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Authors: Parul Singhal, Adreena Mittal, Ritvija Dixit

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A study of etiological spectrum in 106 cases of pancytopenia

Parul Singhal [1], Adreena Mittal [2], Ritvija Dixit [3]

[1] Department of Pathology, Santosh Medical College, Ghaziabad, UP, India

[2] Department of Pathology, Saraswathi Institute of Medical Sciences, Hapur, UP, India

[3] Department of Physiology, Amrita Medical College, Faridabad, Haryana, India

Corresponding author: Parul Singhal**,** email: dr_singhal_parul@yahoo.co.in, vicharpraveen@gmail.com

ORCID

PS: 0000-0002-7614-3011

ABSTRACT

Introduction and aim. Pancytopenia is the simultaneous presence of anemia, leucopenia and thrombocytopenia. The aim of this work was to study the etiological spectrum of pancytopenia in the National capital region of India, and evaluate the relationship of pancytopenia with serum vitamin B12 levels.

Material and methods. This study is of a prospective and analytical type conducted on patients attending the outpatient and inpatient department of Santosh Medical College and the Saraswathi Institute of Medical Sciences tertiary care centers in NCR. Complete blood counts and peripheral blood smear examination was used for morphological classification and typing of anemia. Bone marrow aspiration and vitamin B12 estimation was performed where required.

Results. The maximum number of pancytopenia cases were etiologically attributed to megaloblastic anemia (64.2%) followed by aplastic anemia (19.8%). Malaria was attributed to 6.6% cases of pancytopenia. Iron deficiency anemia and tuberculosis both accounted for 1.9% of cases. each. A history of drug intake and mixed nutritional anemia each contributed to 2.8% of cases. Serum vitamin B12 levels showed a significant relationship with pancytopenic cases.

Conclusion. In our study, the main cause of pancytopenia is megaloblastic anemia which responds very well to treatment if diagnosed correctly in time. A detailed hematological assessment along with vitamin B12 levels should be evaluated in all cases of pancytopenia irrespective of the etiological categorization.

Keywords. anemia, aplastic, leucopenia, megaloblastic, pancytopenia, thrombocytopenia

Introduction

Pancytopenia is the simultaneous presence of anemia, leukopenia as well as thrombocytopenia. The cause is usually a decrease in the production of hematopoietic cells in the bone marrow due to infections, toxins, infiltration of malignant cells, chemotherapy or radiation. For effective management of pancytopenia, its identification is very important. The clinical symptoms of pancytopenia are variable.[1]

Marrow cellularity and composition vary based on the underlying pathological condition.

The marrow is usually hypocellular when pancytopenia occurs due to a primary production defect. Normocellular or hypercellular marrow is seen when cytopenia occurs because of ineffective hematopoiesis, invasive bone marrow procedures, and increased peripheral utilization or destruction of cells. Pancytopenia was not known as a discrete hematological entity before 1919. This term was used as a synonym for aplastic anemia, which is a life-threatening disorder leading to failure of bone marrow, and is associated with a high mortality if left untreated. Aplastic anemia is two to three times more common in Asia than in Europe. Its exact incidence is not clear in India due to the dearth of epidemiological studies. However, in an epidemiological study of children in and around Lucknow, India, the statistics show that the annual incidence of aplastic anemia is around 6.8 cases per million.[2]

Peripheral cytopenia results when there is a reduction in any of the cellular elements of the blood, i.e. red blood cells, white blood cells or platelets. Bicytopenia is the reduction of any of the two cellular elements, the symptoms attributable to anemia or thrombocytopenia. Pancytopenia is reduction of all the three types of cells. In adults with pancytopenia, hemoglobin levels fall below 13.5 g/dL in males and 11.5 g/dL in females, the leucocyte count is less than 4×10^9/L (or absolute neutrophil count of less than 1800 per mL), and the platelet count less than 100×10^9/L. Leukopenia is primarily seen as neutropenia since neutrophils constitute the majority of the leukocytes.[2,3]

This reduction in the number of cells occurs due to increased destruction, reduced production, or increased pooling in the spleen or other organs. Primary or secondary involvement of bone marrow is seen in most of the cases. There are various neoplastic and non-neoplastic causes of pancytopenia. In most cases, pancytopenia occurs due to nutritional deficiencies, thus it can be treated and is reversible. Proper diagnostic evaluation of pancytopenia needs detailed clinical history, physical examination and hematological assessment including precise peripheral blood smear examination and if needs, bone marrow evaluation.[3]

The underlying pathophysiology depends on the cause of pancytopenia. In aplastic anemia, the pathophysiology is an autoimmune-mediated T cell activation which leads to destruction of the hematopoietic stem cells. Bone marrow suppression is also caused by direct cytotoxic effects of medications such as methotrexate, anticonvulsants, and chemotherapeutic agents. Ineffective hematopoiesis is observed in the bone marrow of myelodysplastic syndrome.

The clinical presentation varies widely from mild pancytopenia which may be asymptomatic to severe pancytopenia which may lead to life-threatening emergencies.[4] Patients can manifest any of the decreased

cell lines. Anemia presents as shortness of breath, fatigue and chest pain. Leukopenia manifests as increased infections, while thrombocytopenia presents with bruising, petechiae, and propensity for bleeding. Patients with severe neutropenia suffer from severe infections. Patients with underlying liver disease can present with anorexia, nausea, or lethargy. Patients with splenic sequestration can present with left upper quadrant pain. Constitutional symptoms are seen in patients with underlying autoimmune disorders or malignancies.[5]

Medical history is of utmost importance for an effective evaluation of pancytopenia. It must include investigating the symptoms of autoimmune conditions, malignancies, recent infections, medications, chemotherapy, or radiation therapy. A detailed history of nutritional status should be taken. For inherited aplastic anemia, family history should also be taken into account.

Physical examination may show pallor, petechiae, ulcers and rashes. Signs of underlying liver disease may be seen in patients with cirrhosis. Splenomegaly may be seen in patients with splenic sequestration. Lymphadenopathy can be seen in patients with infections and lymphoma. In patients with eating disorders and alcoholism, the subtle signs of nutritional deficiencies must be evaluated. The neurological examination is a must as it may highlight any impairment of proprioception with a positive Romberg test and ataxia, suggesting subacute combined degeneration of the spinal cord secondary to vitamin B12 (cobalamin) deficiency and macrocytic anemia.[2,5]

Preliminary investigations include a complete blood count and reticulocyte count to determine whether pancytopenia is secondary to decreased production or not. The mean corpuscular volume will indicate megaloblastic anemia. A peripheral blood smear may show abnormal cells such as blasts, dysplastic leukocytes, and immature cells. The investigations should also include assessment of vitamin B12 and folate levels, liver function tests, and lactate dehydrogenase levels. Infections shall also be considered because pancytopenia can be associated with infections such as HIV, malaria, and tuberculosis.[6]

In pancytopenia cases secondary to an acute viral infection, no further tests are required as these infections get cured on their own speedily. In cases of severe infections with sepsis, the termination of the infection and sepsis will also automatically correct.

Bone marrow aspiration and biopsy must be done to evaluate the status of the bone marrow stem cells if no specific etiology is found. The bone marrow aspiration can establish the diagnosis for pancytopenia in 75% of cases.[7] Pathological examination of the bone marrow biopsy is helpful in malignant etiologies. It can show a clonal population of cells, primary/secondary malignant cells, acellular marrow, fibroblasts, granulomas from tuberculosis, sarcoidosis, or fungal infections.[7]

Treatment is designed on the basis of the underlying etiology for pancytopenia. Nutritional deficiencies, if any, should be corrected. Hematologic consequences include macrocytosis, hypersegmented neutrophils, leukopenia, thrombocytopenia, and rarely, pancytopenia. In fact, pancytopenia, in which all blood cell lines are decreased, is found in only 5% of patients with a known B12 deficiency. [9]Any drug that may have

precipitated the disease should be discontinued with immediate effect. Treatment of infections such as HIV or tuberculosis should be started immediately. If an autoimmune condition or malignancy is diagnosed, it should be treated. Aplastic anemia secondary to viral infections such as parvovirus is temporary and symptomatic treatment is sufficient. For patients with severe aplastic anemia, treatment options include hematopoietic stem cell transplant and immunosuppression.[8,9]

Various studies have been done to evaluate the causes of pancytopenia, both benign and malignant. However, very few studies enumerate the specific causes related to pancytopenia encountered in daily hospital practices. The bone marrow correlation is also not emphasized in most studies.

Aim

Our study was targeted to illustrate the causative factors of pancytopenias in hospital patients who were sometimes discovered even accidentally after being admitted with epistaxis or breathlessness. Vitamin B12 deficiency in the absence of megaloblastosis leading to pancytopenia was the most important finding of our study.

Material and methods

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the protocol approved by the Ethical Committee of Santosh Medical College, Santosh Deemed to be University, NCR, India (811/2020/SMC).

The subjects of this prospective study included all adult patients presenting with pancytopenia in the age group between 18 to 60 years who were treated either at the Hematology Department of Santosh Hospital or Saraswathi Institute of Medical Sciences over a period of 2 years from March 2020 to December 2022. Patients on myelotoxic chemotherapy, who were uncooperative or did not give consent and in whom bone marrow examination was contraindicated were excluded from the study. Diagnosed cases of malignancy, including leukemia, receiving chemotherapy or radiotherapy, and patients taking vitamin B12 and Folid acid supplements were also excluded from the study. Out of 118 patients presented to us with pancytopenia, 12 meet exclusion criteria. So, finally 106 patients were included in our study.

Diagnostic criteria for pancytopenia is:

i) hemoglobin less than 10 gm/dL,
ii) total leucocyte count <4000/mm^3,
iii) platelet count less than 1,000,000/mm^3.[10,11]

Detailed clinical history regarding generalized weakness, fever, bleeding tendencies and other symptoms was taken. An examination was performed, pallor, hepato-splenomegaly, lymphadenopathy, and petechiae were assessed.

Blood was withdrawn in EDTA vials for Complete blood counts and peripheral blood smear examination. Hemoglobin (Hb), total leucocyte count (TLC), differential leucocyte count (DLC), platelet count (PC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were assessed. Complete blood counts were carried out using Nihon Coden Automated Hematology Analyzer based on the principle of impedance. Peripheral smear were stained using Leishman Giemsa stain for all the cases and examined in detail. Peripheral smear was used for morphological classification and typing of anemia.

Bone marrow aspiration from iliac crest was done in 28 cases where needed using 16G needle and smears fixed in methanol and stained with MGG. The smears were assessed in detail.

Data was recorded in MS Excel and imported in SPSS v20.0 software (IBM, Armonk, NY, USA) to analyse the variables like mean, median and standard deviation.

Chi-square test and Fisher's Exact test were employed to compare the findings.

Results

In this study, out of the total 106 patients , there were 75 males (70.75%) and 31 females (29.25%) patients and male to female ratio was found to be 2.4:1.

The age distribution shows maximum number of patients in the age group of 20 to 30 years (30.2%) followed by 30 to 40 year group (23%). The minimum number of pancytopenia cases fall in the 50 to 60 year category (9%) (Table 1).

Table 1. Age wise distribution of cases

Age (years)	Number of cases	Percentage
12–20	15	14.2
20–30	32	30.2
30–40	23	21.7
40–50	17	16
50–60	9	8.5
>60	10	9.4

The maximum number of pancytopenia cases were etiologically attributed to megaloblastic anemia (64.2%) followed by aplastic anemia (19.8%). 6.6% cases of pancytopenia resulted due to malaria. Iron deficiency anemia and tuberculosis resulted in 1.9% cases each. 3 cases (2.8%) each were attributed to history of drug intake and mixed nutritional anemia (Fig. 1).

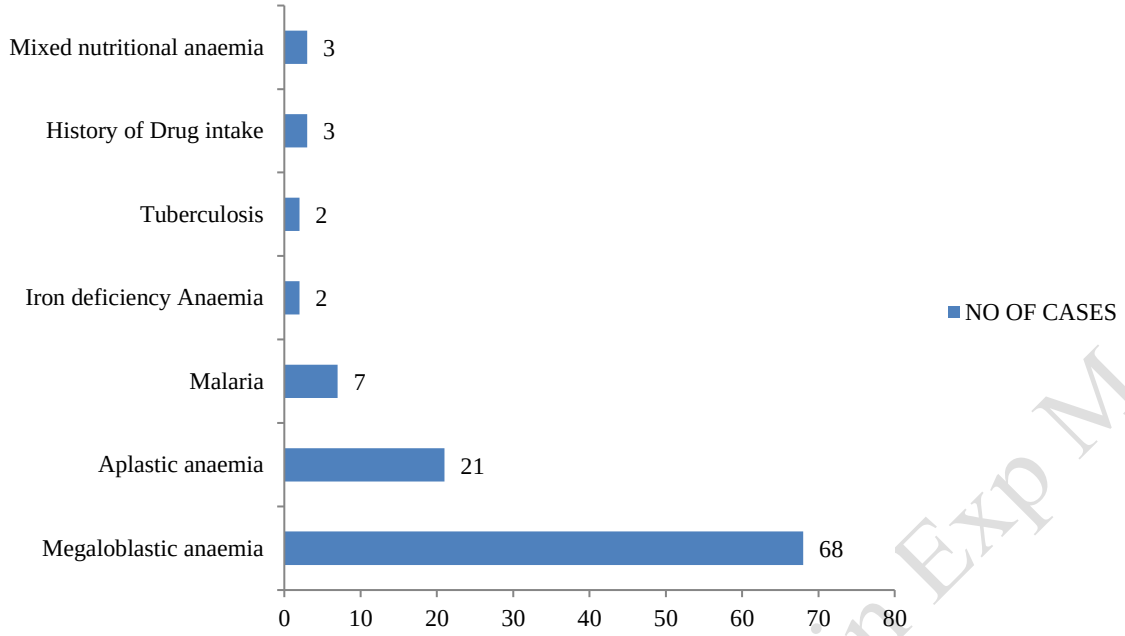

Fig. 1. Etiological distribution of pancytopenia cases

Peripheral smears revealed anisocytosis in 90% cases. Predominant macrocytic picture (cases of megaloblastic anemia) was seen in 60 cases, hyper-segmented neutrophils in 50 cases, normocytic picture in 24 cases, dimorphic in 15 cases and microcytic in 7 cases. Relative lymphocytosis and plasma cells were seen in peripheral smear in 21 cases of aplastic anemia. A few immature cells were discovered in the cases of megaloblastic anemia (Table 2).

Table 2. Peripheral blood findings in 106 cases of pancytopenia

Peripheral Blood Findings	No of cases	Percentage (%)
Normocytic	24	22.6
Macrocytic	60	56.6
Microcytic	7	6.6
Dimorphic	15	14.2
Anisocytosis	90	84.9
Hypersegmented polymorphs	50	47.2
Lymphocytosis	21	19.8
Plasma cells	21	19.8
Immature cells	5	4.7

Vitamin B12 estimation was done in all the patients and it was found that a total of 80 patients were vitamin B12 deficient, i.e. <200 pg/mL. 60 out of 68 patients of megaloblastic anemia showed vitamin B12 deficiency. 15 out of 21 aplastic anemia patients had vitamin B12 levels below 200 pg/mL. This pointed out to the fact that vitamin B12 deficiency has a direct significant association with Pancytopenia. Also, in cases of severe deficiency, an aplastic blood picture can manifest itself. The p value derived by Pearson Chi-Square test was found to be <0.05, i.e significant and conclusive of the fact that vitamin B12 deficiency is linked closely with pancytopenia.

Table 3. Chi Square p value – vitamin B12 deficiency associated with causes of pancytopenia

		B12 deficiency <200 pg/mL	
		No	**Yes**
Causes	Aplastic anemia	6	15
	Drug intake	3	0
	Iron deficiency anemia	2	0
	Malaria	6	1
	Megaloblastic A	8	60
	MNA	0	3
	Tuberculosis	1	1
Total		26	80
Chi-Square Tests			
	Value	df	p
Pearson Chi-Square	37.386	6	<0.05
Likelihood Ratio	35.202	6	<0.05
Fisher-Freeman-Halton Exact Test	31.717		

Discussion

In this study of pancytopenia patients, the highest incidence of 30.2% was in the age group of 20–30 followed by 21.7% in 30–40 age group, with a mean age of 35.53±1.467 years. Similarly, Khodke et al. found the maximum number of pancytopenia in the age group of 12–30 years.[4] About 10% of the cases were above 50 years. Jha et al. and Ishtiaq et al. in their studies found mean ages to be 30 years and 36.7 years, respectively.[14,15] Niazi and Raziq in their study found most common age group of pancytopenia in the range from 21 to 30 years.[16] The common age of 20-30 years clearly shows the increased demand and comparative reduced intake of nutritious food in this age. The high dependence on vegetarian food and

incorporation of junk food in diet of young individuals make them prone to vitamin B12 deficiency causing increased incidence of pancytopenia.

In this study, out of the total 106 patients, there were 75 males (70.75%) and 31 female (29.25%) patients and male to female ratio was found to be 2.4:1.The male to female ratio in the study by Jha et al. was 1.43:1.[14] The ratio was 1.3:1 in the study by Khodke et al.[4] The study by Niazi and Raziq has given the male to female ratio of 2:1.[17] The higher number of male patients seeking medical advice accounts for the male to female ratio being 2:1.

In the present study, 64.2% cases were diagnosed as megaloblastic anemia thereby being the most common cause of pancytopenia while in other similar studies it varied from 0.8% to 80%. The high prevalence of nutritional anemia in India has been cited for increase in frequency of megaloblastic anemia. The age of the patients in this study varied from 12 to 80 years with mean age of 39.14±3.93 years. The male to female ratio was 1.6:1 clearly pointing to the fact that female health is neglected for a long time making the situation worse and the prognosis compromised.

In the present study most common presentation was pallor in 104 cases and early fatigue in 91 cases followed by dyspnea in 54 patients. Fever was the next common presentation in 53 patients followed by splenomegaly in 32 patients and bleeding in 26 cases. Hepatomegaly was seen in 17 cases. Memon et al. in their study have described the presenting features of megaloblastic anemia with pancytopenia as pallor with varying degree of skin and mucosal bleedings.[5] Bleeding manifestations were seen in 24.5% cases in the present study. Pallor is found to be associated with low hemoglobin seen in all anemics, thereby making it the commonest presentation. Reduced platelet counts lead to bleedings from various sites. Hepatomegaly and splenomegaly can be associated with extramedullary hematopoiesis and malaria.[13]

Megaloblastic anemia is characterized by ineffective erythropoiesis leading to macrocytes which are sequestrated in the spleen leading to mild to moderate splenomegaly.[18] Hepatomegaly on the other hand results from extramedullary hematopoiesis.[13,14] In our study, 30.19% cases of megaloblastic anemia presented with splenomegaly and 16% with hepatomegaly. Ishtiaq et al. in their study found 15.4% and 17.9% of megaloblastic anemia with splenomegaly and hepatomegaly respectively.[9] Hepatomegaly (66%) and splenomegaly (21%) were seen in the study done by Keisu et al. in patients with megaloblastic anemia.[19]

In the present study, 68 cases of megaloblastic anemia patients had macrocytic RBCs and 60 cases had hyper-segmented neutrophils, which are the diagnostic features. Increased MCV was found in 62 patients; normal MCV was found in 6 patients and decreased MCV found in 3 patients with mixed nutritional deficiency having both megaloblastic anemia and iron deficiency. MCV is usually increased in severe megaloblastic anemia. Reticulocytes counts below 2% were seen in all 68 patients with megaloblastic anemia. This may be due to the abnormal maturation process. The cellularity of bone marrow ranged from 75% to 95%. Erythroid hyperplasia with predominance of precursors were also noted in the bone marrow aspiration of the megaloblastic anemia. Giant metamyelocytes, hypersegmented neutrophils and an

abnormal proliferation and maturation in the erythroid precursors with large megaloblastic erythroblasts were present in bone marrow of all patients of megaloblastic anemia.[18-20]

In this study, 19.4% cases were diagnosed as aplastic anemia, age of the patients varied from 15 to 74 years with the mean age of 34±2.96 years. The male to female ratio was 6:1.3 and patients in this group were farmers and 2 were painters by profession who were exposed to insecticides and chemicals like benzene. These should be considered as possibilities for causing aplastic anemia. In this study all the cases diagnosed as aplastic anemia had reticulocytes counts below 1%.

In the present study most common presentation was pallor in 104 cases (98.1%) and early fatigue in 91 cases (85.8%) followed by dyspnea in 54 patients (50.9%). Fever was the next common presentation in 53 patients (50%) followed by splenomegaly in 32 (30.19%) patients and bleeding in 26 cases (24.5%). Hepatomegaly was seen in 17 cases (16.03%). These findings were similar to the findings of Memon et al. and Khodke et al.[5,7] Fever (47.7%) and bleeding (33.7%) were present in the patients in the study by Niazi and Raziq.[4] In the present study, splenomegaly was seen in 30.19% and hepatomegaly in 16.03% cases. The frequencies of splenomegaly and hepatomegaly were similar in various studies by Niazi and Raziq and Khodke et al.[4,7]

In this study, the disease processes resulting in pancytopenia in the peripheral blood in order of decreasing frequency were megaloblastic anemia (64.2%), aplastic anemia (19.8%), malaria (6.6%), history of drug intake (2.8%), mixed nutritional anemia (2.8%), iron deficiency (1.9%) and tuberculosis (1.9%).

The findings of our study corresponds with the findings of the study done by Khodke et al and Khunger et al. and Sweta et al. who found megaloblastic anemia 44%,74% and 66% respectively as the most common cause of pancytopenia, followed by aplastic anemia 14%, 14% and 18%.[7,6,15]

In the present study, megaloblastic anemia (64.2%) was the most common cause of pancytopenia. Incidence of megaloblastic anemia varies from 0.8% to 68% in different studies. In our country, high incidence of megaloblastic anemia may be due to high prevalence of nutritional deficiencies of vitamin B12, folic acid or both.[13,14]

Malaria (6.6%) was third most common cause of pancytopenia in this study. Similarly, Tilak and Jain in their study also described malaria as the third most common cause of pancytopenia.[7] In the study by Kumar et al. 3% of pancytopenia was due to malaria.[12]

Vitamin B12 deficiency (<200 pg/mL) was found to be a significant cause of pancytopenia even in patients who did not present with megaloblastic anemia on morphological assessment. The Chi Square test showed a significant p value of <0.05 amongst all the 106 cases irrespective of etiology.

A few limitations of the study include limited number of patients. A larger sample size will give a more comprehensive result for this study. Pancytopenia related to malignant disorders is not included in the study to keep it more focused on everyday clinical admissions.

Conclusion

Megaloblastic anemia was the most common cause of pancytopenia in this study followed by aplastic anemia among the non-malignant disorders. Mixed nutritional deficiency, malaria, tuberculosis and iron deficiency were found to be significant causes of pancytopenia. A comprehensive clinical and hematological workup helps in evaluating the etiology of pancytopenia. In addition, vitamin B12 deficiency is found to be a significant cause of pancytopenia.

Variation in the frequency of disorders causing pancytopenia has been ascribed to differences in methodology, stringency of diagnostic criteria, geographic area, period of observations and genetic differences, after analyzing the observations noted in the present study. Maximum diagnostic yield can be achieved by correlation with clinical findings, peripheral blood findings and with other laboratory and radiological parameters.

Declarations

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Author contributions

Conceptualization, P.S.; Methodology, P.S.; Software, R.D.; Validation, R.D.; Formal Analysis, R.D.; Investigation, P.S.; Resources, P.S.; Data Curation, P.S.; Writing – Original Draft Preparation, P.S.; Writing – Review & Editing, P.S. and A.M.; Visualization, A.M.; Supervision, A.M.; Project Administration, A.M.

Conflicts of interest

The authors of the given original work declare that there are no conflicts of interest.

Data availability

The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the protocol approved by the Ethics Committee of Santosh Medical College, Santosh Deemed to be University, NCR, India (811/2020/SMC).

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