A Clinico-hematological evaluation of Pancytopenia: A Retrospective Cross-sectional study

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ABSTRACT

Objective: To determine the etiology, clinical and hematological manifestations of pancytopenia in patients presenting to pathology department for bone marrow examination.
Study Design: Retrospective cross-sectional study.
Place and Duration: At Hematology Department of Nishtar Medical University Multan, from 1st August 2015 to 30th August 2018.
Methodology: A total of 237 patients having pancytopenia of more than7-day duration who were referred for bone marrow examination were consecutively enrolled in the study. Complete history, clinical examination findings, results of complete blood picture, peripheral film, reticulocyte count, erythrocyte sedimentation rate (ESR), malarial parasites (MP), liver function tests (LFTs) ,renal function tests (RFTs) and viral markers (HBsAg, Anti- HCV) and abdominal ultrasound were also included in the study.
Results: A total of 237 (N) patients, including 137 males with a male: female ratio of 1.3:1, were included in the study. The age of the patients ranged from 10 to 80 years. The age group of 10 - 20 years showed the maximum number of patients (27.8%), followed by 21-30 years (25.3 %) and 31-40 years (17.2%). The commonest cause of pancytopenia was found to be megaloblastic anemia (27.0%) followed by aplastic anemia (15.6%) and acute leukemias (13.1%). Pallor (87.7%) and generalized weakness (83.5%) were the most common presenting clinical features followed by dyspnea (63.2%) and fever (62%).
Conclusion: Bone marrow examination can prove a cardinal diagnostic tool in establishing etiology of pancytopenia in patients presenting with non-specific symptoms like pallor and generalized weakness. Megaloblastic anemia and aplastic anaemia were commonest etiology of pancytopenia.
Keywords: Pancytopenia, Clinical evaluation, Haematological evaluation, Aplastic anemia, Megaloblastic anemia, Myelodysplastic Syndromes, Hypersplenism.

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INTRODUCTION

Pancytopenia can be due to a long list of causes and tests needed to reach a cause are too many, making diagnosis and its management very challenging to physician and haematologists[1]. Geographical differences, genetic makeup, exposure to drugs, radiations, infections and socioeconomic status also effect underlying cause of pancytopenia[2].

Clinically a patient is labelled as having pancytopenia if the hemoglobin is less than 13.5g/dl in males, 11.5g/dl in females, the WBC count is < 4 x 109/L and platelet count is <150x109/L[3].While hematological malignancies and marrow failure syndromes comprise a good proportion of pancytopenia, infections and nutritional deficiencies are important causative factors of pancytopenia that cannot be ignored either[4].

Pancytopenia clinically presents with symptoms of anemia, easy susceptibility to infections and bleeding manifestations in patients[5] and signs of spleen, liver and lymph node enlargement, fever and a tendency to bleed, weight loss and icterus[6]. The management and prognosis of such patients depends mainly in finding out the underlying cause of pancytopenia for which, examination of bone marrow is an extremely helpful tool[7].

Geographical variations, genetic mutations, differences according to age, sex, race, and prevalence of certain infections in those geographical areas are the main contributing factors leading to various disorders associated with pancytopenia[8-10]. In South Punjab malnourishment and infections are common and treatable causes of pancytopenia. By timely diagnosing the treatable causes of pancytopenia we can decrease morbidity. By timely starting therapy of fatal causes of pancytopenia like acute leukemia, malignant infiltration and aplastic anaemia we can decrease mortality. So, our study in South Punjab will help to formulate guidelines for optimal and timely diagnosis of etiology and to establish therapeutic approach by clinicians and hematologists. Our study is aimed to determine the etiology, clinical and hematological manifestations of pancytopenia in patients presenting to pathology department for bone marrow examination.

METHODOLOGY

This retrospective cross-sectional study was done in the Hematology section of Pathology Department, Nishtar Medical University from 1st Aug 2015 to 30th Aug 2018. The study was conducted after permission from ethics review committee, ethical committee letter No.1130/NMU&H, Multan. Medical records of two hundred and thirty seven (237) patients of either gender presenting with pancytopenia, between ages10-80 years, attending or admitted through OPD/Indoor of Nishtar Hospital Multan and having pancytopenia (hemoglobin <11 g/dl), total leukocyte count [TLC] <4x 10^9/L and platelet count <150 x 10^9/L)were included in this study .Already diagnosed cases of cancers, bleeding diathesis, aplastic anemia, chronic liver disease, pregnant females with pancytopenia and patients receiving chemotherapy for malignancy or who had received platelet transfusions recently were excluded from the study.
Detailed history and complete general physical examination findings ,abdominal ultrasound findings, complete blood picture including peripheral film, reticulocyte count, erythrocyte sedimentation rate (ESR), malarial parasites (MP), liver function tests (LFTs), renal function tests (RFTs),serum iron profile, B12/Folate levels, bone marrow cultures, Malaria parasite, HIV, immuno-stains for NHL and Bone marrow metastasis ,viral markers (HBsAg, Anti-HCV) results and bone marrow aspirate and bone marrow biopsy findings were retrieved from bone marrow record registers and included in study. All patients' medical registrations numbers who had pancytopenia were consecutively selected and their demographic, clinical and lab data was retrieved from bone marrow record registers and data put into specially designed proformas.

Data Analysis: Data was analyzed using SPSS version 22.0. Quantitative variables are presented as mean and standard deviation. Qualitative variables were expressed by frequency and percentage. P-value ≤0.05 was considered statistically significant.

RESULTS

A total of 237 patients, including 137 males and 100 females with a male: female ratio of 1.3:1, were included in the study. The age of the patients ranged from 10 to 80 years. The age group of 10 - 20 years showed the maximum number of patients (N=66 ,27.8%), followed by 21-30 years (N=60,25.3 %) ,31-40 years (N=41,17.2%) ,41-50 years (N=28,11.81%) ,51-60 years (N=22,9.2 %) ,61-70 years (N=12,5.06%) and least number of patients 08 (N=8,3.3%) in 71-80 years respectively.
Fig-1 – Frequency (percentage) of different clinical features at presentation in pancytopenia patients (N=237).

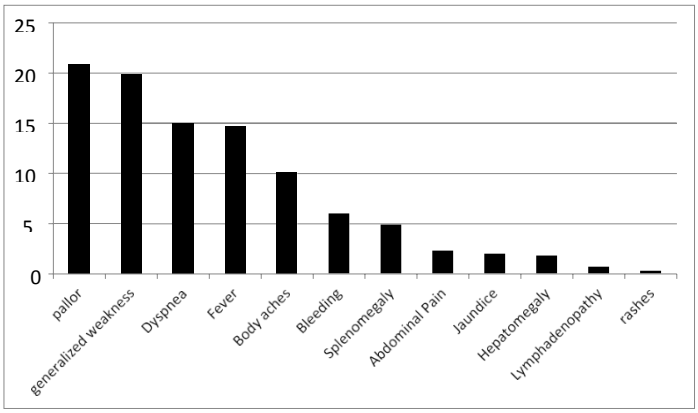

Figure-1: illustrates the clinical features at presentation of pancytopenia patients in this study. The commonest complaint was pallor in 87.7% (n=208) followed by generalized weakness found in 83.54 %(n=198), dyspnea found in 63.29 % (n= 150), fever found in 62 % (n=147) and least common was rashes 1.26% (n= 3).

Table-I: Bone marrow aspiration findings with regard to gender in pancytopenia patients (N=237)

Diagnosis	Male N (%)	Female N (%)	Frequency N (%)
Megaloblastic anemia	39(16.46 %)	25(10.54%)	64 (27.0%)
Aplastic Anemia	26(10.97%)	11(4.64%)	37(15.6%)
Acute Leukemia	17(7.17%)	14(5.9%)	31(13.1%)
Mixed deficiency anemia	10(4.21%)	12(5.06%)	22(9.3%)
NHL	13(5.48%)	08(3.37%)	21(8.9%)
Hypersplenism	05(2.1%)	09(3.79%)	14(5.9%)
MDS	06(2.535)	07(2.95%)	13(5.5%)
Hemophagocytosis	04(1.685)	03(1.26%)	07(3.0%)
Plasma cell myeloma	05(2.15%)	01(0.42%)	06(2.5%)
Erythroid Hyperplasia	03(1.26 %)	02(0.84 %)	05(2.1%)
Granulomatous infection	03(1.26 %)	02(0.84%)	05(2.1%)
Myelofibrosis	02(0.84%)	02(0.84%)	04(1.7%)
Metastatic tumor	01	02(0.84%)	03(1.3%)
Bone Marrow fibrosis	02(0.84%)	01(0.42%)	03 (1.3%)
Malaria	01(0.42%)	01(0.42%)	02(0.8%)
Total	137(57.80%)	100(42.19%)	237(100%)

NHL=Non-Hodgkin's Lymphoma
MDS= Myelodysplastic Syndrome

The most common bone marrow aspiration finding was Megaloblastic anemia in 27% patients, followed by megaloblastic anaemia in 15.6% patients, acute leukemia in 13 % patients and mixed deficiency anemias in 9.3 % patients and malaria were least common seen only in 2 patients respectively. Detail of different causes is described in table-I.

Table-ll: Case distribution according to cellularity (N=237)

Cellularity	No. of Cases (%)
Hypercellular	103 (43.5%)
Normocellular	52 (21.9%)
Hypocellular	48 (20.2%)
Moderately cellular	21 (8.9%)
Dry tap	13 (5.5%)
Total	**237 (100%)**

Distribution of the cases according to the bone marrow cellularity is shown in the table-ll. Hypercellularity was the most common finding observed in 43.5 % cases followed by hypocellular bone marrow found in 20.2 % pts. Dry tap was least common finding observed in 5.5 % cases.

DISCUSSION

Pancytopenia is quite common presentation in medical practice the highest percentage of cases was in 10-20 years age group and a male: female ratio of 1.3:1. However, National study conducted by Rehmani et al in Lahore in 2016 reported the highest percentage of cases of pancytopenia in 21-30 years age groups with a male: female ratio of 1.46:1 respectively[11]. Our results were similar with study conducted by Reddy et al[6] in India, where males were 54.8 % and females were 45.3% respectively.

Pallor was the commonest clinical presentation found in our study, followed by generalized weakness, dyspnea and fever were observed. Studies conducted by Reddy et al[6] documented similar findings; however, weakness, hepatosplenomegaly, bleeding manifestations and abdominal pain were reported as main presenting complaints in other study by Chandra et al[12] and Yadav et al[13].

Different studies conducted on Pancytopenia reported either aplastic anemia or megaloblastic anemia to be the commonest causes of pancytopenia (Table-lll). These variations in different studies have been ascribed due to difference in time period, genetic variations, geographical conditions, nutritional status, methodology employed, acerbity of diagnostic criteria and varying exposure to cytotoxic drugs[14].

In a Mexican tertiary care center study myelodysplastic syndrome was most common cause of pancytopenia seen in 20.2 % cases and megaloblastic anaemia was second most common cause[15]. In our study, the commonest cause of pancytopenia was found out to be Megaloblastic anemia due to Vitamin B12 and Folate deficiency bearing a striking similarity with studies from India[6,13] and a Pakistani study at Peshawar by Mehboob et al[16]. Nutritional deficiency of Vitamin B12 and folate is a well-known documented cause of Megaloblastic anemia leading to cytopenias such as anemia or thrombocytopenia alone, bi-cytopenia or pancytopenia. A higher prevalence of nutritional deficiency leading to megaloblastic anemia in subcontinent reflects low socio-economic class, poor diet, and might also be attributed to malabsorption syndromes, chronic diarrheas and inflammatory disorders of the gut[17]. The second most common cause in our study was found to be Aplastic anemia. Similar results have been obtained by other studies conducted in Pakistan, China and India[6,17-19]. Aplastic anemia can present at any age but common age of presentation is up to 30 years and our majority patients' fall in10 to 40 years of age group that is why it is second most cause of pancytopenia in our study. There are many hypotheses regarding etiology and pathogenesis in Aplastic anemia, immune mediated mechanisms and stem cells abnormalities being the two most important causes[20].

In our study, Acute Leukemias accounted for 13.1% of the cases of pancytopenia bearing similarity with study conducted by Azaad et al[21], wherever reports incidence of acute leukemia as a cause of pancytopenia in 12 % cases. In a Korean study by Bae et al[22], AML was the most common cause of pancytopenia found in 25.9 % cases. In India reported frequency of acute leukemia by Mir et al. Dubey et al and Sharma et al. was 6.81 %, 12.9% and 15 % respectively[23-25]. Comparable to other studies[15,19,22]. Other malignant causes of pancytopenia like non-Hodgkin lymphoma, myelodysplastic syndrome, plasma cell myeloma, myelofibrosis, were not seen in a significant number.

Table-lll: Common causes of pancytopenia in different studies

Study	Country	Year	No. of Cases	1st cause (%)	2nd cause (%)
Dasgupta et al[5]	India	2015	248	Aplastic anaemia (33.47%)	Megaloblastic anemia (20.97%)
Reddy GP et al[6]	India	2016	54	Megaloblastic anemia (38.1%)	Aplastic anemia (26.2%)
Rehmani et al[11]	Pakistan	2015	244	Aplastic anemia (27.0%)	Megaloblastic anemia (20.0%)
Chandra et al[13]	India	2019	131	Megaloblastic Anemia (25.0%)	Acute leukemia (19 %)
Farouqe et al[14]	Pakistan	2020	258	Megaloblastic anemia (41.7%)	Hypersplenism (16.6%)
Vargas-CarreteroCJ et al[15]	Mexcico	2019	109	MDS (20.2%),	Megaloblastic anemia (18.3%)
S Mehboob et al[16]	Pakistan	2017	66	Megaloblastic anemia (49.9%)	Aplastic anemia (15.2%)
Osman et al[17]	Turkey	2016	137	galoblastic anemia (17%)	Chronic liver disease (15%)
Azaad et al[21]	China	2015	25	Megaloblastic anemia (28 %)	Aplastic anemia (20%)
Bae et al[22]	Korea	2015	1580	AML (25.9 %)	Lymphoma (12.7%)
Mir et al[23]	India	2015	132	galoblastic anemia (72.72%)	Acute leukemia (16.81%)
Present study	Pakistan	2018	237	Megaloblastic anemia (27.0%)	Aplastic anemia (15.6%)

Mixed deficiency anemia due to combined iron and Vitamin B12/ folic acid deficiency how assessed was seen in 9.3% cases. In mixed deficiency anaemia bone marrow showed micro normoblastic as well as megaloblastic erythroid maturation. Iron stain on bone marrow aspirate was used to assess iron stores in bone marrow. In an Indian study by Varma et al dimorphic anemia was second most common cause of pancytopenia seen in 17.8 % cases[26]. In contrast to a study conducted in 2015 by Y Subrahmanyam in India where they observed hypersplenism as the number second cause of pancytopenia in 24.53 % cases, and dimorphic anemia seen in 7.5 %[27], in our study hypersplenism was found only in 5.9% patients. It is because most common cause of hypersplenism is cirrhosis and our majority of patients were in age group10 to 40 years, a younger population where cirrhosis due to hepatitis is less common.

Hemophagocytosis due to probable infection and erythroid hyperplasia were seen 3.0% and 2.1 % cases respectively, in contrast to the study of Graham S et al. who reported erythroid hyperplasia in 30% cases[18]. Hemophagocytosis is more common in babies and young children due to viral illness while our study did not include children, that is why Hemophagocytosis was seen less commonly. Erythroid hyperplasia can be due to bleeding, hemolysis or myelodysplastic syndrome. But only myelodysplastic syndrome presents as peripheral pancytopenia with bone marrow erythroid hyperplasia[16] with a median age at diagnosis of 71 years and our majority of patients were of younger age group due to which less cases of erythroid hyperplasia were observed. The possible etiological relationship of erythroid hyperplasia with pancytopenia is unknown but it is postulated that it might represent a phase of evolution in to hypoplastic marrow[19,25].

Cases of Granulomatous infection and metastatic carcinoma and bone marrow fibrosis were also observed with a percentage of 2.1%, 1.3% and 1.3 % respectively, as chronic granulomatous disease is more common under 10 year of age and we included above 10 years of age patients. Now a days metastatic disease is picked early by imaging studies that is why less patients with metastatic disease were observed as a cause of pancytopenia. Primary bone marrow fibrosis is diagnosed at a median age of above 60 years and our majority patients were in 10 to 40 years age group because of that primary bone marrow fibrosis was noted just in 3 %patients.

Our study reported two cases of malarial infection, while study by Rehmani et al[11] reported 9 cases of malaria. The reason of less malaria cases is that although malaria is common in this region but clinicians usually start antimalarials on just clinical suspicion that is why we found less malaria cases as a cause of pancytopenia. The probable underlying mechanisms as hypersplenism, disseminated intravascular coagulation, Hemophagocytosis or direct suppression of bone marrow by parasitic invasion leading to pancytopenia as reported by Mehboob et al in 2017[16.]

In our study, bone marrow examination of various peripheral pancytopenia cases revealed hypercellular marrow as the most common finding, followed by normocellular, hypocellular, moderately cellular and dry tap comparable to a study conducted at Indore, India by Nanwani P et al. in 2017 who also reported hypercellular marrow as the most common findings in 60% cases, normocellular in 17% cases and hypocellular marrow in 23% cases[28].

CONCLUSION

Bone marrow examination can prove a cardinal diagnostic tool in establishing etiology of pancytopenia in patients presenting with non-specific symptoms like pallor and generalized weakness. Megaloblastic anemia and aplastic anaemia were commonest etiology of pancytopenia.

Recommendations: While dealing patients with pancytopenia early bone marrow examination should be opted to identify underlying cause.

AUTHOR'S CONTRIBUTION

Batool Y: Conceived idea, Designed methodology, Literature review, Manuscript writing, Final proofreading
Fatima S: Study design, Data analysis, Critical review of manuscript
Akhter N: Data collection, Data analysis, Data interpretation
Asif M: Study design, Data collection, Manuscript writing
Pervaiz G: Literature review, Manuscript writing, Critical review of manuscript.
Habiba U: Data analysis, Data Interpretation, Final proofreading

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