ORIGINAL ARTICLE

Etiological Spectrum of Pancytopenia Based on Bone Marrow Examination in Children

Shazia Memon, Salma Shaikh and M. Akbar A. Nizamani

ABSTRACT

Objective: To determine the spectrum of pancytopenia with its frequency, common clinical presentation and etiology on the basis of bone marrow examination in children from 2 months to 15 years.

Design: Observational study.

Place and Duration of Study: Department of Paediatrics, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, from October 2005 to March 2007.

Patients and Methods: All patients aged 2 months to 15 years having pancytopenia were included. Patients beyond this age limits, already diagnosed cases of aplastic anemia and leukemia, clinical suspicion of genetic or constitutional pancytopenia, history of blood transfusion in recent past, and those not willing for either admission or bone marrow examination were excluded.

History, physical and systemic examination and hematological parameters at presentation were recorded. Hematological profile included hemoglobin, total and differential leucocyte count, platelet count, reticulocyte count, peripheral smear and bone marrow aspiration/biopsy.

Results: During the study period, out of the 7000 admissions in paediatric ward, 250 patients had pancytopenia on their peripheral blood smear (3.57%). Out of those, 230 patients were finally studied. Cause of pancytopenia was identified in 220 cases on the basis of bone marrow and other supportive investigations, while 10 cases remained undiagnosed. Most common was aplastic anemia (23.9%), megaloblastic anemia (13.04%), leukemia (13.05%), enteric fever (10.8%), malaria (8.69%) and sepsis (8.69%). Common clinical presentations were pallor, fever, petechial hemorrhages, visceromegaly and bleeding from nose and gastrointestinal tract.

Conclusion: Pancytopenia is a common occurrence in paediatric patients. Though acute leukemia and bone marrow failure were the usual causes of pancytopenia, infections and megaloblastic anemia are easily treatable and reversible.

Key words: *Pancytopenia. Etiology. Bone marrow aspiration. Biopsy.*

INTRODUCTION

Pancytopenia is defined as the decrease in number of all the three formed elements of the blood is a triad of findings that result from a number of disease processes.[1]

Pancytopenia can result from either a failure of production of haematopoietic progenitors called aplastic anemia, or peripheral destruction of cellular element either due to infection, immune-mediated damage or hypersplenism.[2,3]

Alterations in peripheral blood counts resulting in bicytopenia or pancytopenia are commonly encountered in paediatric practice. Etiological spectrum in children ranges from common condition like iron deficiency anemia to relatively rare congenital disorders like Fanconi's anemia. It is relatively different in the developing countries from the developed ones.

Primary or genetic causes include Fanconi's anemia, dyskaratosis congenita, Swachman's diamond syndrome, and amegakaryocytic thrombocytopenia.[4] Acquired causes can be idiopathic or secondary to exposure to radiation, drugs and chemicals (chemotherapy, chloramphenicol, sulfa group, anti-epileptic, gold etc), viral infection (cytomegalovirus, Epstein-Barr, hepatitis B or C, HIV etc.), auto-immune, paroxysmal nocturnal hemoglobinuria, and marrow replacement disorders (leukemia, myelodysplasia, myelofibrosis).[5] Frequency may vary from 0.8%[1] and 1.2%[6] to 12.6%.[7]

Megaloblastic anemia and infections such as enteric fever malaria, kala-azar and bacterial infections can be common causes of pancytopenia in the developing countries.[8] Nutritional megaloblastic anemia is also one of the leading causes of pancytopenia in younger children.[9] Clinically, a child presenting with pancytopenia

Department of Paediatrics, Liaquat University of Medical and Health Sciences, Hyderabad.

Correspondence: *Dr. Shazia Memon, Aitmad Bungalows, H.No. 2, Near Citizen Co-operative Housing Society, Jamshoro Road, Hyderabad.*
E-mail: shaziamemon-ap@hotmail.com

Received June 26, 2007; accepted February 04, 2008.

should be evaluated for possibility of either a bone marrow failure syndrome or acute malignancy, particularly when associated with lymphadenopathy or visceromegaly.

Bone marrow examination is one of the most frequent and relatively safe invasive procedures done routinely in paediatric units. Though an invasive procedure, it can be easily performed even in the presence of severe thrombocytopenia with little or no risk of bleeding. Commonly, it is done for the evaluation of unexplained cytopenias and malignant conditions like leukemia. Bone marrow examination is also at times done for the diagnosis or staging of a neoplasm and storage disorders. Trephine biopsy is usually performed when there is hypoplasia or aplasia on aspiration.[10] There are wide variety of disorders in children where bone marrow examination provides diagnostically important information.

The aim of this study was to evaluate the etiological spectrum of childhood pancytopenias, with special reference to the non-malignant presentations, on the basis of bone marrow examination.

PATIENTS AND METHODS

This observational study was conducted in the Paediatric Department, LUMHS, on 250 cases with pancytopenia admitted from October 2005 to March 2007.

The inclusion criteria were patients aged 2 months to 15 years, who had pancytopenia on peripheral blood smear, and attendants consented for admission and bone marrow examination.

The exclusion criteria were the patients beyond these age limits, diagnosed cases of aplastic anemia and leukemia, clinical suspicion of genetic or constitutional pancytopenia, history of blood transfusion in the recent past, and those who were not willing for admission or for bone marrow examination. Pancytopenia was defined as hemoglobin (Hb) < 10g%, absolute neutrophil count (ANC) < $1.5*10^9$/L, platelet count < $100*10^9$/L. The pancytopenia was labeled as severe if patient had two or more of the following: Hb <7 gm%, ANC <$0.5*10^9$/L, and platelet count < $20*10^9$/L.[5]

The patients who fulfilled the inclusion criteria were admitted in the ward and their detailed history was taken after obtaining consent from their parents. Particular emphasis was paid to bleeding tendencies like epistaxis, malena, hematuria and hemetemesis. Also the history of consanguinity, drug intake, especially anticonvulsant (sodium valporate), antibiotics (sulfa group), anti-malarials and anti-tuberculous agents, and recent infections were enquired about. A thorough physical and systemic examination was conducted and all the clinical data was collected on the study proforma. Laboratory investigations performed in all cases included complete blood count {Hb, total leukocyte count (TLC), differential leukocyte count (DLC), platelet count, reticulocyte count and ANC}, peripheral blood smear, and bone marrow examination. Bone marrow biopsy was performed wherever aspiration was inconclusive. Other investigations that were performed in selected cases were peripheral smear for malarial parasite, serological tests for enteric fever and blood culture in suspected cases of septicemia. Bone marrow culture for typhoid was done in those cases where serological tests were negative in spite of strong clinical suspicion.

Data was expressed in percentages.

RESULTS

Two hundred and fifty patients with pancytopenia on their peripheral blood smear that made a frequency of 3.57% out of the 7000 total admissions during the study period. From those, 20 patients failed to complete inclusion criteria, and finally 230 patients were included in the study. Ten patients refused for bone marrow examination, 5 for admission; 3 patients received blood transfusion, 2 days before admission and 2 patients left the ward against medical advice before final diagnosis was made. From those 230 patients, the cause of pancytopenia was identified in 220 cases on the basis of bone marrow and other supportive investigations. Ten cases initially had pancytopenia on peripheral smear, but the bone marrow examination showed normal cellularity. The complete blood count was also improved on repeat analysis and no cause could be found for their initial pancytopenic presentation.

Out of 230 cases, there were 140 (60.86%) male and 90 (40.14%) female patients with male to female ratio of 1.6:1. Most cases seen were in between 6-10 years age group (n=130, 56.52%), while 60 (26.08%) were between 2 months to 5 years of age and 40 (17.39%) were between 11 and 15 years. The most common presenting symptom was pallor in 200 cases (87%) and fever in 150 cases (65%), which was prolonged for more than 2 weeks. Other symptoms were bruises or purpuric spots on the body, epistaxis, haemetemesis, malena, petechial hemorrhages, hematuria and joint pains (Table I).

Table I: Clinical features of pancytopenia at presentation (n=230).

Clinical feature	No. of cases	Percentage
Pallor	200	86.96
Fever	150	65.22
Bruises /purpura	140	60.86
Petechial hemorrhages	50	21.7
Malena	40	17.39
Hematemesis	40	17.39
Joint /leg pain	40	17.39
Bleeding from gums	50	21.7
Epistaxis	60	26.08
Hematuria	30	13.04

Non-malignant pancytopenia was seen in 190 (82.6%) patients and malignant were seen in 40 (17.4%) patients. Table II shows that in the non-malignant etiology, aplastic anemia was the most common cause seen in 55 cases (23.9%), followed by megaloblastic in 30 (13.04%), and iron/mixed nutritional deficiency anemia in 20 (8.69%). Other non-malignant causes were enteric fever, falciparum malaria, septicemia, and hypersplenism.

Table II: Etiological spectrum of pancytopenia (n=230).

Disease	No. of cases	Percentage
Non-malignant etiology		
Aplastic anemia	55	23.9
Megaloblastic anemia	30	13.04
Mixed nutritional deficiency anemia	20	8.69
Enteric fever	25	10.8
Severe malaria (*falciparum/vivax*)	20	8.69
Septecaemia	20	8.69
Hypersplenism	10	4.34
No cause identified	10	4.34
Total	190	82.59
Malignant etiology		
Acute lymphoblastic leukemia	20	8.69
Acute myeloid leukemia	05	2.17
Chronic myeloid leukemia	02	0.89
Lymphoma	05	2.17
Neuroblastoma	04	1.74
Nephroblastoma	04	1.74
Total	40	17.40

Among the malignant hematological disorders, acute lymphoblastic leukemia was the most common seen in 20 (8.69%) cases, followed by acute myeloid leukemia 05 (2.17%) cases and lymphomas 5 (2.17%). Few cases of neuroblastoma, nephroblastoma and chronic myeloid leukemia were also diagnosed during that 18 months period.

DISCUSSION

Pancytopenia is not an uncommon hematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained pallor, prolonged fever, and tendency to bleed. In the present study, the frequency of pancytopenia was 3.57%. The frequency shown in other studies is quite variable. According to a study conducted in Peshawar in the year 2000, it was 0.8%[1], while Kanchanalak *et al.*[6] and Adil *et al.*[7] reported 1.2% and 12.6% respectively.

In this study, many disease entities other than malignancies and bone marrow failure syndromes, importantly megaloblastic anemia and infections, emerged as recognizable causes of varying degrees of cytopenias.

Aplastic anemia was the most common found in 55 cases (23.9%). Epidemiologically, aplastic anemia has a pattern of geographic variation opposite to that of leukemia, with higher frequency in the developing world than in the industrialized West.[11] Large prospective studies indicate an annual incidence of two new cases per million populations in Europe and Israel.[12] Its exact incidence in Pakistan is not known due to lack of population-based studies. Studies from Thailand[13] and China[14], showed the incidence to be about three-fold that in the West. Its exact etiology is still not known but an auto-immune mechanism has been inferred from positive responses to non-transplant therapies and laboratory data. Most of the patients had taken pyramethamine-sulfamethaxazole, trimethoprim-sulfamethoxazole and sodium valporate. European studies have confirmed and quantified medical drugs as risks for the development of marrow failure.[15,16]

Another common etiological factor was nutritional anemia, especially megaloblastic. It accounted for 30 (13.04%) patients presenting with pancytopenia. Megaloblastic anemia due to vitamin B_{12} or folic acid deficiency is now a well-recognized and established cause of cytopenias.[17] It can either present as bicytopenia or pancytopenia, or rarely with thrombocytopenia only.[18] Various studies including all age groups have reported pancytopenia in megaloblastic anemia ranging from 11-47%.[19] In almost all those studies, pancytopenia was the main presentation and so was the case in this study. The usual presenting feature of megaloblastic anemia was pallor (anemia) and varying degree of skin and mucosal bleeding. Though, the underlying cause of megaloblastic anemia could not be determined, but folate deficiency is more common in children, while B_{12} deficiency is more common in adults.[10] The usual presenting age in the developed world is infancy. A possible explanation of folates deficiency in our country could be the various chronic inflammatory disorders of the gut, like chronic diarrheas, parasitic infections and malabsorption states, apart from poor nutrition. Among the other micronutrient anemia, mixed deficiency anemia (microcytic and macrocytic) was seen in 15 cases and iron deficiency (microcytic) was seen in 5 cases only. This percentage is much lower than expected, because 60 – 80% of the world population is affected by iron deficiency anemia, which is the most common preventable nutritional deficiency in the world.[20] The possible explanation is that majority of the cases of iron deficiency anemia and mixed anemias usually presented with anemia rather than pancytopenia and diagnosed on smear examination and were treated as outpatients. This study was hospital-based and on

pancytopenic patients only.

Various infections as cause of pancytopenia have been variedly documented. In this study, 65 (28.2%) patients with infections. Enteric fever accounted for 25 (10.8%) patients and 10 of those had severe pancytopenia. Pancytopenia in enteric fever is caused by varied mechanisms. Bone marrow may undergo histiocytic hyperplasia along with hemophagocytosis or complete necrosis. Immune mediated hemolysis or leucopenia, hypersplenism and transient disseminated intravascular hemolysis are other contributory mechanisms.[21] Varying degrees of cytopenias have been reported in many other series on enteric fever.[22,23]

Besides enteric fever, malaria due to *Plasmodium vivax* and *P. falciparum* was also found in causation of pancytopenia. In this study, 20 (8.69%) patients presented with severe malaria as a cause of pancytopenia. *P. falciparum* was found in 15 cases, while *P. vivax* was seen as etiology in the remaining 5 cases. Aouba reported hemophagocytic syndrome resulting due to *P. vivax* infection as cause of pancytopenia.[24] In this study, *P. falciparum* malaria caused more complication and morbidity as reported in other studies as well.[25, 26]

Malaria causes anemia and thrombocytopenia due to direct invasion by parasite, immune hemolysis, disseminated intravascular coagulation hypersplenism and hemophagocytosis.[27]

Fulminant bacterial sepsis as cause of pancytopenia is scarcely reported in literature. In this study, 20 (8.69%) patients had all three cell lines affected due to sepsis at presentation. Eight of those patients had gram-negative sepsis – 4 with *Klebsiella* and 4 with *Pseudomonas*. However, in other patients, no cause was elicited for their clinical presentation of sepsis with pancytopenia. Garewal *et al.* reported gram-negative sepsis secondary to bone marrow necrosis in 2 patients.[28]

In this study, 40 cases (17.39%) presented with malignant etiology as a cause of pancytopenia. Acute lymphoblastic leukemia was the most common malignancy diagnosed in 20 (8.69%) cases. Acute lymphoblastic leukemia are diagnosed in the United States at a rate of approximately 2500 cases per annum, accounting for about one-third of all the cases of childhood cancers. Eighty percent of these are acute lymphoblastic leukemia (ALL), 17% are acute myeloid leukemia (AML) and the rest are cases of chronic myeloid leukemias.[29] Little is known regarding the epidemiology, etiology and incidence of childhood cancer in developing countries.

CONCLUSION

Pancytopenia is a common occurrence in paediatric patients. Though acute leukemia and bone marrow failure were the usual causes of pancytopenia, infections and megaloblastic anemia are easily treatable and reversible.

REFERENCES

1. Habib-ur-Rehman, Fazil M, Khan FM. The etiological pattern of pancytopenia in children upto 15 years. *Pak Armed Forces Med J* 2003; **53**: 183-7.
2. Pizzo PA, D'Andera AD. The pancytopenias. In: Behrman RE, Kleigman RM, Jenson HB. Nelson textbook of pediatrics. 17th ed. Philadelphia: *Saunders;* 2003:p.1642-6.
3. Lanzkowsky P. Manual of pediatric hematology and oncology . 2nd ed. New York: *Churchill Livingstone;* 1995: p.77-95.
4. Brodsky RA, Jones RJ. Aplastic anaemia. *Lancet* 2005; **365**:1647–56.
5. Alter BP. Bone marrow failure syndromes in children. *Pediatr Clin North Am* 2002; **49**:973-88.
6. Adil SN, Burney IA, Kakepoto GN, Khurshid M. Epidemiological features of aplastic anemia in Pakistan. *J Pak Med Assoc* 2001; **51**: 443-5.
7. Ghorpade K, Baldota S. Pancytopenia - its causes in Bombay. *J JJ Group Hosp Grant Med Coll* 1991; **33**: 30-2.
8. Bhatnagar SK, Chandra J, Narayan S, Sharma S, Singh V, Dutta AR. Pancytopenia in children: etiological profile. *J Trop Pediatr* 2005; **51**: 236-9.
9. Katar S, Nuri Ozbek M, Yaramis A, Ecer S. Nutritional megaloblastic anemia in young Turkish children is associated with vitamin B_{12} deficiency and psychomotor retardation. *J Pediatr Hematol Oncol* 2006; **28**: 559-62.
10. Fazlur Rahim, Ahmad I, Saiful Islam, Hussain M, Khattak TAK, Bano Q. Spectrum of hematological disorders in children observed in 424 consecutive bone marrow aspirations/biopsies. *Pak J Med Sci* 2005; **21**: 433-6.
11. Issaragrisil S, Leaverton PE, Chansung K, Thamprasit T, Porapakham Y, Vannasaeng S, *et al.* Regional patterns in the incidence of aplastic anemia in Thailand. The Aplastic Anemia Study Group. *Am J Hematol* 1999; **61**: 164-8.
12. Young NS. Hematopoietic cell destruction by immune mechanisms in acquired aplastic anemia. *Semin Hematol* 2000; **37**: 3-14.
13. Issaragrisil S, Chansung K, Kaufman DW, Sirijirachai J, Thamprasit T, Young NS. Aplastic anemia in rural Thailand: its association with grain farming and pesticide exposure. Aplastic Anemia Study Group. *Am J Public Health* 1997; **87**: 1551-4.
14. Yang C, Zhang X. Incidence survey of aplastic anemia in China. *Chin Med Sci J* 1991; **6**: 203-7.
15. Kaufman DW, Kelly JP, Levy M, Shapiro S. The drug etiology of agranulocytosis and aplastic anemia. New York: *Oxford University Press;* 1991.
16. Acharya S, Bussel JB. Hematologic toxicity of sodium valporate. *J Pediatr Hematol Oncol* 2000; **22**: 62-5.
17. Chandra J, Jain V, Narayan S, Sharma S, Singh V, Kapoor AK, *et al.* Folate and cobalamin deficiency in megaloblastic anemia in children. *Indian Pediatr* 2002; **39**:453-7.
18. Jan MA. Thrombocytopenia in children. *J Postgrad Med Inst* 2004; **18**: 353-8.

19. Niazi M, Fazli-Raziq. The incidence of underlying pathology in pancytopenia : an experience of 89 cases. *J Postgrad Med Inst* 2004; **18**: 76-9.

20. Zlotkin S. A new approach to control of anemia in "at risk" infants and children around the world. Ryley-Jeffs memorial lecture. *Can J Diet Pract Res* 2004; **65**:136-8.

21. Malik AS. Complications of bacteriologically confirmed typhoid fever in children. *J Trop Pediatr* 2002; **48**: 102-8.

22. Paydas S, Ergin M, Baslamisli F, Yavuz S, Zorludemir S, Sahin B, *et al.* Bone marrow necrosis: clinicopathologic analysis of 20 cases and review of the literature. *Am J Hematol* 2002; **70**: 300-5.

23. James J, Dutta TK, Jayanthi S. Correlation of clinical and hematologic profiles with bone marrow responses in typhoid fever. *Am J Trop Med Hyg* 1997; **57**: 313-6.

24. Aouba A, Noguera ME, Clauvel JP, Quint L. Hemophagocytic syndrome associated with *Plasmodium vivax* infection. *Br J Haematol* 2000; **108**: 832-3.

25. Zvulunov A, Tamary H, Gal N. Pancytopenia resulting from hemophagocytosis in malaria. *Pediatr Infect Dis J* 2002; **21**: 1086-7.

26. Patel DN, Pardeep D, Surti MM, Agerwal SB. Clinical manifestations of complicated malaria: an overview. *J Indian Acad Clin Med* 2003; **4**: 323-31.

27. Ohno T, Shirasaka A, Sugiyama T, Furukawa H. Hemophagocytic syndrome induced by *Plasmodium falciparum* malaria infection. *Int J Hematol* 1996; **64**: 263-6.

28. Garewal G, Marwaha N, Marwaha RK, Das KC. Bone marrow necrosis and pancytopenia associated with gram-negative septicemia. *Indian Pediatr* 1991; **28**: 79-81.

29. Gaynon PS, Bostrom BC, Hutchinson RJ, Lange BJ, Nachman JB, Steinherz PG, *et al.* Duration of hospitalization as a measure of cost on Children's Cancer Group acute lymphoblastic leukemia studies. *J Clin Oncol* 2001; **19**:1916-25.