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Pancytopenia – (?) An obstacle in the diagnosis and outcome of pediatric acute lymphoblastic leukemia

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Abstract

Context: Acute lymphoblastic leukemia (ALL) ranks first among pediatric malignancies. 8–12% of ALL present with pancytopenia and 2% with hypocellular marrow a. Diagnosis of ALL in the background of pancytopenia and aplastic bone marrow is difficult. **Aims:** This study was aimed to compare the clinicopathologic, genetic, and outcome of paediatric ALL patients with and without pancytopenia. **Settings and Design:** This is a retrospective cross-sectional study. **Subjects and Methods:** The study included all ALL patients presenting with pancytopenia. The control group included equal number of randomly selected patients with ALL without pancytopenia treated during the same period. Ethics committee approved this study. The demographic, laboratory, and treatment-related details were retrieved from the records and entered in an Excel sheet. **Statistical Analysis Used:** Data was analyzed with Chi-square test with IBM SPSS statistics 16 software. **Results:** Diagnosis by peripheral smear is significantly lower ($P = 0.015$) in comparison with the control group. There is no significant difference in diagnosis between the groups by bone marrow aspirate ($P = 0.731$) and biopsy ($P = 0.849$). The diagnosis of leukemia is misdiagnosed as hypo cellular/aplastic marrow in 10% of the pancytopenic patients. Flow cytometry yielded the diagnosis in all the pancytopenic patients. Though cytogenetic abnormalities are more common in pancytopenic group, it is not statistically significant ($P = 0.106$). There is no significant difference in treatment outcome between the groups ($P = 0.0827\%$). **Conclusions:** Clinical expertise is highly essential to evaluate a case of pancytopenia to diagnose leukemia. Pancytopenia is an obstacle in the diagnosis of ALL without immunophenotyping. There is no significant difference in the outcome between the two groups.

Key words: Acute lymphoblastic leukemia, flow cytometry, pancytopenia, pediatric acute lymphoblastic leukemia

Introduction

In India, pediatric malignancy includes 1.6–4.8% of all cancers, affecting nearly 38–124 children per million per year. Acute leukemia ranks first among the pediatric cancers with an incidence of 25–40%, almost similar to a worldwide incidence.[1] Acute lymphoblastic leukemia (ALL) is by far, the most common, constituting 60–85% of the above and male children are more commonly affected; most of them being between 2 and 5 years of age.[2] Commonly, the peripheral blood shows blasts, but many times, they go undetected as their population is very minimal, as in a setting of pancytopenia or leukopenia.

In pancytopenia, the marrow can be hypo cellular or hypercellular. The hypoplastic marrow which occurs in 2% of pediatric ALL patients may be misdiagnosed as aplastic anemia.[2,3] Some authors had suggested that aplastic anemia in the pediatric age group, which responded to steroids, was in fact a pre-leukemic phase of ALL as in another case report, ALL occurred within 6 months of diagnoses of aplastic anemia in children.[4,5]

Studies done have shown leukemia to be the second most common cause of pancytopenia in pediatric patients, marginally behind aplastic anemia.[3] The diagnosis of cases presenting with pancytopenia or leukopenia needs complete evaluation of hemogram, peripheral blood and bone marrow picture, immunophenotyping, and cytogenetics with good expertise, especially when there is even the slightest clinical suspicion of leukemia or in a child with unexplained febrile illness. This is essential as the remission, and cure rate for ALL in pediatric age groups are very good with early detection and treatment.

In this study, we describe a group of pediatric patients in whom pancytopenia was the initial hematological finding and with various evaluation methods, the diagnosis of ALL had been made. The pancytopenic group of ALL was compared with ALL children without pancytopenia. Analysis of peripheral blood, bone marrow, immunophenotyping, cytogenetics, were made to find out the importance of each parameter and have a global approach for prompt diagnosis. The clinical outcome of these patients has also been assessed.

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Subjects and Methods

This is a cross-sectional comparative study done in the Department of Pathology and Paediatric Hemato Oncology, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra University for a period of 5 years, July 2009 to June 2014. The study group includes all the twenty-two patients in the pediatric age group who presented with pancytopenia and were evaluated and diagnosed to have ALL in Sri Ramachandra Medical Centre and Sri Ramachandra Medical College Hospital. The criteria for pancytopenia included three factors namely, Total white blood cell (WBC) count <4000 cells/mm^3, hemoglobin <10 g/dl, platelets <1.5 lakh cells/mm^3.[6] The control group includes 22 ALL pediatric patients without pancytopenia diagnosed and treated at the same period in the same center who were randomly selected.

Ethical approval was obtained from the Institutional Ethics Committee. The patient details and the laboratory details were retrieved from medical and laboratory records. The clinical outcome and follow-up details were obtained from the treating oncology team. The data were entered in Microsoft Excel Sheet and the statistical analysis and Chi-square test were done using IBM SPSS statistics 16 software.

Results

The age group of study patients was between 2 and 17 years, and controls were between 7 months and 17 years. Males dominated females with a male:female ratio of 1.2:1 and 1.8:1 in study group and control group respectively. The total WBC count, hemoglobin and platelet values are shown in Table 1. The diagnostic profile of all patients presenting with pancytopenia and without pancytopenia is shown in Table 2.

In the peripheral smear, blasts were detected in 63.6% of the patients without pancytopenia, but only 27.4% yielded

Table 1: Cell counts of study and control group

Patient group (22 vs. 22)	WBC (cells/mm^3)		HB (g/dl)		Platelet number (cells/mm^3)	
	Range	Mean	Range	Mean	Range	Mean
Pancytopenia	1100-3890	2790	3.3-11.4	7.7	0.2-1	0.9
Nonpancytopenia	3600-262,360	40,730	4.6-14.3	8.6	0.15-1	1.7

WBC=White blood cell, HB=Hemoglobin

blasts when there was pancytopenia, and this is statistically significant ($P < 0.05$). There is no significant difference in the positive results by bone marrow aspirate and biopsy between the two groups. Misdiagnosis of aplasia was done in 10% of cases of pancytopenia and as reactive marrow in 10% of the control group which when reviewed blindly by another pathologist showed the same result. Flow cytometry yielded 100% positive results categorizing them into pre-B-ALL, common B ALL, T ALL. Though T ALL was more common in patients without pancytopenia, there is no significant difference in the category between the groups.

Among the patients with pre-B-ALL, 2 patients (22.22%) had cytogenetic abnormalities in the form of hyperdiploidy and 46 XY t(9,22). Both the patients completed the treatment and are in remission since 4.5 years and 3.8 years. Among the 10 common ALL patients, 4 (44.44%) had cytogenetic abnormalities like BCR-abl mutation in 3, and TEL-AML1 positivity in 1. Among these, 3 are in maintenance and one died in relapse within 2 years of treatment. Among the control group, only two patients had cytogenetic abnormality mainly deletion 9(q) and bcr abl fusion gene positivity.

The outcome of the patients till the follow-up period when compared showed no significant difference between the two groups. The median duration of follow-up is 25.23 ± 15.36 months and 23.95 ± 13.99 months in patients with pancytopenia and without respectively without significant difference. The overall survival, death rate and current status of the patients are shown in Figure 1, Tables 3 and 4, respectively.

Discussion

This is the first study of its kind with an analysis of clinicopathological and genetic features and survival outcome of pediatric patients with ALL, presenting with pancytopenia and comparing the features with ALL patients without pancytopenia of the same age group, who were diagnosed and treated at the same period by the same team. Peripheral smear and the bone marrow diagnosis were the most common methods of diagnosis of leukemia in earlier days. Today, advancements such as immunophenotyping and cytogenetics assist in the categorization of the leukemia and estimating prognosis respectively. In comparison with Rana *et al*. and Arora *et al*. acute lymphoblastic leukemia is the most common (33%) pediatric malignancy in our study.[1,7]

Pancytopenia is a hematological condition where all the three blood cell lineages are suppressed. The bone marrow can be hypercellular, or hypo cellular. Hypercellularity is commonly expected in leukemia, megaloblastic anemia, and myelodysplastic syndromes; hypocellularity in aplastic anemia. Jan *et al*. had reported 23.9% of hematological malignancies presenting with pancytopenia in the pediatric age group of which ALL was the commonest with 11.7% of cases.[8] Thus, it is highly essential to differentiate and diagnose the cause of pancytopenia. We have studied 22 cases of pediatric ALL with pancytopenia and control group of 22 pediatric patients with ALL without pancytopenia who were treated in the study center. The age group is from 2 to 17 years, with a mean age of 7.5 years. The maximum number of patients, nearly 50%, was below 5 years of age. Many studies have shown pancytopenia is common in children lesser than 5 years of age.[2,4] According to the literature, 2% of patients with ALL presented with transient marrow aplasia. Marrow aplasia was noted in 10% of patients in this study. In the present study, male and female population were almost equal with 1.2:1 ratio, in contradiction with earlier reports where females were predominating.[2,5] But, the study population was smaller when compared to ours. One large study showed male predominance.[6]

Peripheral neutropenia was noted in all patients except one, ranging from 2% to 54.6%. Lymphocytosis was observed in all cases except one. Ten patients (45.45%) had microcytic, hypochromic anemia. Five patients (22.7%) had dimorphic type of anemia.

According to the literature, pancytopenia is seen 8.69–11.02% of the patients with ALL.[6,8] In the present study, pancytopenia was present in 12.2% of ALL patients of the pediatric age group, in whom blasts were not detected in majority (72.7%), but a greater number of smears show blasts when there is no pancytopenia. Clinical suspicion of hematological disorder led to bone marrow evaluation. There is no difference in the level of diagnosis of ALL between the two groups. Even in bone marrow study 10% were misdiagnosed as an aplastic marrow. Various authors have reported the incidence of aplastic picture in ALL as 0.2%[6] to 2%.[2,9] It is not yet understood whether this aplastic picture is an episode of preleukemic bone marrow failure, spontaneous remission of ALL, infection or transfusion induced remission or immune-mediated reaction to control leukemic proliferation.[2,5,10]

However in the present study, immunophenotyping could detect all the 40 cases of study group and control group, that is, 100% detection. The value of immunophenotyping in the categorization of leukemia is well-known. In our study, immunophenotyping is considered the gold standard for the diagnosis of clinically suspected hematological disorders or leukemia that goes undetected by peripheral smear and marrow studies. These cases are categorized into common-B-ALL which are CALLA positive pre-B ALL, pre-B ALL with CALLA negativity and T ALL. Pancytopenia and aplasia are seen more commonly in pre B ALL, equally distributed between common-B-ALL and pre-B-ALL. Breatnach *et al*.[2] observed six cases of common-ALL presenting with aplasia. Yousif *et al*.[5] has published a case report of a similar patient. Similar presentations have also been observed by Tharmalingam *et al*.,[11] Dharmasena *et al*.[12] adults. However, in the present study, both pre B-ALL and common-B-ALL presented with pancytopenia. This implies that ALL of any category can

Table 2: Evaluation of ALL by different diagnostic methods

Group	PS 22/22		BMA 21/22			BMB 20/20			Flow cytometry 20/20			Cytogenetics 17/17	
	Detected	Nondetected	Detected	Nondetected	Misdiagnosed	Detected	Nondetected	Misdiagnosed	Pre-B	Common B	T-ALL	Abnormality	No-abnormality
Pancytopenia number %	6	16	14	3	4	16	2	2	9	10	1	6	11
	27.4	72.7	66.7	14.3	19	80	10	10	45	50	5	35.3	64.7
Nonpancytopenia number %	14	8	13	5	4	14	2	4	7	10	3	12	15
	63.6	36.4	59	22.8	18.2	70	10	20	35	50	15	11.8	88.2
P	0.015		0.731			0.849			0.741			0.106	

Comparison of pancytopenia versus nonpancytopenia. ALL=Acute lymphoblastic leukemia, BMA=Bone marrow aspirate, BMB=Bone marrow biopsy, PS=Performance status

Table 3: Death rate (<2 years)

Group	Number (%)
Pancytopenia	3 (13.66)
Nonpancytopenia	3 (13.66)

Table 4: Status of the patient treated at center

	Outcome			
	Completed well	Maintenence	Death	Relapse
Pancytopenia				
Count	6	10	3	2
% within code	27.3	45.5	13.6	9.1
Nonpancytopenia				
Count	6	11	3	1
% within code	27.3	50.0	13.6	4.5

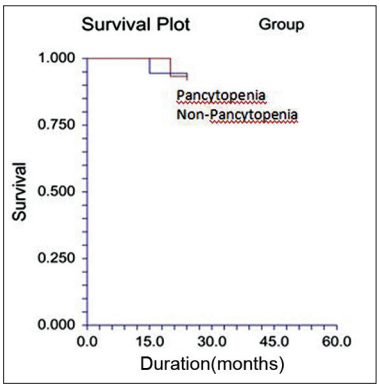

Figure 1: Kaplan Meier survival plot

present with pancytopenia. T-ALL was more common in patients without pancytopenia.

Cytogenetic abnormalities are also seen commonly in ALL in earlier studies (55.5%).[13] In the present study, cytogenetic abnormalities were seen in significant number of patients with pancytopenia than without. It had been known that translocations like t(4;11) and t(9;22) are seen in B-ALL; intrachromosomal amplification of chr 21 is seen in pre-B-ALL.[14,15] In pediatric ALL, high hyperdiploidy and near haploidy were good and poor risk factors respectively. But in the present study, no difference was found in the outcome regarding whether the patient has cytogenetic abnormalities or not. The abnormalities found are hyperdiploidy, translocation (9 22), bcr abl fusion gene and TEL-AML1 positivity. Like previous reports patients with hyperdipoloidy completed treatment and is in remission for 4 years 6 months. One of the patient with t(9 22) has completed treatment and is in remission for 3 years 2 months, and other is in maintenance therapy for 2 months. A patient with bcr abl fusion gene died at 2 years due to relapse while the other is surviving in the maintenance phase. Matloub *et al*. had reported poor outcome in a case of ALL with a prodrome of aplasia and an abnormal clone of 56 chromosomes.[5]

The outcome was compared between patients with and without pancytopenia. There is no significant difference between the two groups when outcome is considered also there is no significant difference in the death rate. The mean survival is 25.23 ± 15.36 months and 23.95 ± 13.99 months in patients with pancytopenia and without respectively without significant difference. Kulkarni and Marwaha have compared 66 pancytopenic and 466 patients without pancytopenia and found the mean outcome was significantly high in patients with pancytopenia.[6] But in the present study, though the study population is less, both the groups are of same sample size and no difference was made out. Though in pancytopenia, the bulky disease and blast percentage in the circulation may be low, thrombocytopenia, bone marrow blast burden and risk of sepsis are higher.

Conclusion

Clinical expertise is highly essential to evaluate a case of pancytopenia to diagnose leukemia. Pancytopenia is an obstacle in diagnosing ALL by peripheral blood. Misdiagnosis of aplasia can occur with bone marrow aspirate and biopsy study when the patients are in the prodrome or the transformation phase of leukemia. Flow cytometry is the gold standard in the diagnosis and categorization of ALL even when the patients are pancytopenic. There is no significant difference in the outcome of patients with and without pancytopenia with respect to duration or status of living. There is no statistically significant difference in the death rate.

Limitations of the Study and Future Perspective

The duration of the study for the survival outcome is short in the present study. Prospective study with 10-year follow- up with more number of patients and clinical variables may throw more light in this subject especially in economically constrained nations.

References

1. Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer 2009;46:264-73.

2. Breatnach F, Chessells JM, Greaves MF. The aplastic presentation of childhood leukaemia: A feature of common-ALL. Br J Haematol 1981;49:387-93.
3. Kelly K, Murphy P. Aplastic anaemia preceding acute lymphoblastic leukaemia in an adult with isolated deletion of chromosome 9q. Leuk Res 2008;32:1936-8.
4. Melhorn DK, Gross S, Newman AJ. Acute childhood leukemia presenting as aplastic anemia: The response to corticosteroids. J Pediatr 1970;77:647-52.
5. Matloub YH, Brunning RD, Arthur DC, Ramsay NK. Severe aplastic anemia preceding acute lymphoblastic leukemia. Cancer 1993;71:264-8.
6. Kulkarni KP, Marwaha RK. Acute lymphoblastic leukemia with pancytopenia at presentation: Clinical correlates, prognostic impact, and association with survival. J Pediatr Hematol Oncol 2013;35:573-6.
7. Rana ZA, Rabbani MW, Sheikh MA, Khan AA. Outcome of childhood acute lymphoblastic leukaemia after induction therapy – 3 years experience at a single paediatric oncology centre. J Ayub Med Coll Abbottabad 2009;21:150-3.
8. Zeb Jan A, Zahid B, Ahmad S, Gul Z. Pancytopenia in children: A 6-year spectrum of patients admitted to Pediatric Department of Rehman Medical Institute, Peshawar. Pak J Med Sci 2013;29:1153-7.
9. Reid MM, Summerfield GP. Distinction between aleukaemic prodrome of childhood acute lymphoblastic leukaemia and aplastic anaemia. J Clin Pathol 1992;45:697-700.
10. Diamond LK, Luhby LA. Pattern of spontaneous remissions in leukemia of childhood, observed in 26 of 300 cases. Am J Med 1951;10:238-9.
11. Tharmalingam H, Naresh K, Bain BJ, Pavlu J. Hypoplastic presentation of acute lymphoblastic leukemia. Am J Hematol 2012;87:702.
12. Dharmasena F, Littlewood T, Gordon-Smith EC, Catovsky D, Galton DA. Adult acute lymphoblastic leukaemia presenting with bone marrow aplasia. Clin Lab Haematol 1986;8:361-4.
13. Padhi S, Sarangi R, Mohanty P, Das R, Chakravarthy S, Mohanty R, *et al*. Cytogenetic profile of paediatric acute lymphoblastic leukaemia (ALL) – Analysis of 31 cases with review of literature. Carylogia 2011;64:33-41.
14. Heerema NA, Sather HN, Sensel MG, Kraft P, Nachman JB, Steinherz PG, *et al.* Frequency and clinical significance of cytogenetic abnormalities in pediatric T-lineage acute lymphoblastic leukemia: A report from the Children's Cancer Group. J Clin Oncol 1998;16:1270-8.
15. Harrison CJ. Cytogenetics of paediatric and adolescent acute lymphoblastic leukaemia. Br J Haematol 2009;144:147-56.

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