

ETIOLOGICAL SPECTRUM OF PANCYTOPENIA USING BONE MARROW ASPIRATION AND BIOPSY

Muhammad Ihtesham Khan¹, Syeda Hina Fatima², Neelam Ahmad¹

¹Khyber Medical College, Peshawar, Pakistan

²Federal Medical and Dental College, Islamabad, Pakistan

ABSTRACT

Objective: The objective of this study was to analyse the etiology of pancytopenia in our setup using bone marrow biopsy, thus highlighting the diagnostic importance of bone marrow biopsy examination and helping to develop an approach in management of this condition.

Study design: Cross sectional descriptive study.

Place and duration of the study: Khyber Teaching Hospital, Peshawar, from 1.1.2016 to 31.12.2016.

Materials & Methods: The 79 patients of all ages and both gender referred for bone marrow biopsy having pancytopenia were included in the study. Hemoglobin level below 10gm/dL, white cell count of less than $4 \times 10^9/L$ and platelet count below 150×10^9 were taken as the criteria for pancytopenia. Pancytopenia was reported by automated cell counter. Low platelet count was confirmed by peripheral blood film examination. Bone marrow aspiration and biopsy were done. The findings were recorded in proforma and results were drawn accordingly.

Results: During the study period, about 79 patients fulfilled the criteria for pancytopenia. About 3 patients had diluted bone marrow aspirate which was unfit for making final diagnosis that's why they were excluded. Remaining 76 patients with pancytopenia were included in the study. Age of study subjects ranged from 1 to 65 years (mean age 31 years \pm 16.3 SD). 41(54%) males, and 35 (46%) females, male to female ratio of 1.2: 1. Among 76 cases, the commonest non-malignant etiology for pancytopenia on bone marrow examination was megaloblastic anemia, which was seen in 16(21%) cases. Commonest malignant etiology was acute leukemia which was seen in 10.6% cases (i.e. 5.3 % Acute myeloid leukemia and 5.3% Acute lymphoblastic leukemia), and mononuclear infiltration (seen in 10.5 % cases). Myelodysplasia and myelofibrosis were seen in 3 (3.9%) cases. Chronic lymphocytic leukemia, Gaucher's disease, mixed deficiency anemia and Niemann pick disease were seen in 2 (2.6%) cases each. Anemia of chronic disorder, Malaria, hemolytic anemia, multiple myeloma, visceral leishmaniasis, and hemophagocytic lymphohistiocytosis were seen in 1 (1.3%) case of pancytopenia.

Conclusion: Megaloblastic anemia was the commonest, non-malignant cause, while acute leukemia was the commonest, malignant cause of pancytopenia. It was through the bone marrow aspiration biopsy examination that such a wide spectrum of diagnoses was made in patients presenting with the single finding of pancytopenia. Hence, bone marrow aspiration biopsy is useful diagnostic tools in evaluating pancytopenia.

Keywords: Pancytopenia, Bone marrow, Megaloblastic anemia.

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INTRODUCTION

Pancytopenia is a condition in which all the three cellular components of the blood (i.e. red blood cells, white blood cells and platelets) are decreased in number [1, 2, 3, 4]. There is decreased hemoglobin, white cell count and platelet count [3]. Such patients have simultaneous anemia, leukopenia and thrombocytopenia, and thus present with pallor, easy bruising, fever, bleeding, and various infections [5]. It is an important entity encountered by physicians and needs work up to find underlying cause [2].

The etiological spectrum of pancytopenia is very wide, ranging from mild nutritional deficiencies to

life threatening malignancies infiltrating the bone marrow [1, 2, 5]. It can be due to decreased production of the haematopoietic cells in the bone marrow e.g. by infections, tumor cell infiltration or marrow failure; or due to peripheral destruction or sequestration of blood cells in enlarged organs like spleen [5]. It can also be caused due to certain drugs, chemotherapy or radiotherapy [2]. Both malignant and non-malignant hematological disorders can cause pancytopenia [1]. If pancytopenia is associated with organomegaly, this usually suggests that there may be underlying hematological malignancy [2, 6]. The underlying mechanism of pancytopenia in such cases is decrease in hematopoietic cell production due to replacement of normal hematopoietic progenitor cells by the malignant tumor cells [1]. It is important to know the cause of pancytopenia because most of the causes are easily treatable [2, 6].

Correspondence: Dr. Muhammad Ihtesham Khan, Pathology Department, Khyber medical College, Peshawar, Pakistan.

Email: ihteshamkhan9@yahoo.com

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Bone marrow aspiration and biopsy examination is indicated in all cases of pancytopenia where the underlying cause is not known [3]. The bone marrow aspiration may show normocellular bone marrow or there may be complete replacement of the bone marrow by malignant cells [2]. The bone marrow findings are interpreted according to the clinical history and physical examination of the patient, and the diagnosis is established accordingly [2].

Different studies are done regarding etiology of pancytopenia worldwide [7] but the data of the developed countries may not be representative of our population. So, the present study was done to determine etiological spectrum of pancytopenia in our setup using bone marrow aspiration.

MATERIALS AND METHODS

This Cross Sectional descriptive study was done in the Department of pathology, Khyber teaching hospital from 1st January 2016 to 31st December 2016. A total of 352 patients underwent bone marrow biopsy during this period out of which 79 patients fulfilled the criteria of pancytopenia. Pancytopenia was reported by automated cell counter (Sysmex). Hemoglobin level below 10gm/dL, white cell count of less than $4 \times 10^9/L$ and platelet count below 1, 50000/mm³ were taken as criteria for pancytopenia [8]. Low platelet count was confirmed manually by peripheral blood film. Bone marrow aspiration and biopsy were performed in all cases. Special stains like myeloperoxidase were done when necessary. Various causes or diagnoses of pancytopenia were recorded in a proforma, and results were drawn accordingly. Patients of all ages and both sexes fulfilling the criteria of pancytopenia i.e. having Hemoglobin (Hb) < 10gm/dl, Total leucocyte count (TLC) < $4 \times 10^9/L$, Platelet count < $1.50 \times 10^9/L$ were included. Patients whose bone marrow aspirate sample were scanty and could not give any diagnosis were excluded. Mean and standard deviation were calculated for quantitative variables e.g. age. Frequencies and percentages were calculated for qualitative variables like diagnosis and gender. Data was analysed using SPSS version 16.

RESULTS

During the study period, 352 patients were referred for bone marrow aspiration biopsy, out of which 79 patients fulfilled the criteria for pancytopenia. Bone marrow aspiration and trephine were done in all the cases. About 3 patients had

diluted marrow samples unfit for making final diagnosis. so, they were excluded from the study. Remaining 76 patients with pancytopenia were included in the study.

Age of study sample ranged from 1 to 65 years (mean age 31 years \pm 16.3 SD). There were 41 (54%) males, and 35 (46%) females, with male to female ratio of 1.2:1. Causes of pancytopenia diagnosed through bone marrow biopsy are shown in table 1, and further elaborated as malignant and non-malignant etiologies in Table-2.

DISCUSSION

Pancytopenia is a hematologic entity that is common in general population [3]. It should be suspected when patient presents with simultaneous anemia, bruises or bleeding tendencies, and fever or infections [1, 5]. There is a wide range of malignant and non-malignant hematological disorders that present with pancytopenia [3]. Bone marrow examination is indicated in all patients of pancytopenia to determine the cause of pancytopenia [1].

Numerous studies are done on the etiological spectrum of pancytopenia, and data is presented from different parts of the world. The pattern of underlying etiology of pancytopenia is different in different areas of the world [3]. The diseases causing pancytopenia vary in different studies due to differences in geographical areas, nutritional status, genetic differences, variety of infections and exposure to drugs causing bone marrow suppression [7].

In the present study, the most common cause of pancytopenia was megaloblastic anemia which was seen in 16 (21%) cases (Table 1). Blood film in these cases showed microcytosis and hyper-segmented neutrophils. Bone marrow showed megaloblastic change in the erythroid lineage. Iron stores were increased in bone marrow. Clinicians were requested to monitor blood counts of these patients after trial of vitamin B 12 and folic acid to the patients. Study done by Memon S and colleagues in 2008 in India showed that megaloblastic anaemia is the most common cause of pancytopenia followed by aplastic anaemia [9]. In one study done by Prabhala in 2014, data of 172 patients having pancytopenia was analysed and it was showed that megaloblastic anemia was the commonest cause of pancytopenia [1]. Megaloblastic anemia was seen in 44% cases of pancytopenia in a study done by Khodke and colleagues [8]. Megaloblastic anaemia is found to be common cause of pancytopenia in developing world

due to nutritional deficiencies [3]. Usual causes of megaloblastic anemia in our country are chronic

Aplastic anemia was seen in 5 (6.6%) patients of pancytopenia in the present study

Table-1: Etiological Spectrum inpatients of pancytopenia (n=76).

Diagnosis in patients of Pancytopenia	n (%)
Megaloblastic anemia	16 (21%)
Peripheral destruction	15 (19.7%)
Mononuclear infiltration	8 (10.5%)
Aplastic anemia	5 (6.6%)
Normocellular marrow	4 (5.3%)
Acute Lymphoblastic Leukemia	4 (5.3%)
Acute Myeloid Leukemia	4 (5.3%)
Myelodysplasia	3 (3.9%)
Myelofibrosis	3 (3.9%)
Chronic Lymphocytic Leukemia	2 (2.6%)
Gaucher disease	2 (2.6%)
Mixed deficiency Anemia	2 (2.6%)
Niemann Pick disease	2 (2.6%)
Anemia of Chronic Disorder	1 (1.3%)
Malaria	1 (1.3%)
Hemolytic anemia	1 (1.3%)
Multiple Myeloma	1 (1.3%)
Visceral leishmaniasis	1 (1.3%)
Hemophagocytic lymphohistiocytosis	1 (1.3%)

Table-2: Causes of pancytopenia.

Categories	n (%)	Diagnoses	
Non-malignant disorders	57 (75%)	Megaloblastic anemia	16(21%)
		Peripheral destruction	15(19.7%)
		Aplastic anemia	5(6.6%)
		Normocellular marrow	4(5.3%)
		Myelodysplasia	3(3.9%)
		Myelofibrosis	3(3.9%)
		Gaucher disease	2(2.6%)
		Mixed deficiency Anemia	2(2.6%)
		Niemann Pick disease	2(2.6%)
		Anemia of Chronic Disorders	1(1.3%)
		Malaria	1(1.3%)
		Visceral leishmaniasis	1(1.3%)
		Hemolytic anemia	1(1.3%)
		Hemophagocytic lymphohistiocytosis	1(1.3%)
Malignant disorders	19 (25%)	Mononuclear infiltration	8 (10.5%)
		Acute Lymphoblastic Leukemia	4 (5.3%)
		Acute Myeloid Leukemia	4 (5.3%)
		Chronic Lymphocytic Leukemia	2 (2.6%)
		Multiple Myeloma	1 (1.3%)

inflammatory disorders of the gastrointestinal tract and malabsorption syndromes apart from poor nutrition [3].

In the present study, about 15 (19.7%) patients had peripheral lowering of blood counts secondary to organomegaly (Table-1). In one study done by Singh G and colleagues in 2016, about 9.1% patients had pancytopenia secondary to enlarged spleen [2]. Pancytopenia may be due to splenic sequestration of blood cells or alloimmune destruction of the blood cells [2].

(Table-1). It was the third commonest non-malignant cause of pancytopenia in the present study (Table-2). The commonest cause of pancytopenia reported in different studies worldwide is aplastic anaemia and its frequency varies from 10% to 52.7% in different studies [3, 10, 11]. In one study done by Singh G and colleagues in 2016, aplastic anemia was seen in 1.1% cases of pancytopenia and was the least common cause of pancytopenia [2].

Acute lymphoblastic leukemia (ALL) and Acute myeloid leukemia (AML) were seen in 4 (5.3%) patients each (Table-2). Together, AML and ALL

constitute 10.6% cases of acute leukemia, and are thus the commonest malignant cause of pancytopenia in the present study (Table 2). In a study done by Singh G and colleagues in 2016, acute leukemia was the second most common cause of pancytopenia, constituting about 18.2% of cases of pancytopenia [2]

Myelodysplasia was seen in 3 (3.9%) cases of pancytopenia in the present study (Table-1). In a study done by Singh G and colleagues in 2016, myelodysplasia was seen in 2.7% cases [2]. In another study done by Prabhala and colleagues in 2014, about 2.3% cases had myelodysplasia and was the least common cause of pancytopenia [1].

Mixed deficiency anemia was seen in 2 (2.6%) cases of pancytopenia in the present study (Table 1). In one study done by Singh G and colleagues in 2016, most common cause of pancytopenia was mixed deficiency anemia secondary to malnutrition, and was seen in 27.3% of cases of pancytopenia [2]. Similar findings were presented by Chandra et al from Delhi and Borelli et al from Brazil [12, 13]. If there is malnutrition of multiple micronutrients, the hematopoietic cells of the bone marrow cannot produce normal haemopoietic cells and this leads to pancytopenia.

Anemia of chronic disorder was seen in 1 (1.3%) case of pancytopenia in the present study. The blood film showed normochromic normocytic anemia, bone marrow showed hypercellularity with increased iron stores. These blood and bone marrow findings are suggestive of anemia of chronic disorder [1, 3]. In one study, about 1.1% of patients of pancytopenia had anemia of chronic disorder on bone marrow aspiration examination [2]. This finding is consistent with that in the present study. Similar results were present in study done by Rathod in 2015 [14].

Hemolytic anemia was seen in 1 (1.3%) case of pancytopenia in the present study (Table.1). In a study done by Prabhala, about 19% cases of pancytopenia had hemolytic anemia and was the second most common cause of pancytopenia [1]. Similar finding was presented in a study done by Desalpine M [3]. Auto immune diseases may present with pancytopenia and associated autoimmune hemolytic anemias [15]. Clinicians should be careful about drug induced hemolytic anemias and blood counts should be monitored in patients receiving such medications that are known to cause hemolysis [3]. Coomb's test should be performed in such patients [3].

Malaria was seen in 1 (1.3%) case of pancytopenia. This report is comparable with study done by Khunger and colleagues, who reported an incidence of 1%, [10]. In one study done by Singh G and colleagues in 2016, Malaria was the cause for pancytopenia in 5.9% of the cases [2].

Multiple Myeloma was seen in 1 (1.3%) case, and was thus the least common malignant etiology of pancytopenia (Table-2). Same finding was shown by study done by Prabhala, in which Multiple myeloma was seen in 0.5% cases of pancytopenia, and was the least common cause of pancytopenia [1].

In the present study, 57 (75%) cases of pancytopenia had non-malignant etiology and 19 (25%) cases had malignant etiology (Table-2). Non-malignant etiology was common than malignant etiology. Same findings were presented in a study done by Jan A and colleagues in 2013, which showed that 24% cases of pancytopenia had malignant etiology and 76% cases had non-malignant etiology [16]. Similar finding is showed in study done by Singh G from India in 2016, in which 81.8% cases of pancytopenia had non-malignant disorders and only 18.2% cases had malignant disorders [2]. Bhatnagar and colleagues showed in their study that 21.9% cases of pancytopenia had malignant etiology [17]. Gupta and colleagues showed that 25% cases of pancytopenia had malignant etiology [18]. In all these studies, non-malignant etiology was more common than malignant etiology. Non-malignant causes are easily treatable as compared to malignant causes. Timely referral of pancytopenic patients for bone marrow biopsy can give early diagnosis and early treatment, which in turn can reduce morbidity and improve quality of life.

Thus, the present study showed that megaloblastic anemia is the commonest etiology of pancytopenia in our setup, followed by acute leukemias. Education of the general population about nutrition and diet may help lower the incidence of megaloblastic anemia and reduce morbidity. The study also showed that it was through the bone marrow examination that such a diverse spectrum of diagnoses was made in patients presenting with the single finding of pancytopenia. The morbidity and mortality associated with the reduced peripheral counts is related to overwhelming bacterial infections (neutropenia) and bleeding (thrombocytopenia). This is controllable and treatable, if a simple B-12 or Folate deficiency is promptly treated. Thus bone marrow biopsy examination has proved to be important diagnostic tool in evaluating pancytopenia.

CONCLUSION

Megaloblastic anemia is the commonest non-malignant etiology of pancytopenia, while acute leukaemia is the commonest malignant etiology in our setup. Bone marrow aspiration and trephine biopsy is useful diagnostic tool for early identification of cause of pancytopenia. If treatable causes are identified without delay, prognosis of such patients can be improved.

AUTHORS CONTRIBUTION

Muhammad Ihtesham Khan: Principal author, main idea

Syeda Hina Fatima: Literature review, result compilation

Neelam Ahmad: Help in literature review and proof reading

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