International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 6|Issue 01 (January-February)|2023 Page: 60-66

Original Research Paper

Etiological Profile and Clinico-hematological Parameters of Pancytopenia at a University Hospital in Rajasthan

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Article Received: 02-12-2022 Revised: 22-12-2022 Accepted: 11-01-2023

ABSTRACT:

Introduction: Pancytopenia is defined as a reduction in the number of red cells, white cells, and platelets. It can manifest as a laboratory finding of many diseases which directly or indirectly affect the bone marrow function. **Objectives:** The study is aimed to evaluate the etiological causes of pancytopenia in adult patients in a university hospital. **Materials and Methods**: This is a prospective observational study over a period of one year conducted at a university Hospital in Rajasthan. All adult patients 18 years and above who were admitted due to pancytopenia between June 2021 and May 2022 were included and evaluated for etiology of pancytopenia. After a detailed history and medical examination, basic hematological investigations like complete blood count, reticulocyte count, and peripheral smear examination were performed in each case. Bone marrow aspiration was subsequently carried out in the indicated individuals. The etiological and clinico-hematological correlation was done in all cases before reaching a definitive diagnosis. Results: A total of 132 patients was evaluated. 76 (57.58%) were male and 56 (42.42%) were female. The mean age was 37.7 years. Easy fatigue and pallor were noted in all (n=132; 100%) patients. Breathlessness (n: 71; 53.78%) and splenomegaly (n: 60; 45.45%) were common clinical features. The etiological causes of pancytopenia were as megaloblastic anemia (n: 76; 57.58%), aplastic anemia (n: 26; 19.70%), hypersplenism (n: 12; 9.09%), acute leukemia (n: 7; 5.28%), malaria (n: 7; 5.28%), myelodysplastic syndrome (n: 2; 1.5%), and lymphoma (n: 2; 1.5%). Almost half of the patients had severe pancytopenia. Bone marrow examination was indicated in 68(51.5%) patients; although only 57(43.2%) consented for it. **Conclusion:** The etiological causes of pancytopenia vary depends on patients' age, gender, nutritional status, infections, and geographical areas. It should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever, and a tendency of mucocutaneous bleed. Serum B12 deficiency is the most common treatable cause of pancytopenia. Most of the etiological causes could be diagnosed with routine hematological investigations, without the need of a bone marrow examination. Also, many causes of pancytopenia are completely curable while others are manageable.

Key words: Pancytopenia, megaloblastic anemia, hypersplenism, myelodysplastic syndrome, malaria, bone marrow.

INTRODUCTION:

Pancytopenia is a reduction in the three major components of blood cells below the normal range leading to the simultaneous presence of anemia, leucopenia, and thrombocytopenia. It exists when the hemoglobin count is less than 13.5gm/dl in males or 11.5gm/dl in females, the leucocyte count is less than 4000/mm3 and the platelet count is less than 1.5 lakh/mm3.[1] Pancytopenia is not a disease by itself, rather it is a triad of cytopenia in peripheral blood smear consisting of anemia, leucopenia, and thrombocytopenia. Leukopenia is primarily seen as neutropenia since neutrophils constitute the most leukocytes. Pancytopenia can be a manifestation of a variety of diseases that primarily or secondarily affect the bone marrow.[2] It occurs either due to a fall in hematopoietic cell production as seen in cases of aplastic anemia, trapping of normal cells in the hypertrophied and overactive reticuloendothelial system as seen in hypersplenism, ineffective hematopoiesis in megaloblastic anemia, or malignant tissue in bone marrow, defective cell production, antibody-mediated sequestration, or destruction of cells. Pancytopenia can be due to disorders of bone marrow regulation, which can be further classified as either primary or secondary. It is commonly associated with multiple benign and malignant conditions. Pancytopenia could be a result of decreased production of the cells or increased destruction. Anyone presenting with pancytopenia requires a thorough evaluation to identify the underlying etiology. The presenting symptoms are usually attributable to anemia, leucopenia, or thrombocytopenia. Management and outcome of pancytopenia are determined by two factors- the severity of the pancytopenia and the underlying pathology. Thus, identification of the correct cause will guide us in implementing the effective management and appropriate treatment protocol. In Rajasthan, the etiological causes of pancytopenia in research studies are not well defined, so the present study has been undertaken to evaluate the various causes and to correlate the peripheral blood findings with relevant hematological and bone marrow findings.

Research Question:

What are the etiological causes and hematological findings in pancytopenia patients in this part of the country?

Aim and Objectives:

The study is aimed to evaluate the etiological causes of pancytopenia in adults. The objectives of the study are to observe the clinical features; to find out the etiological causes; and to reach a hematological diagnosis among adult patients of the pancytopenia in this part of the country.

MATERIAL AND METHODS:

The study was carried out over a period of one year from June 2021 to May 2022 in the department of General Medicine, Pacific Medical College, and Hospital, Udaipur. **Inclusion and exclusion criteria** were defined. The patients were explained in detail about the collection of data for the study. Informed written consent was obtained from bone marrow biopsy indicated patients. The study was approved by the institutional ethics committee. Inclusion criteria of the study were patients of both sexes aged18 years and above; the presence of all three of the following: hemoglobin (Hb) <13.5g/dL in males and 11.5 gm/dL in females, total leukocyte count (TLC) <4,000 /cumm and platelet count <150,000/ microlitre.[1] Patients on cancer chemotherapy and radiotherapy; and < 18 years of age were excluded. All patients were subjected to relevant detailed medical history including age, sex, smoking status, alcohol intake, history of any chronic illness, intake of or exposure to potentially toxic chemicals, agents, or drugs, radiation exposure, history of any symptoms like bone pains, fever, night sweats, malaise, weight loss, and pruritus were taken. A detailed physical examination of every patient in the study was done for pallor, jaundice, hepatosplenomegaly, lymphadenopathy, sternal tenderness, and gum hypertrophy. Hematological investigations including complete blood count, reticulocyte count, and peripheral smear, liver function tests, serum iron profile, serum B12 concentration, TSH, LDH and HIV by ELISA were done in each case. Abdominal ultrasound was performed in all patients of pancytopenia. Bone marrow examination was subsequently carried out in indicated patients only using Salah bone-marrow aspiration needle, under aseptic precaution. All the patients thus selected were investigated in a systematic and precise manner, the cause of pancytopenia was ascertained and the data were analyzed based on etiology, clinical and hematological findings. The etiological and clinico-pathological correlation was done in all cases before reaching a definitive diagnosis.

STATISTICAL ANALYSIS:

Continuous variables were described as mean and numbers. Percentile values were described with decimals.

RESULTS:

A total of 132 patients were included in the current study. The distribution of various etiological, clinical, and hematological parameters is described here in the detail.

A. Clinical findings:

Table 1. Sex distribution:

Gender	n=	%
Male	76	57.58%
Female	56	42.42%

Out of 132 patients, 76 (57.58%) were male and 56 (42.42%) were female. Male to female ratio was 1.35:1. The age ranged from 14 to 72 years with a mean age was 37.7 years. Most of the patients were in the third decade of life (Table 1).

Table 2. Common symptoms:

Presenting Symptoms	n=	%
Generalized fatigue and weakness	132	100%
Breathlessness	71	53.78%
Fever	56	42.42%
Weight loss	18	13.63%
Bleeding manifestation	15	11.36%

The commonest mode of presentation was generalized fatigue cum weakness seen in 132 (100%) patients, other symptoms were breathlessness, fever, and weight loss in 53.78%, 42.42%, and 13.63% respectively (Table 2).

Table 3. Physical findings and common signs:

Physical findings	n=	%
Pallor	132	100%
Splenomegaly	60	45.45%
Hepatomegaly	42	31.81%
Jaundice	12	9.10%
Lymphadenopathy	6	4.54%

The most common physical finding was pallor present in 100% of cases, followed by splenomegaly and hepatomegaly seen in 45.45% and 31.81% respectively (Table 3).

Etiological finding:

Table 4. Distribution of various causes of pancytopenia:

Causes	n=	%
Megaloblastic anemia	76	57.58%
Aplastic anemia	26	19.70%
Hypersplenism (chronic liver disease)	12	9.09%
Acute leukemia	7	5.28%
Malaria	7	5.28%
Myelodysplastic syndrome	2	1.50%
Lymphoma	2	1.50%

B. Hematological findings:

Anisocytosis of varying severity was the commonest morphologic type. The predominant blood picture on the peripheral smear was of macrocytic anemia, followed by dimorphic anemia. Peripheral smear also showed macrocytes followed by normocytic normochromic anemia and normocytic hypochromic anemia. Anemia, leucopenia, and thrombocytopenia were seen in all cases. The most common cause of pancytopenia was megaloblastic anemia seen in 31 cases (57 58%) followed by aplastic anemia (19.7%) and hypersplenism (9.09%) (Table 4). Megaloblastic anemia was observed in 47 males and 29 females. Hyper-segmented neutrophils were the commonest peripheral blood finding in megaloblastic anemia. Reticulocytosis was seen in 18 out of 132 cases of pancytopenia (13.6%). 27 (22.5%) patients had high LDH; while aplastic anemia (AA) was present in 20 male and 9 female patients. Aplastic anemia was twice in males as compared to females. The hemoglobin levels of patients in the current study ranged from 2 to 9.8 gm/dl. 49 cases (37.1%) had hemoglobin levels between 2 to 5 gm/dl suggesting severe degree of anemia at the time of presentation of pancytopenia. All 49 patients required blood transfusion. The TLC of patients in our study ranged from 900-4000/mm3. 82(62%) patients were in the range of 3000-

4500/mm3. The platelet counts of patients in our study ranged from 6,000/ mm3 - 1.40 lakh/mm3. Platelet counts <10,000, 10,000-20,000 and; 20,000-50,000 were observed in 7(5.3%), 20(15.2%) and 35(26.5%) patients respectively. 30(22.7%) patients had platelet counts between 50,000/mm3 - 1 lakh /mm3. Overall, 29(22%) patients required platelets transfusion. 57(43.2%) patients underwent bone marrow examination, although it was indicated in 68(51.5%) patients; 11 patients did not give consent for the same. Out of 44 cases of megaloblastic anemia who underwent BM biopsy, iron was increased in 32 (72.7 %) cases. Out of 9 cases of dimorphic anemia, iron was reduced in 4 (44.4%), Reticulin was normal in all cases except for myelodysplastic syndromes, in which it was increased. Dimorphic anemia, i.e., combination of iron deficiency and megaloblastic anemia in varying proportions were seen in almost half of the patients in the category of megaloblastic pancytopenia. Both the patients of myelodysplastic syndrome (MDS) had progressive pallor, bleeding manifestations, fever, and breathlessness as the presenting clinical features.

DISCUSSION:

There are a very limited number of studies done to study the various causes of pancytopenia in Rajasthan. A careful physical examination and history is imperative because bone marrow suppression may be caused by multiple environmental and genetic factors. The severity and presentation of pancytopenia vary due to the differences in causative factors such as geographic area, environmental factors, nutritional status, the prevalence of the infective disorder, genetic differences, gender, age, period of observation, and methodology. Many diseases cause pancytopenia. Vitamin B12 deficiency and infective causes are common in underdeveloped and developing countries, while malignant causes predominate in developed country.[3] The common presentation of anemia includes malaise, sleepiness, irritability, exercise intolerance, shortness of breath, and pallor. A rapid drop in red blood cell hemoglobin due to acute hemolysis may abruptly trigger clinical symptoms that are reminiscent of a large blood volume loss due to hemorrhage. In contrast, an insidious-onset anemia is associated with relatively mild symptoms as the cardiopulmonary and biochemical compensatory mechanisms activate over time. Leukopenia impairs the immune system's ability to fight infections. Neutropenia (low absolute neutrophil count [ANC]) is frequently encountered in clinical practice. Patients with severe neutropenia (defined as ANC <500/μL [0.5×10^9/L]) face a high risk of life-threatening bacterial and fungal infections. Acute onset neutropenia is a medical emergency. In the absence of trauma, normally thrombocytopenia does not lead to clinical symptoms until the count decreases below 10,000-20,000/μL. Patients with severe thrombocytopenia develop spontaneous bruising, bleeding, and petechiae. Menstruating females experience heavy and prolonged periods.[4] Although our study had small number of patients, it included pancytopenia cases living in southern Rajasthan from both urban and rural areas and all socioeconomic background. In the current study, the most common cause was serum B12 deficiency, followed by aplastic anemia and hypersplenism secondary to chronic liver disease (CLD). Serum B12 deficiency was the most common cause in the young adults whereas aplastic anemia and CLD more common in older adults. A study from South Africa of 195 cases with pancytopenia observed that bone marrow failure (67.7%), aplastic anemia (11%), serious infections (9.7%), and hypersplenism (7.7%), respectively were the common causes.[5] The incidence of megaloblastic anemia varies from 0.8% to 32.26% of all pancytopenia patients.[6,7] In the current study we observed high incidence of megaloblastic anemia i.e., 57.58%. Our study was supported by the study of Tilak et al, Kumar et al and Khunnger JM et al.[8-10] The incidence of megaloblastic anemia in these studies was 68%,37%, and 72% respectively. Our study show incidence of aplastic anemia was 19.7% which correlated with the study done by Khunger JM et al.[10] The incidence of aplastic anemia varies from 10.0% to 52.7% of all pancytopenia patients.[11,12] The commonest cause of pancytopenia reported from various studies throughout the world has been aplastic anemia.[13,14] This is in contrast with the result of our study in which the commonest cause of pancytopenia was megaloblastic anemia. This seems to reflect the higher prevalence of nutritional anemia in Indian subjects. The current study observed that leucopenia and thrombocytopenia in megaloblastic anemia are usually milder than anemia and that the reduction in leucocytes and platelets, increases with the severity of the anemia. Megaloblastic anemia is a common cause of macrocytic pancytopenia and by far the most readily treatable cause.[15] Hypersplenism was the cause of pancytopenia in 12 cases (9.09%) of our study. In hypersplenism, there is peripheral pooling or trapping and destruction of cells in an enlarged spleen resulting in cytopenia. Increasing severity of the condition causes pancytopenia, as is seen in patients with chronic liver disease and thus hypersplenism may come out to be a common cause for pancytopenia.[16,17] In our study, there was a 5.30% incidence of leukemia. Kumar R et al reported a 12% incidence of leukaemia.[9] This is supported by the study of Khunger JM et al which showed 5% incidence.[10] Out of 132 cases, 7 cases (5.28%) were due to malaria. In

previous Indian study the incidence of malaria related pancytopenia was 1% to 3.9%.[8-10] Studies from Europe reported fewer incidence of malaria related pancytopenia.[18,19] In our study, pancytopenia due to Myelodysplastic syndrome was noted in 2 cases (1,5%) with severe degree of anemia. Hypercellularity of bone marrow with abnormal cells confirmed the diagnosis. Pancytopenia due to lymphoma was noted in 2 cases (1.5%) in our study. Ma et al have described pancytopenia in a case of adult leukemia and lymphoma.[20] PNH is an acquired bone marrow disorder that leads to pancytopenia and thrombosis due to complement- mediated breakdown of blood cells. Destruction of blood cells causes pancytopenia.[21] Vitamin B_{12} and folate deficiencies are major causes of megaloblastic anemia. Causes of B_{12} deficiency include pernicious anemia, gastric surgery, intestinal disorders, dietary deficiency, and inherited disorders of B_{12} transport or absorption. The prevalence of folate deficiency has decreased because of folate fortification.[22] Clinical features of megaloblastic anemia include anemia, pancytopenia, jaundice, and typical megaloblastic marrow morphology.[23] Neurologic symptoms occur in B_{12} deficiency, but not in folate deficiency. Management includes identifying any deficiency, establishing its cause, and replenishing B_{12} or folate parenterally or orally. As a complication of chronic liver disease, portal hypertension diseases lead pancytopenia by hypersplenism.[24] MDS is the deterioration of blood cell production in the bone marrow and often accompanies with other hematopoietic stem cell diseases. It is especially diagnosed in older men with pancytopenia.[25] Bone marrow examination is extremely helpful in the evaluation of pancytopenia. 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., hypoplasia of marrow is found in aplastic anemia, hypoplastic MDS and paroxysmal nocturnal hemoglobinuria. Hypercellular marrow is found in megaloblastic anemia, MDS, hypersplenism caused by portal hypertension (CLD), malaria and autoimmune hemolysis. The findings of the current study will be a good clinical knowledge building material to be applied on etiology, clinical features, and hematological parameter; and the management of pancytopenia in this geographic area. Although, large-scale longitudinal, multicentric studies are required to know more about etiological causes of pancytopenia in this region.

Strengths Of the Study:

The major strength of this study is the quite large number of adult pancytopenia patients in a large university hospital. Ours is the first published study from the southern Rajasthan on etiology of adult pancytopenia. Furthermore, the bone marrow correlation with the etiology was the basis to start timey and effective treatment of the treatable cases of pancytopenia and improved quality of life as well as outcome of the sufferers.

Limitations Of the Study:

The current study has certain limitations. First, we could not examine bone marrow of all the indicated patients as 11(8.3%) patients did not give consent for it. Second, post-discharge follow-ups not done. Third, it is a single center study.

CONCLUSION:

Pancytopenia should be suspected on clinical grounds when a patient presents with unexplained fatigue, pallor, prolonged fever, and or a history of mucosal bleeding. The present study concludes that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients help understand the disease process and to diagnose or to rule out the causes of cytopenia. These are also helpful in planning further investigations and management. Megaloblastic anemia and aplastic anemia are the major causes of pancytopenia. Many causes of pancytopenia are completely curable while others are manageable. With the help of detailed clinical history, physical examination, and hematological investigations, etiology of pancytopenia can be diagnosed and timely effectively treated. Megaloblastic anemia predominantly due to serum B12 deficiency, particularly nutritional in origin seems to reflect the higher prevalence of pancytopenia in Indian patients. In our study bone marrow examination was needed only in half of the patients. In the current study most of the etiological causes of pancytopenia were associated with nonhematological and treatable diseases and were diagnosed with laboratory tests without the need of a bone marrow examination. A clinician should thoroughly search the easily treatable causes of pancytopenia including megaloblastic, parasitic, and dimorphic anemia. This will help to reduce patients suffering, improves the quality of life, and prolong survival; although etiological causes of pancytopenia and their rates may differ in each study from same and different countries.

Fundings:

No funding was received for this study.

Declaration Of Competing Interest:

Competing interests: none to declare.

Acknowledgments:
We are thankful to the pathology department and the ethical committee of Pacific Medical University.

Author Contributions:
JV proposed the original study idea and design, drafted the original manuscript. RKS and PG were the major contributors to the data analysis and assisted with editing the manuscript and reviewing the final article. SR and AM assisted with data analysis and reviewed the results. JK and KRS did literature review and proof readings. All authors read and approved the final manuscript

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