Original Article

FREQUENCY OF CAUSES OF PANCYTOPENIA IN BONE MARROW SAMPLES OF PATIENTS

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ABSTRACT

Objective: The aim of this study is to find out the common causes that lead to pancytopenia in our population specially in the province of Punjab.

Material and Methods: This is a cross sectional study that was conducted at Chughtai Institute of Pathology, Lahore. The duration of the study was from June 2020 to December 2021. A total of 210 patients were included in the study. A through history was taken and complete physical examination was done prior to the bone marrow biopsy procedure. Peripheral blood sample was run on Sysmex XN 9000 automated hematology analyzer. Bone marrow aspirate and trephine biopsy were thoroughly examined and immunohistochemical stains were applied where required. The data was analyzed using SPSS 23.0 and frequencies were calculated.

Results: Most common causes of pancytopenia in our study were megaloblastic anemia (18.1%) followed by aplastic anemia (12.9%), immune mediated causes (12.4%), acute myeloid leukemia (11%), hypocellular marrow (9%) myelodysplastic syndrome (6.2%), hypersplenism (5.2%) and Precursor B acute lymphoblastic leukemia (5.2%) (Fig. 2). Other causes include B cell non-Hodgkin lymphoma (4.8%), mixed deficiency anemia (4.2%), hypersplenism (3.8%), Gaucher's disease (1.4%), infections (1%) and other miscellaneous causes (4.8%).

Conclusion: The study conducted at our institute showed that majority of patients had benign causes (69.2%) leading to pancytopenia, the most common cause being megaloblastic anemia. Malignant causes constitute only a minority of cases of pancytopenia.

Key Words: Bone marrow biopsy, Frequency, Pancytopenia

This article can be cited as: Rasool I, Minhas AM, Fatima M, Umar S, Imran A, Malik NA, Chughtai AS. Frequency of causes of pancytopenia in bone marrow samples of patients. Pak J Pathol. 2023; 34(2): 51-55.

DOI: 10.55629/pakjpathol.v34i2.742

INTRODUCTION

A large number of patients present to medical facilities with decreased blood cell counts on a routine complete blood count (CBC). A reduction in all three cell lines is known as pancytopenia. Pancytopenia is not a disease itself but represents an underlying disease process which may be autoimmune, infective, malignant, nutritional or genetic in nature [1]. According to the De Gruchy criteria pancytopenia is defined as leucopenia with total leucocyte count (TLC) less than 4 x 10^9/L, thrombocytopenia with platelet counts less than 150 x 10^9/L and anemia with hemoglobin (Hb) less than 13.5g/dL in males and less than 11.5g/dL in females [2]. Patient with pancytopenia may present with multiple symptoms like fever, fatigue, dizziness, weight loss, night sweats, pallor, bleeding, splenomegaly, hepatomegaly and lymphadenopathy [3]. All these symptoms along with pancytopenia suggest bone marrow failure either due to a primary disorder or secondary to some other disease process. These disorders can either be inherited or acquired. Furthermore, the ethnicity, geographical variations, gender, age, nutritional status, socioeconomic status and occupational hazards all can influence the severity of pancytopenia [4].

Pancytopenia is a commonly encountered medical entity which must be promptly diagnosed so that timely treatment can be done. Often a comprehensive panel of tests is conducted to reach the diagnosis for pancytopenia. One of these tests is bone marrow biopsy. Bone marrow aspiration and biopsy is an invasive procedure which can be safely used to diagnose patients with pancytopenia. Due to its high diagnostic value, it is performed throughout the world to diagnose hematological as well as non-hematological malignancies. It is also performed to diagnose pyrexia of unknown origin, other malignancies, for staging of lymphomas and to monitor treatment response after chemotherapy or bone marrow transplant [5].

Pancytopenia may be caused by a benign disorder like megaloblastic anemia, aplastic anemia or might be drug induced but on the other hand it may be a symptom of a malignant disease like lymphoma or leukemia [6]. Therefore, it is important to identify the major causes that lead to pancytopenia in our population. Thus, the purpose of this study is to

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Received: ***16 Dec 2022****; Revised:* ***17 Mar 2023****; Accepted:* ***13 Apr 2023***

find the major causes that cause pancytopenia in our population. This will help us in understanding the epidemiological pattern of disease in our population.

MATERIAL AND METHODS

This is a cross sectional study that was conducted at Chughtai Institute of Pathology, Lahore after getting approval from the ethical and research committee of the institute. We received patients from throughout Punjab especially from Lahore, Sargodha, Faisalabad and Multan. The duration of the study was from June 2020 to December 2021. A total of 210 patients were included in the study through non probability snowball sampling technique after taking their informed consent. The sample size was calculated using Openepi calculator, version 3 by taking the prevalence of pancytopenia as 21.1%(7), 5% precision and 95% confidence interval. Patients of 1-85 years of age and of both genders who fulfilled the criteria of pancytopenia were included in the study. Already diagnosed patients and those undergoing chemotherapy were excluded from the study. A through history was taken and complete physical examination was done prior to the bone marrow biopsy procedure. During physical examination special attention was paid on examining liver, spleen and lymph nodes. Then 2ml peripheral blood sample was taken in EDTA vial and was run on Sysmex XN 9000 automated hematology analyzer to determine degree of pancytopenia. Bone marrow biopsy was performed using trephine needle under aseptic conditions. Xylocaine analgesic was used to minimize the pain and patient's comfort was ensured. The bone marrow aspirate slides were stained using Giemsa stain and Leica Pylorius tissue processor was used to prepare the trephine. The aspirate and trephine were thoroughly examined and immunohistochemical stains were applied where required. Data was analyzed using SPSS 23.0. Frequencies were calculated along with their mean and standard deviations. Ranges with minimum and maximum values of numerical variables including Hb, TLC and Platelet count were also calculated.

RESULTS

A total of 1340 bone marrow biopsies were done at Chughtai Institute of Pathology during our study duration out of which 245 cases fitted into the category of pancytopenia. 35 cases of pancytopenia were excluded from the study as they were undergoing chemotherapy and were undergoing bone marrow biopsy for remission assessment. A total of 210 (n=210) patients were included, out of which 101patients (48.1%) were females and 109(51.9%) were males. 40% of the patients were less than 20 years old, 48% of the patients range between 20-60 years of age and 12% of the patients range from more than 60 years to 85 years of age. Mean Hb was 7.3±1.8 (range: 2.3g/dl—8.7g/dl), mean TLC was 2.46±0.9 (range: 0.20x109/L – 3.9x109/L), mean Platelet count was 48.1±36.8 (1x109/L – 140x109/L). 176 patients (83.8%) had no visceromegaly, 29 patients (13.8%) had splenomegaly and only 5 patients (2.4%) had hepatosplenomegaly (Figure-I). Most common causes of pancytopenia in our study were megaloblastic anemia (18.1%) followed by aplastic anemia (12.9%), secondary causes (12.4%), acute myeloid leukemia (11%), hypocellular marrow (9%) myelodysplastic syndrome (6.2%), hypersplenism (5.2%) and Precursor B acute lymphoblastic leukemia (5.2%) (Figure-II). Other causes include B cell non-Hodgkin lymphoma (4.8%), double deficiency anemia (4.2%), Gaucher's disease (1.4%), infections (1%). Acute promyelocytic leukemia, HIV, hemophagocytic lymphohistiocytosis, Hodgkin lymphoma, granulomatous disease and myelofibrosis constitute minority of the cases. Majority of the patients presented with pallor (26.2%), fever (24.3%), weight loss (13.3%), fatigue 11.4%, lymphadenopathy (9.5%) and jaundice (1%) as shown in Table-I. Etiological factors according to age and gender are tabulated in Table-II.

Table-I: Symptoms and their frequency.

Symptoms	Frequency	Percentage (%)
Pallor	55	26.2
Fever	51	24.3
Weight loss	28	13.3
Fatigue	24	11.4
Lymphadenopathy	20	9.5
Jaundice	2	1
Others	30	14.3

Table-II: Etiological factors causing pancytopenia according to age and gender.

S#	Etiological causes	Gender (frequency)		Age (frequency)		
		Female	Male	<20 yrs	20-60 yrs	> 60 yrs
1.	Pre-B ALL	6	5	2	7	2
2.	Myelofibrosis	4	5	7	2	0
3.	Megaloblastic anaemia	20	14	18	15	1
4.	MDS	5	8	2	6	5
5.	Infections	3	6	4	5	0
6.	Immune mediated causes	14	8	2	17	3
7.	Hypo cellular bone marrow	15	4	8	7	4
8.	Hyper	5	6	2	9	0

	splenism					
9.	Hodgkin's lymphoma	0	2	0	2	0
10.	Hairy cell leukemia	1	0	0	1	0
11.	Gaucher's disease	0	3	3	0	0
12.	Double deficiency anemia	3	6	5	4	0
13.	B cell NHL.	3	7	0	9	1
14.	Aplastic anaemia	11	16	15	8	4
15.	AML	16	13	3	19	7
16.	Acquired sideroblastic anaemia	1	0	0	1	0
17.	Chronic granulomatous diseased	1	0	1	0	0
18.	Mixed phenotype carcinoma	1	0	1	0	0
19.	APML	0	2	2	0	0
20.	HLH	1	0	0	0	1

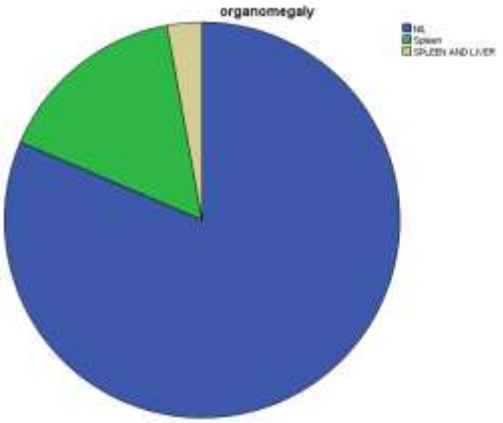

Figure-I: Frequency of organomegaly in the study population.

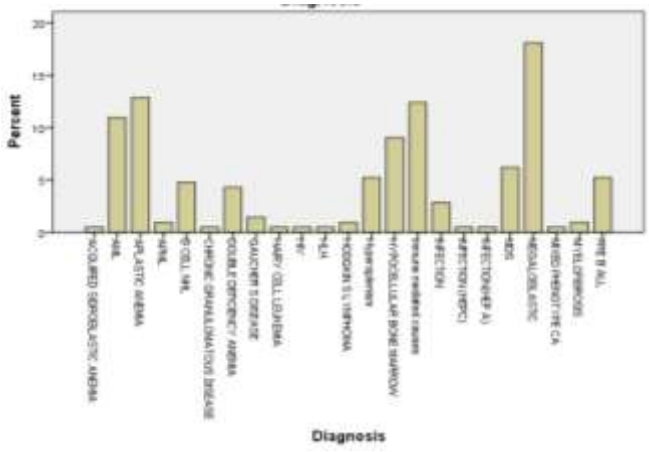

Figure-II: Major causes causing pancytopenia.

DISCUSSION

The clinical symptoms and severity of pancytopenia is dependent on the underlying etiology of the disease [8]. The term aplastic anemia is used for peripheral blood pancytopenia along with hypocellular bone marrow. It has both acquired and inherited causes. The acquired aplastic anemia is mostly idiopathic but a number of cases occur as a result of a viral infection or due to exposure to certain drugs/chemicals or radiations. Aplastic anemia is a bone marrow failure syndrome which overlaps with other clonal disorders of bone marrow failure like myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), paroxysmal nocturnal hemoglobinuria (PNH) and acute lymphocytic leukemia (ALL)/ lymphomas. The rare inherited causes of aplastic anemia include Fanconi anemia, dyskeratosis congenita and Schwachman- Diamond Syndrome [9].

The most common cause of pancytopenia in our study was megaloblastic anemia. Megaloblastic anemia is a type of macrocytic anemia which is mainly caused by deficiencies of vitamin B12 and folic acid. Vitamin B12 and folic acid are involved in DNA synthesis. Thus, their deficiencies will cause defective DNA synthesis which will eventually lead to ineffective hematopoiesis which presents as peripheral pancytopenia despite a hypercellular bone marrow [10]. In a study conducted in Gujarat, India megaloblastic anemia was also found out to be a major cause of pancytopenia [11]. In a study conducted in Azad Jammu & Kashmir, 74% of patient with pancytopenia were found out to have megaloblastic anemia which is much higher as compared to the population of Punjab [12]. Thus, it can be concluded that nutritional deficiencies of vitamin B 12 and folic acid are much more prevalent in developing countries and have major contribution in cases of pancytopenia.

Another cause of pancytopenia in our population is MDS. MDS is a clonal stem cell disorder characterized by pancytopenia with morphological dysplasia. It also has an increased tendency to transform into leukemia [13]. It is much less prevalent in our population when compared to the Mexican population where 20% of patients with pancytopenia have MDS [14].

Acute leukemia also often presents with pancytopenia. In India 14.3 % patients of acute leukemia presented with pancytopenia [15] These findings are consistent with our results as well. However, in Ethiopia comparatively less patients of acute leukemia had pancytopenia [16].

Hypersplenism is a term used to describe the syndromes with splenomegaly and increased destruction of blood cells leading to pancytopenia [17]. Hypersplenism is another cause leading to pancytopenia. Research conducted in Islamabad

found out that 16% patients with pancytopenia had hypersplenism [18]. These values are more as compared to our findings were only 5.2% of patients had hypersplenism.

A study conducted in India showed that 0.96% patient with pancytopenia had storage diseases which is quite close to our population in which only 1.4% patient had Gaucher's disease [19]. We can conclude that inherited disorders like storage disorders are less frequent in the subcontinent [20]. Cases of pancytopenia caused by infections like malaria and hepatitis are less prevalent in Punjab as compared to Baluchistan where it was found out in research conducted at Bolan medical college that malaria is responsible for 30% and hepatitis for 15% cases of pancytopenia. As compared to these results only a negligible number of patients with infections developed pancytopenia in Punjab [21]. Malaria proved to be the major cause of pancytopenia in Yemen where there is prevalence of malaria, leishmania and other infectious diseases [22].

Most patients in our study presented with pallor, fever and fatigue. These findings are similar to those found out by Jain *et al* in which 85% patients had pallor, 49% had fever and 54% complained of fatigue [23].

CONCLUSION

We conclude in our study that megaloblastic anemia is the most important cause leading to pancytopenia. Therefore, we propose that attention should be paid on the dietary habits of our local population specially on the intake of vitamin B12 and folic acid. This will help prevent hematological and neurological complications.

ACKNOWLEDGEMENT

We would like to acknowledge the support and help of our nursing staff in helping us in performing the bone marrow biopsy and for taking care of the patients. We would also like to acknowledge our technical staff for helping us in staining marrow aspirate slides and for processing the bone marrow trephines.

CONFLICT OF INTEREST: None

AUTHOR CONTRIBUTION

Iqra Rasool: Data collection and literature review
Aiman Mahmood Minhas: Article writing
Mavra Fatima: Statistical analysis and proofreading
Shereen Umar: Data collection
Ayisha Imran: Overall supervision of study
Nauman Aslam Malik: Overall supervision of study

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