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Original Article

Etiological Profile of Childhood Pancytopenia with Special References to Non Malignant Presentation

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ABSTRACT

Background: Bone marrow play a vital role in understanding the etiology of pancytopenia, in time recognition of the underlying pathology will not only have an impact on the mortality and morbidity of the vulnerable pediatric patients but will also help us treat the most simple and easily treatable condition.

Aims: The aim of this study is to identify the etiological spectrum and bone marrow morphology of pancytopenia patients.

Material & Methods: Patient's age group between 6 months to 15 years from 1st September 2014 to 31st August 2015 admitted in children hospital, S.P. Medical College, Bikaner. Pancytopenia was reported by automated cell counter "Symex CBC 18PAR KX-21". Hemoglobin <10gm%, TLC <4000mm^3 and Platelet count <1 lac/mm^3 were taken as criteria pancytopenia. Platelet count was confirmed by PBF manually.

Results: The present study showed the majority of patients belonged to age group 1-5 years (51.6%) & least common age group was >5-10 years where only 9.2% patients were found and severe acute malnutrition was present in 27.3% of patients.

Conclusion: In our study 81.8% cases of pancytopenia were of non-malignant etiology. Severe malnutrition, dengue fever, thalassemia with hypersplenism, malaria, brucella and enteric fever were important treatable causes of pancytopenia.

KEYWORDS: Bone marrow, Hemoglobin, Pancytopenia, Peripheral blood film.

INTRODUCTION

Pancytopenia is an important clinico-hematological entity encountered in our day-to-day clinical practice. It is a disorder in which all three major formed elements of blood (red blood cells, white blood cells and platelets) are decreased in number[1]. It is not a disease entity but a triad of findings that may result from a number of disease processes – primarily or secondarily involving the bone marrow[2]. The severity of pancytopenia and the underlying pathology determine the management and prognosis of the patients[3]. Although various studies had shown the association of pancytopenia with different etiology in India[3,4], the predominant causes of pancytopenia are not well defined.

The etiology of pancytopenia varies widely in children, ranging from transient marrow suppression due to viral infection to marrow infiltration by life-threatening malignancy. These may also be caused iatrogenically, secondary to certain drugs, chemotherapy or radiotherapy for malignancies. The bone marrow picture may vary depending on the etiology, from normocellular with non-specific changes to hypercellular being replaced completely by malignant cells. According to etiology, degree and duration of the impairment, clinically these cytopenia can lead to fever, pallor, infection, or serious illness and death. Knowing the exact etiology is important for specific treatment and prognostication. While there are several published studies on the hematological diagnosis of pancytopenia on basis of bone marrow morphology, few have attempted to explore the underlying etiology and clinical course of the disorders leading to this condition. In this study, we hoped to evaluate the demographic, nutritional, socioeconomic and age patterns of the myriad disorders which cause pancytopenia and develop an approach to the diagnosis of this condition in our patient population.

Pancytopenia itself is not a disease but actually a triad of findings that may result from a number of disease processes associated with bone marrow both affecting it primarily or secondarily and resulting in pancytopenia[5]. Most often the Pancytopenia is associated with organomegaly and lymphadenopathy usually suggests the possibility of malignancies or bone marrow failure syndromes but there are a number of other causes which can present in the similar way and are very easily treatable[6].

The aim of this study is to identify the etiological spectrum and bone marrow morphology of pancytopenia patients. The study focused on identifying treatable and reversible causes of pancytopenia.

MATERIALS AND METHODS

The present study was conducted in the Department of Pediatrics, S.P. Medical College and P.B.M. Associated Group of Hospitals, Bikaner (North West Rajasthan).

Source of Data

Patient's age group between 6 months to 15 years from 1st September 2014 to 31st August 2015 admitted in children hospital, S.P. Medical College, Bikaner. Pancytopenia was reported by automated cell counter "Symex CBC 18PAR KX-21". Hemoglobin <10gm%, TLC <4000mm^3 and Platelet count <1 lac/mm^3 were taken as criteria pancytopenia. Platelet count was confirmed by PBF manually.

Inclusion criteria

- All admitted cases from 6 months to 15 years of age in Department of Pediatrics, S.P. Medical College and P.B.M. Associated Group of Hospitals, Bikaner with pancytopenia.
- Informed consent by guardian.

Exclusion criteria

- Patients on Chemotherapy, radiotherapy and known cases of hematological malignancy.

A systematic review of causes, detailed history, clinical examination and laboratory parameters for etiology causing cytopenia were recorded in preset proforma. Hematological profile included hemoglobin, red cell indices, total and differential leukocyte counts, platelet count, peripheral blood smear morphology and bone marrow aspiration or biopsy were done. Relative test was done to establish diagnosis of various diseases appropriately.

PBF was prepared with standard staining method and seen and counter checked by pathologist. Bone marrow aspiration and trephine biopsy were carried out as per the clinical indication. The bone marrow procedure and further staining were carried out by standard methods[7-9].

All the bone marrow aspirate smears and trephine biopsies were stained with May-Grunwald Giemsa and hematoxylin and eosin, respectively. Special staining for myeloperoxidase, Sudan black B, periodic acid Schiff and Perl's stain on aspirate smears and reticulin stain on biopsy were done, when indicated.

Appropriate statistical analysis was applied as and when required using SPSS statistical software version 10.0. A p-value <0.05 was taken as significant.

RESULTS

In our study, total 10040 indoor patient's CBC reports were analyzed and 1.86% patients had pancytopenia (table 1). Finally total 153 (81.8%) non-malignant patients who had pancytopenia were included in the study (table 2).

The present study showed the majority of patients belonged to age group 1-5 years (51.6%) & least common age group was >5-10 years where only 9.2% patients were found (table 3).

According to bone marrow findings, majority of patients had megaloblastic erythropoisis (53.6%) and least common bone marrow finding was microcytic erythropoisis (14.4%) (table 4). The our results shows the distribution of cases according to etiology. Severe acute malnutrition was present in 27.3% of patients followed by Leukemia (18.2%), dengue and thalassemia with hypersplenism (9.1% each), celiac disease (8.5%), brucella and malaria (5.9% each), down's syndrome with hypothyroidism, Enteric fever, Myelodysplastic syndrome and systemic lupus erythmatosus (2.7%) each, aplstic anemia, chronic kidney disease and measles (1.1% each) while 2.1% patients had unknown etiology (table 5).

Table no. 1 Show the distribution of cases according to CBC report

	No.	%
Total target CBC reports	10040	100.0
Hb <10gm%	4470	44.5
TLC <4000	809	8.1
Platelet <1 lac	2370	23.6
Hb <10 + TLC <4000	459	4.6
Hb <10 PT <1lac	1329	13.2
PLT <1lac+TLC <4000	322	3.2
Pancytopenia	187	1.86

Table 2: Show the malignant & Nonmalignant etiology of pancytopenia

	No.	%
Total no of patients with Pancytopenia	187	100
Malignant Etiology	34	18.2
Non Malignant	153	81.8

Table 3: Distribution of cases according to age group in nonmalignant causes of pancytopenia

Age Group	Frequency	%
6 month – 1 year	17	11.1
1-5years	79	51.6
>5-10 years	14	9.2
>10 years	43	28.1
Total	153	100

Table 4: Distribution of cases according to bone marrow findings

Bone Marrow	Frequency	Percent
Hypocellular Bone Marrow	27	14.4
Megaloblastic Erythropoisis	100	53.6
Microcytic Erythropoisis	6	3.2
Normoblastic Erythropoisis	20	10.7
Malignant cell of Myeloid series	7	3.7
Malignant Cell of Lymphoid Series	27	14.4
Total	187	100.0

Table 5: Distribution of cases according to etiology

Etiology	Frequency	Percent
Severe Acute Malnutrition	51	27.3
Leukemia	34	18.2
Dengue	17	9.1
Thalassema with Hypersplenism	17	9.1
Celiac Disease	16	8.5
Brucella	11	5.9
Malaria	11	5.9
Down with Hypothyroidism	5	2.7
Enteric Fever	5	2.7
Myelodysplastic syndrome	5	2.7
Systemic Lupus Erythmatosus	5	2.7
Unknown	4	2.1
Aplastic Anaemia	2	1.1
Chronic Kidney Disease	2	1.1
Measles	2	1.1

DISCUSSION

During the study period of one year we studied the eligible candidates (6 months to 15 years patients with informed consent). Total 10040 patients were analysed, out of them 187 patients CBC and PBF reports were showing pancytopenia so prevalence was 1.86%.

The prevalence in previously done studies is comparable with our results like Memon et al[10] in year 2008, 3.57% prevalence and Zeb Jan[11] 2013, 1.4% prevalence and Rathod et al[12] 2015 at Vadodara, Gujrat, prevalence was 2.02%.

A study done by Tilak[3] after evaluating 205794 OPD and IPD patients show overall incidence of pancytopenia of 374/million hospital attendance per year.

The present study shows that out of 187 patients of pancytopenia there were 34(18.2%) cases of malignant etiology. In study done by Bhatnagar[13] in Delhi in year 2005 showed 21.6% of malignancies. Gupta et al[14] 2008 also revealed similar results of 25%. Zeb Jan[11] in year 2013 in Pakistan 23.9% of malignant etiology was present.

Most of patients belong to age group of 1-5 years 51.6%, followed by more than 10 years 28.1%. Our study result is in line with results of studies previously done by Zeb Jan[11] in 2013 in which maximum numbers of patients were in the age group of 6 months to 5 years 42.44% followed by 35.13% in age group 6-10 years. The study

done by Sharif[15] 2012 also shown that maximum number of patients belongs to age group 2 months to 5 years (61%)., Gupta et al[14] also shown similar results 1 years to 5 years cases while 58% of total cases. Study done by Rathod et al[12] 2015 also show that maximum number 39% was in age group of 6 months to 5 years.

The present study results compared to Chhabra[16] in 2012, marrow was cellular in 71.4% and hypocellular in 28.5%., Lakhey[17] in 2012 marrow was hypocellualr in 29.2% and hematological malignancies 27.7%, megaloblastic anemia in 24.1%, normocellular with erythroid hyperplasia in 18.5% cases. According to Khodke[18] which shown megaloblastic anemia as in 44% cases of pancytopenia. It is important to confirm megaloblastic anemia picture or dimorphic anaemia picture on bone marrow examination. This rule out aplastic anemia and leukemic transformation and are more yield full than Vitamin B_{12} and folate level.

The our results shows that most important and common cause of pancytopenia was severe malnutrition (27.3%). This multiple micronutrient and protein energy deficient state leads to depleted and changed bone marrow. Potent hematopoetic cell stop further maturation and this leads to pancytopenia. The CBC and bone marrow finding are comparable to PBF expert showing megaloblastic anemia but in severe malnutrition many important factors which are needed for cellular maturation are deficient. These results are in line with study done by Chandra et al[19] in 2002 in Delhi and Borelli et al[20] in 2009 in Brazil.

Second most common cause was leukemia and related blood malignancies in 34(18.2%). Third most common cause of pancytopenia in our study was dengue fever in 17(9.1%) cases. In dengue there is hemoconcentration leucopenia and thrombocytopenia. These may be due to immunological suppression of bone marrow or hemophagocytic syndrome.

Similar incidence of pancytopenia was seen in 17(9.1%) cases of thalassemia with large spleen. Pancytopenia may be due to hypersplenism or alloimmune destruction of cells or bone marrow depression due to iron toxicity or acute viral infection leads to pancytopenia.

Celiac disease is also prevalent in our area. 16(8.5%) cases of pancytopenia were diagnosed as having celiac disease. In celiac disease due to chronic exposure to gluten antigen the duodenal mucosa get inflamed and surface area reduced. This lead to deficiency of micro nutrient absorbed at here or this area important for absorption and overall deficient state for iron, zinc, calcium, vitamins, folate and Vitamin B_{12}. Deficiency of these leads to pancytopenia. It may be present in celiac crisis. Fisgin[21] in 2004 shown hematological manifestation in celiac disease.

Malaria was causative for pancytopenia in 11(5.9%) cases there was 6 cases of Plasmodium falciparum and 5 cases of Plasmodium vivax study results are comparable with Khunger et al[22] who reported an incidence of 1%, Tilak et al[3] reported incidence of 3.9%.

Brucella also an important cause of pancytopenia in 11(5.9%). Hypersplenism haemophagocytosis and granulomatosis lesion in bone marrow play a fundamental role in producing these abnormalities in peripheral blood. al-Eissa and al-Naseer[23] studied the hematological manifestation of brucella and shown that in a prevalent area this should be considered in a patient whose blood picture reveals hemolytic anemia leucopenia, thrombocytopenia or pancytopenia with other clinical triad of fever, hepatosplenomegaly and joint pain.

In our study 5 cases (2.7%) were of Down's syndrome with hypothyroidism. These patients shows pancytopenia with normocytic erhthropoesis in bone marrow at presentation.

Enteric fever also contributed to 5 cases (2.7%). This may be due to total or partial bone marrow suppression. James and Dutta[24] in 1997 shown that in enteric fever 8.3% prevalence of pancytopenia was present.

Five SLE cases also contributed to pancytopenia, It may be due to autoimmune destruction, hypersplenism or bone marrow suppression. These may be due to concurrent use of steroid.

Aplastic anaemia and myelodysplastic syndrome contribute to 7 cases (3.8%) pancytopenia.

Usually in developed countries and higher medical institute this is most common or second most common cause as these patient usually referred from peripheral centers to them. In our study aplastic anemia was less compared to others.

In our study 2 cases (1.1%) of chronic renal failure, this may be due to prolonged raised urea and creatinine which lead to depression of bone marrow. Similar results were present in study done by Rathod[12] in 2015.

Two cases of measles with bronchopneumonia also presented as pancytopenia. These cases were of severe septicemia Klebsiella was grown on culture media in these patients. Pancytopenia may be due to depression of bone marrow due to viral infection or severe sepsis. After going through all available investigations 4 cases (2.2%) remain undiagnosed.

CONCLUSION

In our study 81.8% cases of pancytopenia were of non-malignant etiology. Severe malnutrition, dengue fever, thalassemia with hypersplenism, malaria, brucella and enteric fever were important treatable causes of pancytopenia. Peripheral blood film examination and bone marrow biopsy examination were important methods to exclude malignant etiology.

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