Cytopenias in children: clinical, hematological and etiological profile

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ABSTRACT

Objective: To determine the frequency of various clinical presentations, hematological findings, etiological profile and outcome of cytopenias in children.

Study Design: Cross-sectional descriptive study

Place and Duration: At Department of Pediatrics, Nishtar Hospital Multan from 1st January 2017 to 31st December 2017

Methodology: Fifty three patients of either gender aged 1 month to 15 years presenting with bicytopenia/ pancytopenia were enquired about presenting complaints (pallor, fever, bleeding bruising and bone pains), examined for visceromegaly (liver / spleen) and lymphadenopathy and laboratory investigation were done for blood counts (Hemoglobin, TLC, DLC, reticulocyte count and peripheral film) and bone marrow examination was done for pathological findings.

Results: Out of total 53 patients, 64.2% were males. Mean age at the time of presentation was 6 years. Fifty two percent patients were malnourished. Pallor (98.11%) and fever (90.57%) were the commonest signs at presentation. Pancytopenia was found in 62.26% of patients. Hematological malignancy (26.40%) followed by infections (24.50%) and megaloblastic anemia (22.60%) were the leading cause of the condition. Infections and megaloblastic anemia were common in bicytopenic patients compared to pancytopenic children (30 % vs. 21% and 25 % vs. 21 % respectively).

Conclusion: Fever and pallor are non-specific but commonest presentation of bi/pancytopenia in children. Hematological malignancies were commonest etiology of bi/pancytopenia but infections and megaloblastic anemia can also present similarly.

Keywords: Children, Etiology, Pancytopenia, Bicytopenia, Hematology, Bone marrow

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INTRODUCTION

Pancytopenia and bicytopenia constitute the most significant cases of cytopenic pediatric patients requiring hospitalization. Pancytopenia is comprised of decrease in the number of erythrocytes, leukocytes and platelets. The term of bicytopenia is used when there is reduction of 2 blood cell lines but the approach for diagnosis is similar as for pancytopenia[1].

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The signs and symptoms are mostly related to low hemoglobin and platelets. Leukopenia is rarely seen as a common reason of first presentation but when present, can prove life-threatening to the patient. Clinical features include pallor, headache, palpitations, shortness of breath, exhaustion, body swelling, gum bleeding, petechial rashes, repeated infections and oral ulcers[2].

Congenital causes of pancytopenia include Fanconi anemia, shwachman-diamond syndrome and dyskeratosis congenita[3] whereas the acquired causes include non-inherited aplastic anemia, malignant marrow infiltrative disorders (i.e. acute leukemia), non-malignant infiltrative disorders(i.e. storage disorders), infections (i.e. tuberculosis, malaria), toxins, immune disorders, peripheral destruction of blood cells i.e. hypersplenism[4] and megaloblastic anemia due to nutritional deficiency[5]. Bone marrow examination has its major part in identifying underlying cause of pancytopenia[6].

A retrospective study presented 6-year spectrum of children with pancytopenia according to which common underlying causes were aplastic anemia (28.3%) followed by hematological malignancies (23.9%), megaloblastic anemia (19.5%) and idiopathic thrombocytopenic purpura (ITP) (7.8%)[7]. In 2005, Bhatnagar et al showed an analysis of 109 children admitted

with pancytopenia in a retrospective study. They found that the underlying reasons were megaloblastic anemia, acute leukemia and aplastic anemia in 28%, 21% and 20% cases respectively while among all infectious causes, 30% patients had enteric fever[8]. In 2017, Tufail et al conducted similar study in Allied Hospital Faisalabad and concluded that fever was the most frequent clinical feature (92%) followed by pallor (83.2%) and enlarged viscera (64.8). Malignancy and aplastic anemia were the commonest causes of pancytopenia[9].

The underlying etiology of bi/pancytopenia varies from region to region and has changed over time due to different genetic background, changing life style, dietary habits, increasing day to day radiation exposure, increased exposure to medicinal drugs and increased understanding and diagnosis of metabolic genetic disorders. Every year significant proportion of children get admitted with provisional diagnosis of cytopenia. Evaluation and management of children presenting with cytopenias is challenging both for the clinicians and pathologist. There is a large exhausting list of causes and laboratory tests while taking care of these patients. On the other hand, early and accurate diagnosis is important for parental counselling as well as future planning for next kids to come. All the obtained data will be helpful in establishing the investigative and therapeutic approach to children with bi/pancytopenia. The objective of our study was to determine the frequency of various clinical presentations, hematological findings, etiological profile and outcome of cytopenias in children.

METHODOLOGY

This cross-sectional descriptive study was done at Pediatrics Department, Nishtar Hospital Multan over a time span of one year from 1st Jan 2017 to 31st Dec 2017, after approval by ethical review committee of the same institute. Fifty-three admitted children, presenting with suppression of two or more blood cell lines, of age 1month to 12years and either gender was enrolled into study after informed consent of the parents. Children already diagnosed for any established cause of pancytopenia, receiving chemotherapy for neoplasm, with recent history of blood transfusion and those whose parents did not give consent for bone marrow procedure were excluded.

We considered pancytopenia and bicytopenia as decrease in all three or two cellular components of blood respectively. Cut off values for hemoglobin (Hb, g/dl) were 9.4 for infants up to two months, 11.0 for >2 – 6 months, 10.5 for > 6 month – 2 years and 11.5 for > 2 years – 12 years. Age specific leukocyte (/mm^3) cut off values taken were < 6000 for 2 months – 2 years, < 5500 for > 2 – 4 years, < 5000 for >4 – 6 years and < 4500 for > 6 – 12 years. Platelet count (/mm^3) of< 150,000 was considered in all children >1 month – 12 years. All the complete blood counts were done through Abbott cell-dyn 1700 analyzer. Bone marrow examinations were part of standard institutional protocol and advised by physician in-charge of the patient for the work-up of bi/pancytopenia.

Consecutive sampling technique was used and sample sizeof 53 patients was calculated by WHO sample size calculator, using anticipated population proportion (p) of pancytopenia as 3.57%[10] with confidence level (1-α) of 95% and absolute precision (d) of 0.05.

Demographic data, history including fever, bleeding, bony pains and examination including growth parameters, pallor, petechial rash, lymphadenopathy, hepatosplenomegaly were noted. Malnutrition was labeled in children with <60% weight for age (moderate to severe degree according to Gomez classification). Hematology parameters including complete blood picture, peripheral film, reticulocyte counts along with bone marrow aspiration and trephine biopsy were obtained from the clinical laboratory reports. All the data was collected on predesigned performa.

Data Analysis: All the data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 20.0. Graphs and tables are used to present the results. Mean ± standard deviation is calculated for continuous variables. Frequency and percentage are calculated for categorical variables. Chi-square test is used to compare the etiology between bi/pancytopenia. A p-value of ≤ 0.05 is taken as significant.

RESULTS

We included 53 admitted children in the study out of which 34 (64.15%) were males. Male to female ratio was 1.7:1. Mean age at presentation was 6years. There was no significant difference in percentage of children below and above 5 years of age. Twenty-eight (52.83%) patients were malnourished. Pallor (98.11%) and fever (90.57%) were the commonest signs of presentation. Hepatomegaly was found in 32 (60.38%), splenomegaly in 22 (41.51%) and lymphadenopathy in 18 (34.96%) patients. Bicytopenia and pancytopenia was found in 20 (37.74%) and 33 (62.26%) patients respectively. Mean hemoglobin, reticulocyte percentage, median leukocyte and platelet counts were 5g/dl, 0.8%, 3300/mm^3, 50,000/mm^3 respectively. Out of 53 patients, 31 (58.5%) were discharged, 17 (32.1%) were referred, and 5 (9.4%) were expired (Table-I).

Hematological malignancy in 14 (26%) patients was found as the leading cause of the condition followed by infections in 13 (24%) and megaloblastic anemia in 12 (22%) patients. Aplastic anemia in 10 (18%) patients was another important cause. Among 14 children with hematological causes, acute lymphoblastic leukemia (ALL) was present in half (n = 7) of the patients. Among patients with infections, common causes were enteric fever, sepsis and tuberculosis (n = 3, 23 % each respectively). In others, 3 cases of Gaucher disease and 1 case of Chediak-Higashi syndrome were also diagnosed (Figure-1).

Patients with bicytopenia were compared with those having pancytopenia. Results showed no prominent difference in etiology. But Infections (n = 6, 30 % vs. n = 7, 21%, p-value 0.47) and megaloblastic anemia (n = 5, 25% vs. n = 7, 21 %, p-value 0.73) were common in bicytopenic patients compared to pancytopenic children respectively) (Figure-2).

Table-I: Demographic and Clinico-hematological features and outcome of children with pancytopenia (N=53)

Variable		N (%)
Age in years (mean, SD)		6.02 (3.92)
Gender	Male Female	34 (64.15%) 19 (35.85%)
Clinical Presentation	Malnourished	28 (52.83%)
	Fever	48 (90.57%)
	Pallor	52 (98.11%)
	Bleeding	24 (45.28%)
	Bone pains	14 (26.42%)
	Hepatomegaly	32 (60.38%)
	Splenomegaly	22 (41.51%)
	Lymphadenopathy	18 (33.96%)
Complete Blood Picture	Hemoglobin (g/dl) (mean ± SD)	5.62 (2.12%)
	Leukocyte count (x/mm^3) (median, IQR)	3300 (4730)
	Platelets (x /mm^3) (median, IQR)	50,000 (76,500)
	Reticulocyte count, % (mean ± SD)	0.88 (0.82%)
Cytopenias	Bicytopenia Pancytopenia	20 (37.74%) 33 (62.26%)
Outcome	Discharged	31 (58.5%)
	Referred	17 (32.1%)
	Expired	05 (09.4%)

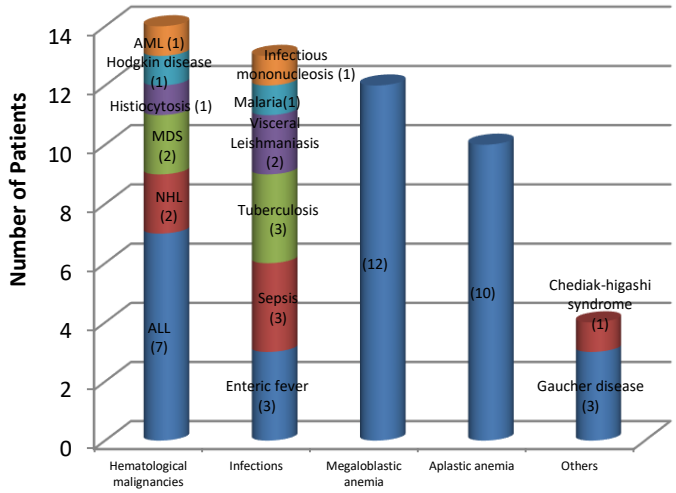

Fig-1: Etiological frequency of children with bi/pancytopenia (N=53)

DISCUSSION

Pancytopenia is a usual blood picture seen in daily clinical routine. It is suspected if a child comes with unexplained fever, pallor and bleeding. In the present study, total 53 children with bi/pancytopenia were included and evaluated for clinical presentation, complete blood profile and bone marrow examination, causes of bi/pancytopenia and final outcome and results were compared with those previously published in literature.

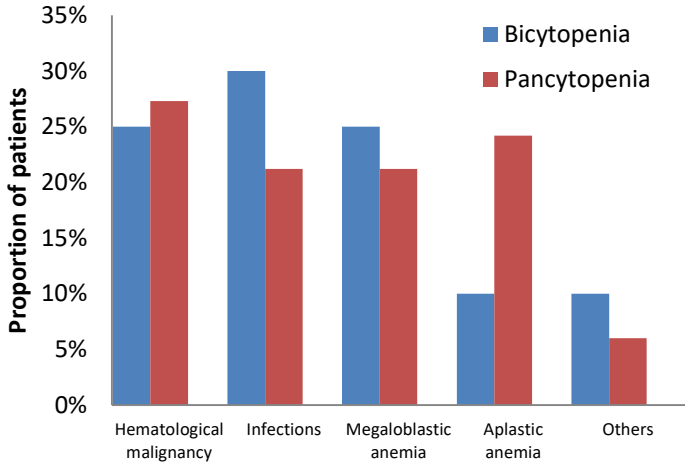

Fig-2: Comparison of Etiology in children presenting with Bicytopenia (n = 20) and Pancytopenia (n = 33)

In this prospective observational study, mean age of patients was 6 years. Almost equal proportion of patients fell into categories of below and above 5 years. Participants comprised of 64% males with male-to-female ratio was 1.7:1. Male preponderance coincides with the study conducted in Central India where M:F ratio was 1.4:1[11]. Compared to 71%of malnourished children in a study by Sharif M, et al[12]; only 52 % children in our study were malnourished.

Most prominent presenting symptoms of pallor and fever in this study were comparable to a study conducted in Jamshoro, Sindh in 2008, showing pallor (87%) and fever (65%)[7]. Results also match with those shown in study conducted in Peshawar in 2013 where pallor (82%) and fever (62%) were major complaints in pancytopenic children[10]. Most common clinical findings of hepatomegaly and splenomegaly were much higher compared to a study conducted in 2012, where splenomegaly and hepatomegaly were found only in 27.5%, 25% respectively[13].

In our study, frequency of pancytopenia was much higher compared to a study published in Indian journal in 2011 (62.3% vs. 17.7% respectively) [14]. Etiological diagnosis in our study is comparable to study done by Khan et al[16] and Jan et al[7] which showed hematological malignancy as the most frequent (32%) cause and second most frequent (23.9%) cause respectively. Raphael et al also found acute leukemia as the commonest cause of pancytopenia in children[13]. Similarly in one study, acute leukemia was common cause (66.9%) in bicytopenic children[15]. However, it was in contrast to those published by Agarwal et al where malaria was commonest (30%) cause followed by aplastic anemia (14.2%) and tuberculosis (12.8%)[14].

Infections were the second most common cause of pancytopenia in our study. Results are relatable to a review study over 5-year period, by Pine et al which showed infections as the leading cause of Pancytopenia (64%) of admitted children followed by hematological causes (28%)[16].

Megaloblastic anemia was the third common etiology found in pancytopenic children. Deficiency of B12 or folic acid in diet leads to megaloblastic anemia. Though this condition can be suspected by the presence of oval macrocytes on peripheral

blood film but bone marrow examination helps in confirmation of diagnosis. Studies conducted by Dubey[11], Osama[17], Chhabra[18] and Bhatnagar[8] found that megaloblastic anemia was present in 41.4%, 39%, 31.8% and 28.4% cases respectively.

Frequency of aplastic anemia in our study was comparable to a study by Memon et al[10]. It was also second commonest cause of pancytopenia in some other studies[19,20]. Less number of malaria cases in our study can be due to frequent use of anti-malarial drugs even on clinical suspicion.

This discrepancy in the frequency of diseases manifesting as pancytopenia is attributed to dissimilarities in methodology, constricted diagnostic criteria, different geographical places, length of survey, genetic variability, and vulnerability to different cytotoxic agents.

We compared Patients with bicytopenia with those having pancytopenia. Though results showed no prominent difference in etiology but infections and megaloblastic anemia were common in bicytopenic patients compared to pancytopenic children (30 % vs. 21% and 25 % vs. 21 % respectively).

CONCLUSION

Fever and pallor are non-specific but commonest presentation of bi/pancytopenia in children. Hematological malignancies were commonest etiology of bi/pancytopenia but infections and megaloblastic anemia can also present similarly.

CONTRIBUTION OF AUTHORS

Rasheed J: Conceived idea, Manuscript writing, Data collection
Urooj S: Data collection, Literature review, Manuscript writing
Bashir R: Data Collection, Literature review
Khalid M: Data analysis, Statistical analysis, Critical review of manuscript
Zafar F: Manuscript writing, Proof reading

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