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Original Research Article

A clinico-hematological study of 95 cases of pancytopenia in a tertiary care hospital in India

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Abstract

Objectives: Pancytopenia is defined as the simultaneous existence of anemia, leucopenia and thrombocytopenia. It is not an uncommon clinico-hematological entity and such cases are encountered in our day-to-day clinical practice. Knowing the underlying pathology and determining its severity are the key to its appropriate management. The aim of this study was to obtain detailed clinical and hematological spectrum of the common pathological conditions producing pancytopenia and to determine the frequency of the various etiological factors.

Material and methods: It was a prospective study and 95pancytopenic patients were evaluated clinically along with haematological parameters in Central Laboratory, Department of Pathology, Mahatma Gandhi Medical College, Jaipur from a period of September 2015 to September 2017.

Results: A total of 95 patients were evaluated and the etiological factors were as follows: Megaloblastic anemia (71.6%), aplastic anemia (6.3%), hypersplenism (4.2%), connective tissue disorders (3%), infections (3%), subleukemic leukemia (3%), malaria (1%), multiple myeloma (1%), dengue (1%) and myelodysplastic syndrome (1%).

Conclusion: The present study on pancytopenia concludes that detailed hematological investigations and relevant hematological assays provide invaluable information in the evaluation of pancytopenic patients which further helps in systematic planning of the management of the case. In our study the most common cause of pancytopeniain India is megaloblastic anemia, seen in 71.5% of the cases. Thus, a large proportion of pancytopenia cases are treatable and the etiology causing them is reversible.

Keywords: Megaloblastic anemia, myelodysplastic syndrome, aplastic anemia, subleukemic leukemia.

1. Introduction

Bicytopenia is defined as the reduction in any of the two cell lines [1] and pancytopenia is reduction in all the three cell lines. [2] Till 1919, pancytopenia was not a discrete entity. The term pancytopenia was then used synonymously for hypoplasticanemia, the latter being the most common cause of pancytopenia in Western countries. [3,4] Pancytopenia is defined as the simultaneous existence of anemia, leucopenia and thrombocytopenia. The criteria for defining a case of pancytopenia are: Hemoglobin< 9gm/dl; Total leucocyte count < 4000/µl and platelet count < 100000/µl.[5]

Pancytopenia is not an uncommon clinico-haematological entity.[6] The presenting complaints are usually due to leucopenia, anemia or thrombocytopenia. [2] Pancytopenia is caused due to a multitude of etiological factors. The underlying mechanisms are- suppression of bone marrow growth and differentiation as seen in megaloblastic anemia; replacement of the normal bone marrow elements by malignant tissue like multiple myeloma, lymphomas and leukemias; bone marrow destruction by radiation or toxins as in hypoplasticanemia; myelofibrosis, hypersplenism, systemic infections and connective tissue disorders.[7,8]

Physical findings and preliminary hematologic investigations provide relevant information in the work up of pancytopenic patients and help in planning further investigations.[9] The present study was carried out with the aim to obtain detailed clinical and hematological

spectrum of the common pathological conditions producing pancytopenia, to determine the various etiological factors of pancytopenia which would further help in proper management of the patients.

2. Material and methods

The present prospective study was undertaken for a period of 2 years, from September 2015 to September 2017, at Central laboratory, Department of Pathology, Mahatma Gandhi Medical College, Jaipur. Patients of age groups 2-90 years and both sexes were included. Case selection was based on clinical features and supported by laboratory evidence, which included peripheral blood counts for hemoglobin, leukocytes and platelets. Inclusion criteria were presence of all 3 of the following: hemoglobin, <9 g/dL; total leukocyte count (TLC), <4,000 / µL; platelet count, <100,000/ µL.[2] Patients on myelotoxic chemotherapy were excluded.

A written informed consent was obtained from all the patients after having fully explained the purpose and protocols of the study as well as risk to the patients. In all patients, a complete relevant medical history including age, gender, smoking status, alcohol intake, history of any treatment, intake of or exposure to potentially toxic chemicals, agents or drugs, radiation exposure, history of symptoms such as bone pains, fever, night sweats, malaise, weight loss and pruritus was taken. A detailed meticulous physical examination of every patient was done for pallor, jaundice, hepatosplenomegaly, lymphadenopathy, sternal tenderness and gum hypertrophy. Basic hematological investigations like CBC, reticulocyte count, and peripheral smear examination were performed in each case. A bone marrow examination was done whenever and wherever required. Wherever indicated, other investigations performed included ESR, urine and stool examination, liver and renal function tests, other serological investigations; the investigative workup being directed by the suspected underlying pathology and the provisional diagnoses.

All the patients thus selected were investigated in a systematic manner, cause of pancytopenia was ascertained and the data was analyzed on the basis of etiology, clinical and hematological findings. Clinico-pathological correlation was done in all cases before reaching a definitive diagnosis.

2.1 Statistical methods

Collected data was analysed by frequency tables and percentages.

3. Results

A total of 95 patients who presented with pancytopenia were studied. Of the 95 cases, 58 (61%) were males and 37 (39%) were females with the male to female ratio of 1.56:1 showing slightly more occurrence in males. The age of the patients ranged from 4 to 90 years with the mean age of 34.9 years. 48% cases belonged to the age group of 21-40 years thus showing that pancytopenia is more common in the younger age group.

3.1 Presenting complaints and physical findings:

The commonest mode of presentation in the patients presenting with pancytopenia was generalized weakness which was seen in 90 (94.7%) cases; other main symptoms were dyspnea, fever, chills and rigors, weight loss and bleeding manifestations in the form of epistaxis, menorrhagia and melaena. The common physical findings were pallor, hepatomegaly, splenomegaly, with lymphadenopathy and bony tenderness in a few cases. The most common presenting complaint in our study is pallor which was seen in 83 (87%) cases, followed by splenomegaly in 38 (40%) cases.

3.2 Hematological parameters in the 3 subgroups of pancytopenia

Table 1: Hematological Parameters in three Subgroups of Pancytopenia

Parameters	Megaloblastic Anemia	Aplastic Anemia	Hypersplenism
Hb (gm/dl)	1.3-8.9	3.8-7.9	4.2-6.8
TLC (µL)	200-3900	900-2100	800-2420
Platelets (µL)	5000-90000	7000-50000	40000-59000

3.3 Frequency wise distribution of etiological factors of pancytopenia

Table 2: Distribution of Various causes of Pancytopenia

S. No.	Causes	No. of cases	Percentage (%)
1	Megaloblastic Anemia	68	71.57
2	Aplastic Anemia	6	6.31
3	Subleukemic Leukemia	3	3.15
4	Malaria	1	1.05
5	Multiple Myeloma	1	1.05
6	MDS	1	1.05
7	Dengue	1	1.05
8	Nutritional Anemia	4	4.21
9	Connective Tissue Disorders	3	3.15
10	Infection	3	3.15
11	Hypersplenism	4	4.21
	Total	95	100

Megaloblastic anemia was observed in 46 males and 22 females, their age ranging from 4 to 90 years, with a mean age of 34.9 years. Vitamin B-12 deficiency was found in 36 (52.9%) cases. Since B_{12} and folate levels could not be estimated as a routine, both folic acid and parenteral hydroxycobalamine therapies were administered to all, and they showed complete clinical and hematological remission. In the rest of the 32 (47%) cases of megaloblastic anemia, bone marrow aspiration studies were done and the bone marrow was hypercellular in all the cases. Bone marrow aspiration showed megaloblastic erythroid hyperplasia.

Aplastic anemia was seen in 6 cases; their age ranged from 15 to 78 years, with a male to female ratio of 2:1.Out of 6 cases of aplastic anemia, cause was not known in 3 cases and these were classified as idiopathic bone marrow hypoplasia. One patient was a farmer who had exposure to pesticides. Another patient gave history of treatment with carbamazepine for treatment of epilepsy. The third patient was on anti-thyroid medication for hyperthyroidism. Bone marrow showed hypocellularity with suppression of erythropoiesis, myelopoiesis and megakaryopoiesis. Nutritional anemia was diagnosed in 4 (4.21%) patients with pancytopenia presented who presented with both Vitamin B-12 and iron deficiency. Bone marrow was hypercellular in all the cases with presence of micronormoblastic erythropoiesis with varying degrees of megaloblastic maturation.

4 patients presented with pancytopenia where the cause was diagnosed as hypersplenism. The age of the patients ranged from 23 years to 32 years. Splenomegaly was seen in all the cases and hepatomegaly in 2 out of the 4 cases. We encountered 3 patients of subleukemic leukemia; their age ranged from 4 to 30 years. 2 cases in our study were diagnosed with B-ALL and one with AML Bone marrow was hypercellular in all the cases. Majority of the cells were myeloblasts and lymphoblasts. Blasts in all the 3 cases ranged from 34 to 43%. All the cases were confirmed with flow cytometric analysis.

4. Discussion

The age of the patients ranged from 4 years to 90 years of age. The mean age in our study was 34.9 years. The youngest and the eldest case both presented with pancytopenia due to megaloblastic anemia. Majority of patients in our study were in age group between 21-40 years with 48% cases belonging to this age group. Of the 95 cases, 58(61%) were males and 37 (39 %) were females. The male to female ratio is 1.56:1.Our findings are in accordance with other studies which also suggested that pancytopenia is more commonly seen in younger age group and is slightly more common in males.

The most common presenting complaint in our study is pallor which was seen in 83 (87%) cases, followed by fever in 58 (61%) cases. These findings ware similar to findings of Gupta *et al*[10] and Naseem *et al*[11]. Fever (47.7%) and bleeding (23%) were present in the patients in the study by Niazi and Raziq[12]. 9.5% patients in our study presented with bleeding manifestations. In the present study, splenomegaly was seen in 40 % and hepatomegaly in 27 % of the cases. The frequencies of splenomegaly and hepatomegaly are similar in various studies by Gayathri and Rao [13] and Tilak *et al*[19].

In our study, megaloblastic anemia presented as the most common cause of pancytopenia and was diagnosed in 71% of the cases. Incidence of 72% was reported by Khunger *et al*[14] and 74% by Gayathri and Rao [13]. The incidence of megaloblastic anemia in similar studies varied from 0.8 to 80 %[12]. The high prevalence of nutritional anemia in India has been cited for increase in frequency of megaloblastic anemia.[5] In our study apart from pallor, dyspnea in 36 (52.9%), fever in 39 (57.3%) and pain abdomen in 16 (23.5%) were the other clinical manifestations in patients of pancytopenia with megaloblastic anemia. Memon *et al*[15] in their study have described the presenting features of pancytopenia as pallor with varying degree of skin and mucosal bleedings. Bleeding manifestations were seen in 9.5 % cases in the present study. In the present study, 24 (35%) and 16 (23.5%) cases of megaloblastic anemia, presented with splenomegaly and hepatomegaly. Sweta *et al*[16] in their study found 29% and 11% cases of megaloblastic anemia with splenomegaly and hepatomegaly respectively. Bone marrow aspiration studies are uncommon in cases where diagnosis of megaloblastic anemias is suspected. If hematological assays are not available, bone marrow aspiration is indicated. In our study Vitamin B-12 deficiency by Vitamin B-12 assays were found in 36 (52.9%) cases of megaloblastic anemia.

In this study 6 (6.31%) cases were diagnosed as aplastic anemia. The male to female ratio is 2:1.These results are similar to studies done by Tilak *et al*[9] in which 7.7% incidence of aplastic anemia was found and Raphael *et al*[17] where 8.7% of the cases of pancytopenia presented with aplastic anemia. Out of 6 cases of aplastic anemia, cause was not known in 3 cases and these were classified as idiopathic bone marrow hypoplasia. One patient was a farmer who had exposure to pesticides. This should be considered as possibility for causing aplastic anemia as shown by the work of Snyder and Kocsis[18] in which they found association with aplastic anemia. Another patient gave history of treatment with carbamazepine for treatment of epilepsy. The third patient was on anti-thyroid medication for hyperthyroidism.

4(4.21%) patients with pancytopenia presented with both Vitamin B-12 and iron deficiency and the cases were diagnosed as nutritional anemia. The age of the patients ranged from 17-36 years. The main complaints were fever, easy fatigue and dyspnea. Bone marrow was hypercellular in all the cases with presence of micronormoblastic erythropoiesis with varying degrees of megaloblastic maturation. The study done by Devi *et al*[19] states 8% incidence of nutritional anemia and that by Metikurke *et al*[20] states it as 24%.

In our study 3(3.15%) cases who presented with pancytopenia were diagnosed as subleukemic leukemia. This is consistent with the study done by Sweta *et al*[16] with 2% incidence of subleukemic leukemia. In the studies done by Khodke *et al*[8] and Tilak V[9] 1.3% cases of pancytopenia presented with subleukemic leukemia.

We had 3 (3.15%) cases of pancytopenia due to infections. The incidence in similar studies varied from 0.5% to 25%. Two patients were diagnosed to be suffering with acute viral hepatitis. Other case was that of tuberculosis. The study done by Jain and Nainwadekar[21] has also shown pancytopenia due to acute viral hepatitis and tuberculosis.

3(3.15%) cases in the present study with pancytopenia had connective tissue disorder (SLE).The main presenting complaints were fever, rash and joint pain. All the patients presented with raised ESR and were ANA positive. Studies done by Azaad *et al*[22] and Osama *et al*[23] also state SLE as one of the causes of pancytopenia with an incidence of 4% and 6% respectively.

In this present study, 1(1.05%) patient of pancytopenia was diagnosed with multiple myeloma. The patient presented with fever, generalized weakness, and bony tenderness. Serum electrophoresis showed M-band. There were 43% plasma cells in the bone marrow aspirate. Studies done by Sweta *et al*[16], Gayathri and Rao[13] and Jain and Naniwadekar[21] report the incidence of multiple myeloma presenting with pancytopenia as 2%, 0.96% and 0.8% respectively.

Malaria was present in 1(1.05%) of the total cases in our study. The peripheral blood smear showed gametocytes of *plasmodium vivax*. Studies conducted by Dasgupta *et al*[24] had 2% incidence of malaria with pancytopenia while those by Gayathri and Rao[13] had an incidence of 1.93%.

We found a single (1.05%) case of pancytopenia due to Myelodysplastic Syndrome (MDS) of Refractory anemia with excess blasts type 1(RAEB-1). Similar studies report the incidence of MDS varying from 0% to 18%. MDS-RAEB type present with pancytopenia more commonly than other types of MDS.[14,25]

Table 3: Frequency of Various Causes of Pancytopenia in Different Studies

Study	Country	Year	No. of Cases	Most Common Cause	Second Most Common Cause
Tilak *et al*[9]	India	1998	77	Megaloblastic Anemia (68%)	Aplastic Anemia (7.7%)
Khodke *et al*[8]	India	2000	166	Aplastic Anemia (29.5%)	Megaloblastic; Anemia (22.3%)
Khunger *et al*[14]	India	2002	200	Megaloblastic Anemia (72%)	Aplastic Anemia (28%)
Gayathri and Rao[13]	India	2011	104	Megaloblastic Anemia (74%)	Aplastic Anemia (18.3%)
Jain and Naniwadekar[21]	India	2013	250	Hypersplenism (29.2%)	Infection (25.6%)
Sweta *et al*[16]	India	2014	100	Megaloblastic Anemia (66%)	Aplastic Anemia (18%)
Dasgupta *et al*[23]	India	2015	248	Aplastic Anemia (33.47%)	Megaloblastic Anemia (21%)
Present Study	India	2017	95	Megaloblastic Anemia (71%)	Aplastic Anemia (6.31%)

5. Conclusion

Pancytopenia is not an uncommon hematological problem. As severity of pancytopenia and its underlying etiology determine the management of the case, therefore, the identification of the correct cause is essential. There is limited data on pancytopenia which demands for continued research in this area.

The present study on pancytopenia concludes that detailed hematological investigations, bone marrow examination and relevant hematological assays provide invaluable information in the evaluation of pancytopenic patients. This further helps in systematic planning of the management of the case.

In our study the most common cause of pancytopenia is megaloblastic anemia, seen in 71.5% of the cases. This corresponds to the findings observed in other similar studies done in India. So, the nutritional habits of most of the vegetarian population in our country should be supplemented with regular intake of Vitamin B-12 and folic acid to avoid the occurrence of megaloblastic anemia.

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