenia. Incidence of megaloblastic anemia was 39% in our study. Incidence of 72% was reported by Khunger *et al.,* 2002 and 74.04% by Gayathri *et al.,* 2011.Incidence of aplastic anemia varies from 10% to 52% among pancytopenic patients. The incidence of aplastic anemia in our study was 29%. Khunger *et al.,* 2002 found 14% cases of aplastic anemia. An incidence of 29.5%, was reported by Kumar *et al.,* 2001 Our study found subleukemic leukemia in 15% of cases.

Kumar *et al.,* 2001 reported 12.04% incidence of aleukemic leukemia. Khunger *et al.,* 2002 reported subleukemic leukemia in 5% cases. Other causes included lymphoma ,multiple myeloma, myelodysplastic syndrome, myelofibrosis, infections, hyperspleenism and SLE (17%). In most of the studies in other countries, aplastic anemia was the commonest cause which in contrast to Indian studies.

When the study was compared with western studies, it was observed that in western countries most common cause was neoplastic condition such as leukemia followed by aplastic anemia. Megaloblastic anemia was next common cause. A French study of 213 patients by Imbert *et al*., 1989 throws a marked contrast to the studies published in India and other developing nations. Malignant myeloid disorders represented 42% of the cases and aplastic anemia in 10 % of the cases whereas vitamin deficiencies accounted for only 7.5 % .similarly, Keisu *et al.* 1990, also showed acute leukemia in 32 % cases and aplastic anemia in 19 % cases,among 100 patients studied. This shows that clinico-hematological spectrum of pancytopenia differ according to the geographic region.

Conclusion

The present study on 100 patients of pancytopenia revealed that megaloblastic anemia was the most common cause of pancytopenia constituting 39% of cases. This could be due to higher prevalence of nutritional deficiency in our country. The next common cause in our series was aplastic anemia (29 %) and aleukemic leukemia (15%). However, in western countries, the most common cause of pancytopenia was leukemia followed by aplastic anemia.which happens to be the most common cause in western countries.

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