Research Article

Etiological Spectrum of Pediatric Pancytopenia: Insights from Bone Marrow Biopsy Analysis

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Abstract

Objective: To determine the etiological spectrum of pediatric pancytopenia using bone marrow biopsy findings and analyze associated hematological parameters.

Materials and Methods: This cross-sectional study analyzed 100 children (aged 1-15 years) with pancytopenia confirmed by complete blood count (CBC) and bone marrow biopsy at a pediatric tertiary care hospital in Lahore from January to May 2024. Hematological parameters, peripheral smear findings, and bone marrow biopsy results were statistically analyzed using SPSS version 23.0, with $p \leq 0.05$ considered significant.

Results: Aplastic anemia (16%) and megaloblastic anemia (14%) were the most common causes of pancytopenia, followed by acute leukemia (10%), metastatic disease (7%), hemophagocytic lymphohistiocytosis (8%), and myelodysplastic syndromes (4%). Bone marrow biopsy revealed hypocellularity in 39% and hypercellularity in 17% of cases. Peripheral blood film findings varied, with megaloblastic anemia showing macrocytes and hypersegmented neutrophils, while acute leukemia often presented with a microcytic hypochromic picture and blasts. Hemodilution or afragmented aspirates were noted in 16% cases, while 15% showed hemorrhage, 4% necrosis, and 2% fibrosis. No significant variations were found in hematological parameters across different etiologies ($p > 0.05$).

Conclusion: Aplastic and megaloblastic anemia are the leading causes of pediatric pancytopenia. Bone marrow biopsy remains essential for definitive diagnosis, providing crucial insights for targeted management and improved patient outcomes.

Keywords: Pediatric pancytopenia, bone marrow biopsy, hematological parameters, childhood malignancies, diagnostic tools.

INTRODUCTION:

Pancytopenia, characterized by the concurrent reduction of red blood cells, white blood cells, and platelets, is a critical condition in pediatric patients due to its varied and potentially severe causes and outcomes.[1] These include bone marrow failure syndromes, malignancies, viral infections, autoimmune conditions, and nutritional deficiencies.[2] Early identification of the underlying cause is essential for effective treatment and better clinical outcomes. Initial evaluation relies on hematological parameters such as hemoglobin, total white blood cell count, platelet count and reticulocyte index, which offer insights into the severity of bone marrow dysfunction.[3] Peripheral smear examination provides additional diagnostic value by revealing specific abnormalities. However, these tests are often insufficient to confirm the exact cause.[4]

Bone marrow examination, including aspiration and biopsy, is the definitive diagnostic tool for evaluating pancytopenia. It provides direct evidence of marrow cellularity, abnormal cell populations, and potential infiltration or fibrosis, aiding in diagnosing disorders such as leukemia, aplastic anemia, myelodysplastic

syndromes, and marrow infiltration by infections or metastatic conditions. These findings are critical for formulating treatment plans, such as immunosuppressive therapy, stem cell transplantation, or disease-specific targeted therapies.[5]

The prevalence of pancytopenia among pediatric patients in Pakistan varies across different studies reported as 1.4% to 3.57%.[6,7] These variations may be attributed to differences in study populations and diagnostic criteria. Aplastic anemia is a significant non-malignant hematological disorder in Pakistan, ranking second in prevalence after thalassemia. Notably, the condition is more prevalent in Asian countries, including Pakistan, with rates two to three times higher than in other regions.[8] Local factors like delayed healthcare access, socio-economic disparities, high rates of infectious diseases (e.g., tuberculosis and hepatitis) and nutritional deficiencies (Megaloblastic anemia) further complicate timely diagnosis and management of pancytopenia.[8] Understanding the local etiological profile through bone marrow evaluation is essential to guide targeted treatments, optimize resource allocation, and improve clinical outcomes in children. This study aims to fill the gap by providing data on the etiological spectrum of pediatric pancytopenia, thereby contributing to evidence-based management strategies in the context of Pakistan's unique healthcare challenges.

MATERIALS AND METHODS:

Study design

It was a retrospective cross-sectional study conducted at the Department of Hematology and Transfusion Medicine, of a pediatric tertiary care hospital in Lahore, including patient data from five-month period that is January to May 2024. Study was carried from June-July 2024. Convenient Consecutive sampling was done.

Inclusion & Exclusion Criteria

One hundred children of age 1-15 years of both genders, presenting with pancytopenia on Complete Blood Count (CBC) and investigated through Bone marrow aspirate or trephine biopsy were included through bone marrow biopsies record which comprised of both inpatient and outpatient units. Neonates, patients on chemotherapy and those with incomplete medical record were excluded.

Data Collection and lab investigations:

A self-designed questionnaire was used for data collection, which included demographics, CBC and peripheral blood film findings. In CBC, the parameters such as hemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), platelet count (PC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were noted. Bone marrow aspirate and trephine biopsy findings were noted.

Data Analysis:

The data collected was statistically analyzed to obtain the frequencies, chi-square and p-values using SPSS version 23.0. The correlations where p-value was ≤0.05 were considered significant.

Ethical Considerations:

The study was approved by institutional Ethical Review Committee (Letter no. 1257/SAHS dated 5/10/2023). Informed consent was obtained from parents/guardians of all enrolled children telephonically.

RESULTS:

Among the total patients, the males were 53% while females were 47%. The mean age ±SD was 6.36 ±±3.184 years. According to ethnicity groups, there were 60% Punjabi, 18% Pathan, 4% Balochi, 9% Sindhi, 4% Afghani, and 5% Kashmiri.

The two most common etiologies for pancytopenia among children were found to be Aplastic anemia (16%) and megaloblastic anemia (14%). Among Aplastic anemia group majority patients were from 6-12years age bracket. The other causes found to be Acute leukemia, lymphomas, metastatic disease particularly neuroblastoma (6/7), erythroid hyperplasia with splenomegaly, infections associated, familial and acquired HLH, osteopetrosis, storage disorder and myelodysplastic syndrome (MDS) which included Refractory cytopenia of childhood (RCC) and MDS with excess blasts I and II. [Table 1]

Table 1: Frequency of different etiologies of pancytopenia in children

Etiology/ Cause	Frequency	Percentage
Acute leukemia	10	10%
Aplastic anemia	16	16%
Fanconi anemia	8	8.0%
Megaloblastic anemia	14	14%
Erythroid hyperplasia	8	8.0%
HLH	8	8.0%
MDS	4	4.0%
HL	4	4.0%
NHL	3	3.0%
Metastatic disease	7	7.0%
Sepsis/Infections	8	8.0%
Storage disease	7	7.0%
Osteopetrosis	1	1.0%
Hypersplenism	2	2.0%
Total	100	100.0%

HLH: Hemophagocytic lymphohistiocytosis, MDS: Myelodysplastic syndrome, HL: Hodgkin Lymphoma, NHL: Non-Hodgkin Lymphoma

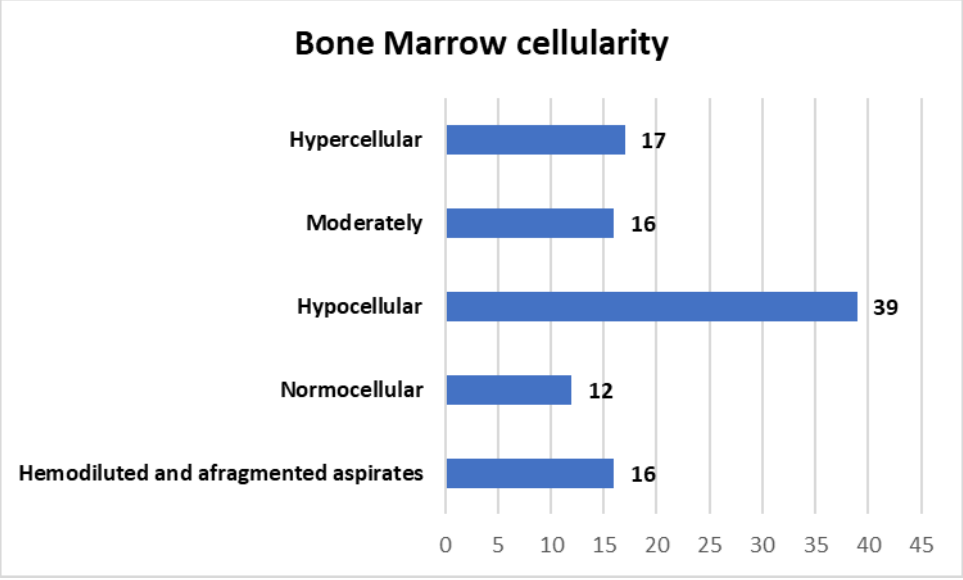
Table 2: Hematological parameters among different causes of pancytopenia in children

Etiology	Mean WBC count (x103/L)	Mean RBC count (x1012/L)	Mean HB (g/dl)	Mean of PLT (x103/L)
Acute leukemia	2.29	2.86	8.27	65.4
Aplastic anemia	2.73	2.07	7.51	38.6
Fanconi anemia	2.48	2.33	7.50	77.86
Megaloblastic anemia	2.50	2.67	6.62	70.02
Erythroid hyperplasia	2.50	2.44	8.04	72.6
HLH	2.56	2.83	6.53	84.33
MDS	2.16	2.19	6.28	61.6
HL	4.06	2.39	8.31	37.83
NHL	1.86	3.27	8.46	44.83
Metastatic disease	1.84	2.44	7.6	52.81
Sepsis	2.20	2.63	7.60	76.33
Storage disease	2.34	2.84	7.17	50.4
Osteopetrosis	2.30	2.19	6.50	54.0
Hypersplenism	1.67	2.30	7.24	35.6
p-value	0.74	0.62	0.56	0.55

The mean WBC count, RBC count and platelets count did not show any significant variation among different causes of pancytopenia. [Table 2]

On peripheral blood film, majority of Acute leukemia patients had microcytic hypochromic picture (7/10) with two showing leucopenia with few blasts. Normochromic normocytic RBC picture was seen in Aplastic anemia, Fanconi anemia, HLH and MDS patients. Macrocytes with hyper-segmented neutrophils were found in megaloblastic anemia (8/14). Nucleated RBCs were appreciated in osteopetrosis and storage disorder (3/7) cases, Dimorphic RBC were seen in sepsis, erythroid hyperplasia and acute leukemia.

Figure 1: Frequency of Bone marrow cellularity in children with peripheral blood pancytopenia



Hemodiluted and afragmented bone marrow aspirates were obtained in 16% patients. The cellularity was normal and moderate in 12% and 16% patients respectively. This group included patients of megaloblastic anemia,

MDS, Sepsis, metastatic and storage disorder. Hypocellular marrow for age was seen in 39% (Aplastic anemia: 16%, Fanconi anemia: 7%, HLH: 7%, HL: 4%, Osteopetrosis:1%) patients while 17% (Acute Leukemia: 6%, Erythroid hyperplasia: 6%, Megaloblastic anemia: 2%, sepsis: 3%) had hypercellular bone marrow. Hemorrhage was seen in 15%, necrosis in 4% and fibrosis in 2% biopsies. [Fig 1]

Table 3: Comparative analysis of different causes of pancytopenia in children from local and international studies

Study Reference	Study Location	Study Period	Sample Size	Common Etiologies
Local Studies				
Zil-e-Rubab et al9 2022	Southern Punjab	Not specified	121	Aplastic Anemia: 41.3% Acute Lymphoblastic Leukemia (ALL): 23.9% Infections: 10.8% Megaloblastic Anemia: 2.2%,
Memon S et al.10 2008	Karachi	2005-2007	230	Megaloblastic Anemia: 13.04% Aplastic Anemia: 23.9% Acute Leukemia: 13.05% Enteric fever: 10.8%
Zeb Jan A et al.6 2016	Peshawar	2006-2012	205	Aplastic anemia: 28.3% Hematological malignancies: 23.9% Megaloblastic anemia: 19.5%
Fazal W et al.11 2024	Peshawar	Not specified	106	Infections: 17.9% Megaloblastic anemia: 17%
International studies				
Harish C, et al.12 2019	Uttarakhand state of India	2017-2019	68	Megaloblastic anemia: 25% Aleukemic leukemia and hypoplastic/aplastic anemia: 19.1% (each)
Gayathri BN et al.13 2010	Davanagere	2005-2007	104	Megaloblastic anemia: 74.04% Aplastic anemia: 18.26%
Ghartimagar D et al.14 2017	Western Region of Nepal	2011-2016	138	Hypoplastic marrow: 27.5% Megaloblastic anemia: 18.8% Acute Leukemia: 13.76%

DISCUSSION

Pancytopenia in pediatric patients remains a critical hematological concern with diverse underlying causes. Our study identified aplastic anemia (16%) and megaloblastic anemia (14%) as the most common etiologies, which is consistent with findings from recent studies conducted in South Asia, including Pakistan and India.[6,15] The high prevalence of aplastic anemia may be linked to genetic predisposition, environmental toxins, and viral infections, as previously reported in multiple studies.[16,17] Additionally, megaloblastic anemia, commonly caused by vitamin B12 and folate deficiencies, aligns with previous research highlighting nutritional deficiencies as a major contributor to pancytopenia in developing countries.[18]

Our findings also indicate that acute leukemia (8%) and hemophagocytic lymphohistiocytosis (HLH) (8%) were significant causes. The majority cases of acute leukemia revealed pancytopenia but the marrow was packed with blast cells. The findings are concordant with the studies where hematological malignancies accounted for a substantial proportion of pediatric pancytopenia cases.[19,20] This reinforces the importance of early bone marrow biopsy for differentiating between benign and malignant causes, as highlighted in literature emphasizing its role as a definitive diagnostic tool.[21,22]

Bone marrow biopsy findings in our study showed hypocellularity in 39% of cases and hypercellularity in 17%, with hemorrhage (15%), necrosis (4%), and fibrosis (5%). These findings mirror those reported in international studies where hypocellular marrow was primarily associated with aplastic anemia, while hypercellular marrow suggested malignant infiltration or marrow activation due to infections or hematological malignancies.[23,24] The presence of necrosis and fibrosis further supports the utility of bone marrow trephine biopsy in identifying the underlying conditions such as Hodgkin lymphoma and metastatic diseases, which were also present in our cohort. The findings are consistent with other study.[25]

Peripheral blood film analysis in our study provided key diagnostic insights. Macrocytes with hypersegmented neutrophils in megaloblastic anemia, microcytic hypochromic RBCs with occasional blasts in acute leukemia, and dimorphic RBCs in sepsis and erythroid hyperplasia were consistent with previously documented hematological findings in pancytopenic patients.[26] However, as observed in prior research, CBC and peripheral smear alone were insufficient for a conclusive diagnosis, reaffirming the necessity of bone marrow evaluation.[27]

Overall, our study reinforces the findings from existing literature that aplastic anemia and megaloblastic anemia are among the leading causes of pediatric pancytopenia, while malignancies and infections also play a significant role. Early diagnosis through bone marrow biopsy, alongside hematological and peripheral smear analysis, remains essential for accurate classification and timely intervention. Future studies should focus on region-specific risk factors and genetic predispositions to improve diagnostic and therapeutic approaches for pediatric pancytopenia.

Limitations of the study: It was a single center study including limited cases. The selection bias was there because of convenient consecutive sampling as only the patients who underwent bone marrow biopsy were included, potentially missing those with benign disorders. The study also did not assess the long-term outcomes of such patients, so limiting insights into disease progression and treatment outcome. The future studies can focus on molecular and genetic determinants in pancytopenia pediatric patients.

CONCLUSION

Pancytopenia in children presents a diagnostic challenge due to its varied underlying causes. This study identified aplastic anemia and megaloblastic anemia as the most prevalent etiologies, emphasizing the role of bone marrow failure and nutritional deficiencies. While peripheral blood smear and hematological parameters offer preliminary diagnostic clues, bone marrow biopsy remains essential for definitive diagnosis. Early detection and appropriate management are crucial for improving patient outcomes in pediatric pancytopenia.

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Conflicts of interest

There are no conflicts of interest.

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