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Evaluation of aberrant expression of CD markers in acute leukemia cells

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Abstract

Background and objective: Worldwide immunophenotyping by flow cytometry (FCM) in acute leukemia (AL) is the golden step in the diagnosis. It's very common for acute leukemias to aberrantly express antigens or cluster of differentiation (CD) markers which are usually expressed in other lineages of the disease hence this study aimed at determining the prevalence of aberrancy in AL and to find out the frequency of each aberrant CD marker and their association with the clinic-hematological profile of the cases.
Methods: Following history and clinical examination of enrolled patients, blood and/or bone marrow aspirate was drawn for morphological examination and immunophenotyping by FCM from 86 newly diagnosed acute leukemia cases then multiple steps procedure was applied followed by interpretation of the results.
Results: The prevalence of aberrant phenotype was 46.5%. The proportional frequency of aberrant phenotype in acute myeloid leukemia (AML) was 41%, in B-acute lymphoblastic leukemia (B-ALL) was 48.8% and in T-acute lymphoblastic leukemia (T-ALL) was 66.6%. The commonest aberrant CD markers in AML were CD22 and CD2, in B-ALL were CD66c and CD13 while in T-ALL were CD13 and CD33. The aberrant phenotype harbored lower white blood cell (WBC) count and blast percentage in PB, also splenomegaly was more frequent in lymphoid positive (Ly+) AML and myeloid positive (My+) T-ALL while in B-ALL, splenomegaly was more frequent in myeloid negative (My-) B-ALL.
Conclusion: Aberrant phenotype prevalence in our study sample was comparable to other studies, considerable frequency of aberrant markers is present in cases of AL and some variations exist regarding the clinical and hematological profile of the aberrant group.
Keywords: Aberrant phenotype; Flow cytometry; Acute leukemia; AML; B-ALL; T-ALL

Introduction

Acute leukemia is a term used to define the malignant transformation that affects the stem cell precursors of the myeloid lineage (red blood cells, while blood cells and platelets) and/or the lymphoid lineage (B and T lymphoid cells) which evolves rapidly due to the underlying genetic aberrations that induce the neoplastic alterations and clonal proliferation.[1-3]
In order to accurately diagnose and classify AL, integrative multiple steps are crucial to be done which are clinical history and examination, morphological, cytochemical, immunophenotypic and cytogenetic and molecular analysis.
The immunophenotyping by multi parametric FCM of the immature malignant blast population of AL is vital to determine the lineage of the blast cell and hence to classify AL.[4]
The leukemic blast cells harbor immunophenotypic markers which are also called as antigens or CD markers on their surfaces, however, sometimes the blast cells express an anomalous expression

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which contradicts their usual familiar phenotype pattern and this is denoted as aberrant expression or aberrant phenotype. [5]

The aberrant phenotype could be organized into several types including: cross-lineage aberrancy that's when the myeloid CD marker is expressed on B-ALL and T-ALL blasts or when B or T lymphoid CD marker is expressed on AML blasts, the other type is asynchronous expression in which the most immature CD markers are co-expressed with the most mature ones and the last type is antigen overexpression giving the appearance of abnormal light scatter pattern.[6]

The clinical and prognostic significance of such aberrant antigens is still uncertain.[7] To know the prevalence and frequency of expression of such aberrant markers in cases of AL is quite important to avoid diagnostic confusion with mixed phenotype AL, to decide the treatment plan and to determine the prognosis through minimal residual disease examination (MRD).[8,9] Analysis of the aberrant phenotype in relation to the clinical and hematological profile of the cases also helps in determining the prognostic significance of their expression.[10] so the objective of this study is to find out the prevalence of aberrant phenotype and the frequency of each aberrant CD marker and their association with clinic-hematological profile of the cases.

Methods

This prospective observational cross-sectional study was conducted in Nanakaly Hospital for Blood Diseases in Erbil, Kurdistan region, Iraq (clinical flow cytometry unit) over a period extending from 1st September 2021 to 1st April 2022. A total number of 86 cases were included in the study and they were chosen by non-random convenient sampling method which was based on including every case of new onset de novo acute leukemia (AML, B-ALL and T-ALL) of any age or gender attending Nanakaly Hospital. Relapsed cases, cases receiving chemotherapy, secondary AML and MPAL were all excluded from the study. Cases were divided into adult age group ≥ 15 years old and pediatric age group < 15 years old.

Following history taking and physical examination, 2-3 cc blood was drawn from each patient for morphological examination and another 2-3 cc of BM or PB sample was taken (in 58 cases BM sample was used and in 28 cases PB sample was used) and placed in EDTA tubes for immunophenotyping study of cytoplasmic/ nuclear or surface antigenic markers by FCM which utilized three laser light sources. Daily calibration of the device was performed and to avoid overlapping between different fluorochromes, compensation by using BD ™ FC Beads was done on monthly basis.

Immunophenotyping was performed using BD FACSCanto ™ II Flow Cytometer (BD Biosciences, San Jose, CA), within 24 hours of sample collection using the standard stain-lyse-wash method for surface antigens and lyse-stain-wash method upon adding reagent A initially for fixation followed by reagent B for lysing for cytoplasmic antigens. The myeloid specific markers were (MPO, CD13, CD33, CD15 and CD117), the monocytic markers were (CD11c, CD64, CD14 and CD36), B-lymphoid specific markers were [CD19, CD22, CD10, CD79a and CD20], T-lymphoid/natural killer specific markers were (CD1a, CD2, CD3, CD4, CD5, CD56 and CD7) and the common markers were [CD45, CD99, CD34, HLA-DR, Terminal deoxynucleotidyl transferase (TdT) and CD38].

The sample was acquired as soon as possible on the FCM, the cells (events) appeared on the computer, a minimum of ten thousand events were acquired per tube. Blast cells population identification was done by using gating strategies either using forward scatter (FSC) versus side scatter (SSC) or CD45 versus SSC. The surface markers were considered positive

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when they were expressed by 20% of the cells while the cytoplasmic markers were considered positive when they were expressed by 10% of the cells according to the consensus by European Group of Immunological Characterization of Leukemia (EGIL).[11] Diagnosis was made based on the 2016 World Health Organization (WHO) criteria.[12] The clinical response of the cases was assessed by evaluation of the BM aspirate morphology post induction chemotherapy as blast count of less than 5% was considered as complete remission (CR) along with normal blood counts and clinical status.

Ethical consideration

A detailed questionnaire was used for this purpose and verbal consent was taken from the cases or their caregivers and the study was approved by the Scientific and Research Ethics Committee of College of Medicine, Hawler Medical University.

Statistical analysis

The data was analyzed using Statistical package for social sciences 26 (SPSS). Numerical data were expressed as mean and standard deviation (SD) while categorical data were expressed as frequency and percentage. Chi square test and Fisher`s exact test were used to find out associations between qualitative variables while Man-Whitney test was used to compare between continuous dependent variable for two independent groups. A *P* value of ≤ 0.05 was considered to be statistically significant.

Results

This study included 86 [AML n= 39 (45%), B-ALL n=41 (48%), T-ALL n=6 (7%)] newly diagnosed cases. According to gender distribution they were composed of 44 (51.2%) male and 42 (48.8%) female while according to age group, they were divided into adult age group (52 cases) and pediatric age group (34 cases) with a range between (14 days - 80 years old) with a mean age of 5.06 ± 3.8 years for pediatric age group and a mean age of 40.36 ± 20 years for adult age group. The commonest presenting symptom was fatigue in 69 (80.2%) of cases while the main sign on presentation was pallor in 52 (60.5%) of them followed by fever in 50 (58.1%) of the cases. 46 (53.5%) cases showed conventional phenotype while 40 (46.5%) cases showed aberrant phenotype (Figure 1). No significant difference was detected regarding the distribution of the aberrant expression between the two age groups (*P*-value = 0.280). The mean hematological values of the cases are shown in Table 1.

The proportional frequency of aberrant phenotype in addition to the frequency of aberrant CD markers expression among each type of AL is shown in Table 2.

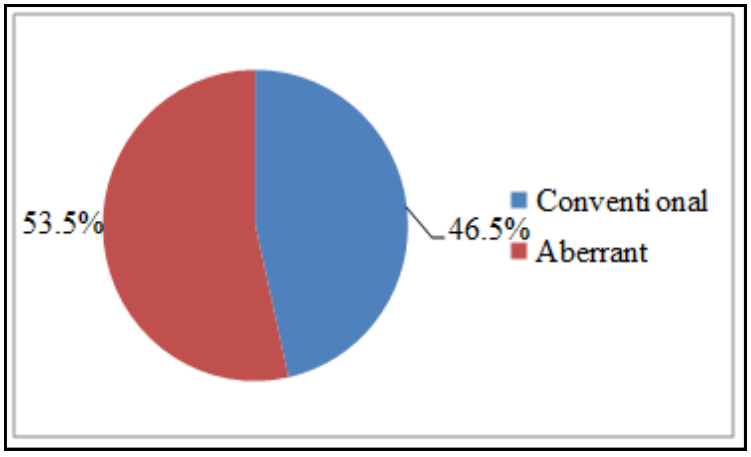

Figure 1 Prevalence of aberrant phenotype

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Table 1 Mean hematological values

Hematological Parameter	Mean ± SD	Minimum	Maximum
Hb (gm/dl)	8.7 ± 2.4 gm/dl	37	17
WBC count	35.8 ± 67.1 X 10^9	0.4 x 10^9	365.5 x 10^9
Platelet count	65.5 ± 70.3 X 10^9	7 x 10^9	409 x 10^9
Blast count-PB	43.9 ± 32.7	0	94%
Blast count-BM	71.4 ± 23	6%	98%
Blast count-FCM	71.1± 21.1	22%	98%

Table 2 Frequency and percentage of expression of each CD marker among B-ALL, AML and T-ALL cases

Cases	Frequency	%
B-ALL	**n=41**	
Aberrant expression		
With aberrant expression	20	48.8%
With conventional expression	21	51.2%
Aberrant CD markers		
CD66C	11	26.8%
CD13	7	17%
CD33	5	12.2%
CD2	3	7.3%
CD117	1	2.4%
CCD36	1	2.4%
CD64	1	2.4%
CD15	1	2.4%
CD11c	1	2.4%
AML	**n=39**	
Aberrant expression		
With aberrant expression	16	41%
With conventional expression	23	59%
Aberrant CD marker		
CD22	7	18%
CD2	4	10.2%
CD7	4	10.2%
TdT	4	10.2%
CD56	3	7.7%
CD19	1	2.6%
T-ALL	**n=6**	
Aberrant expression		
With aberrant expression	4	66.6%
With conventional expression	2	33.3%
Aberrant CD markers		
CD13	3	50%
CD11c	2	33.3%
CD33	1	16.6%

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The clinical profile of the cases showed significant difference between aberrant and conventional group regarding gum bleeding being presented mainly in the conventional group (*P* = 0.028), significant difference was detected between Ly+ and lymphoid negative (Ly-) AML in splenomegaly on presentation which was higher in Ly+ AML than Ly- AML cases and also lymphadenopathy (LAP) was more frequent in My- B-ALL than myeloid positive (My+) B-ALL cases (Tables 3 & 4).

Table 3 Phenotype pattern expression in acute leukemia in relation to clinical profile

Clinical profile	Conventional phenotype No (%) n=46	Aberrant phenotype No (%) n=40	Total No (%) n=86	*P* value
Splenomegaly	13 (43.3)	17 (56.7)	30 (100)	0.167*
Gum bleeding	6 (100)	0 (0)	6 (100)	**0.028****
LAP	17 (63)	10 (37)	27 (100)	0.233*

*by Chi square test ** by Fisher`s exact test

Table 4 Phenotype pattern expression in acute leukemia types in relation to clinical profile

Clinical profile	Ly+ AML No (%) n=16	Ly- AML No (%) n=23	Total No (%) n=39	P value	My+ B-ALL No (%) n=20	My- B-ALL No (%) n=21	Total No (%) n=41	P value	My+ T-ALL No (%) n=4	My- T-ALL No (%) n=2	Total No (%) n=6	P value
Splenomegaly	6 (75)	2 (25)	8 (100)	0.045**	8 (44.4)	10 (55.6)	18 (100)	0.623*	3 (75)	1 (25)	4 (100)	1.000**
Gum bleeding	0 (0)	5 (100)	5 (100)	0.066**	0 (0)	1 (100)	1 (100)	1.000**	0 (0)	0 (0)	0 (0)	
LAP	5 (45.5)	6 (54.5)	11 (100)	0.734**	3 (25)	9 (75)	12 (100)	0.050*	2 (50)	2 (50)	4 (100)	0.467**

*by Chi square test ** by Fisher`s exact test

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Regarding the association of the pattern of phenotype expression and the hematological profile of the cases, between the aberrant and conventional groups in general, significantly lower median WBC count and median blast percentage in the PB was noticed in the aberrant phenotype group (*P* value = 0.034 and 0.045 respectively). Among the types of AL, higher mean Hb value in the PB was noticed among Ly+ AML cases (*P* value = 0.024). No significant difference was detected between My+ and My- B-ALL cases and also between My+ and myeloid negative (My-) T-ALL cases. (Details are shown in Tables 5 and 6).

Post induction of chemotherapy, 50 (58.1%) of AL cases achieved CR, 14 (16.3%) failed to achieve CR, 13 (15.1%) died during or before induction chemotherapy and 9 (10.5%) of them were lost to follow up.

The association between remission status post induction chemotherapy and the phenotype pattern expression is shown in Table 7.

In comparison between the two groups (CR and No-CR) in relation to the type of aberrant CD marker, no significant association was noticed as most of them were associated with higher frequency of CR except CD56 and CD64, both were associated with No-CR when expressed but the significance level was not reached.

Table 5 Comparison of hematological parameters between cases with conventional and aberrant phenotype

Hematological parameter	Conventional n=46		Aberrant N=40		P value
	Mean ± SD	Median	Mean ± SD	Median	
Hb (gm/dl)	8.46 ± 2.54	8.2	9.06 ± 2.18	8.9	NS*
WBC count	53.27± 85.52	21.2	21.6 ± 28.73	7.8	0.034**
Platelet count	53.78 ± 65.62	31	79 ± 73.94	51.5	NS
Blast % in PB	50.58 ± 32.53	63	36.2 ± 31.52	29.5	0.045**
Blast % in BM	69.41 ± 26.15	80	74.25 ± 18.5	80	NS
Blast % on FCM	69.1 ±22.84	78.5	73.42 ± 18.95	80	NS

* Not significant **By Mann-Whitney test

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Table 6 Comparison between the aberrant and conventional groups of acute leukemia types in relation to the hematological profile

Hematological parameters	Ly+ AML N=16		Ly- AML N=23		*P* value
	Mean ± SD	Median	Mean ± SD	Median	
Hb (gm/dl)	8.8 ± 2.05	8	7.5 ± 1.53	7.7	0.024
WBC count	24.8 ± 37.4	5.3	68.7 ± 111.4	24.4	NS
Platelet count	73.3 ± 60.57	56.5	37.3 ± 25.76	33	NS
Blast % in PB	31 ± 42.8	26	27.2 ± 35.73	30	NS
Blast% in BM	61.46 ± 21.19	60	59.36 ± 28.87	65	NS
Blast% on FCM	68.9 ± 19.1	71	59.36 ± 28.9	70	
	My+ B-ALL N=20		**My- B-ALL N=21**		
Hb (gm/dl)	9.1 ± 2.41	9	8.7 ± 2.22	8.5	NS
WBC count	17.2 ± 19.5	8.8	27 ± 26.8	19.8	NS
Platelet count	85.5 ± 88.2	48	73 ± 90.5	28	NS
Blast% in PB	43.1 ± 35.7	45.5	56.9 ± 28.5	64	NS
Blast% in BM	84.45 ± 8.08	90	77.3± 21.2	83.5	NS
Blast% on FCM	77.6 ± 19.1	83	70.9 ± 24.3	80	NS
	My+ T-ALL N=4		**My- T-ALL N=2**		
Hb (gm/dl)	9.3 ± 1.93	10	16 ± 1.34	16	NS
WBC count	30.2 ± 32.1	27	151 ± 51	150.9	NS
Platelet count	69 ± 53.5	49	40 ± 29	40	NS
Blast% in PB	22 ± 20.4	20.5	73 ± 2.1	73.5	NS
Blast% in BM	71.2 ± 18.1	73.5	86 ± 8.4	86	NS
Blast% on FCM	70.5 ± 16.2	68	83.5 ± 9.2	83.5	NS

*By Mann- Whitney test

Table 7 Association between remission status post induction chemotherapy and the pattern of expression

Phenotype	CR	No-CR	Dead	Loss of follow up	Total	*P* value
Conventional	24 (52.2%)	10 (21.7%)	5 (10.9%)	7 (15.2%)	46 (100%)	
Aberrant	26 (65%)	4 (10%)	8 (20%)	2 (5%)	40 (100%)	0.131*
Total	50 (58.1%)	14 (16.3%)	13 (15.1%)	9 (10.5%)	86 (100%)	

* by Fisher`s exact test

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Discussion

Multi parametric FCM is a golden method used worldwide to diagnose and classify acute leukemia (AL) and that means making an initial diagnosis of AL, lineage identification whether myeloid or lymphoid, and also for further sub classifying the disease, moreover, FCM helps in determining the prognosis of the disease through MRD examination.[13-15] in the current study, 86 newly diagnosed de novo AL cases were studied and the prevalence of the aberrant phenotype among the blast cells of AL cases was 46.5% which was comparable to the result reported by Ahuja and Malviya (Indian study) who reported a prevalence of 56.7%.[16] Abdulateef et al. from Saudi Arabia reported a prevalence of 56%,[9] Gupta et al. from India reported a prevalence rate of 39% and Tipu et al. from Pakistan reported 21.2%, both lower than the result of the present study. [17, 18]

Aberrant expression in AML

The proportional frequency of aberrancy in AML in our study was 41%, other Iraqi studies reported results of 42% and 46.7% which were comparable to our results.[5,15] other studies reported frequencies of 23%, 67.5% and 43.1%.[14,9,19]

CD22 was expressed in 18% of AML cases in our study which was comparable to other studies from India and Iran who reported frequencies of 19% and 12.2%[4,20] while CD2 was detected in 10% of AML cases in our study, sharma et al. and Hussein and Jawad reported frequencies of 15.8% and 14%.[19,15] CD7 and TdT were both expressed in 10% of AML cases for each, most of the studies reported results higher than ours as for CD7 (43%, 40%, 33%, 18% and 12%).[4,14,21-23] As for TdT, other studies reported frequencies of (6.2% and 15.4%)[8,24] CD19 was expressed 2.6% of AML cases in our study while most of the studies reported higher frequencies of (27%, 15.8% and 10.7%)[4,16,20] CD56 was expressed in 7.7% of AML cases in our study, the majority of studies reported higher frequencies (15% and 17.3%).[13,25]

Aberrant expression in B-ALL

The frequency of aberrant phenotype in B-ALL cases in the current study was 48.8% higher result of 71% was reported by Jalal et al. while Ahuja and Malviya reported a frequency of 60%.[26,16] frequencies of (43% and 26%) were also reported.[27, 28] CD66c was the commonest myeloid marker which was aberrantly expressed in 27% of B-ALL cases; higher frequencies of 81% were reported by Tang et al. and 52% by Jain et al.[29, 30] CD13 was aberrantly expressed in 17% of B-ALL cases in our study, comparable frequencies reported from other studies were (16.3% and 20%) [28, 8] and higher frequencies of 49.8% and 42% were also reported.[26, 16]

CD33 was aberrantly expressed in 12% of B-ALL cases in our study, very close results to ours were reported of (9.7% and 13.3%)[28, 8] and higher rates were also reported of (35.7% and 28%) [26, 27] CD2 was expressed in 7.3% of B-ALL cases, other studies reported frequencies of (2.1% and 12%).[26, 9] CD15, CD117, CD36 and CD64 were each aberrantly expressed in 2.4% of B-ALL cases, frequencies of (3.7% and 3.4%) were reported regarding CD15 [26, 31] while regarding CD36, Jalal et al reported a frequency of 2.2%[26] and as for CD117, frequencies of (2% and 2.5%) were reported[13, 26]

Aberrant expression in T-ALL

In our study, the frequency of aberrancy in T-ALL cases was 66.6% and very close results were reported of (66.7% and 60%). [4, 17] lower frequencies of (50%, 40% and 26.8%) were also reported[16, 28, 26] CD13 was expressed in 50% of T-ALL cases, frequencies of (75% and 42%) were reported[16, 14,] and the lowest frequency of 2.4% was reported by Jalal et al.[26] CD33 was expressed in 16% of T-ALL cases in our study, higher frequencies of (50% and 21.7%) were reported[16, 27] and lower frequency of 2.4% was also reported by Jalal et al[26]. The huge differences in the reported frequencies and prevalence rates are attributed to sample size dissimilarities,

geographical variation, and differences in the monoclonal antibody panels used between studies, environmental changes, variation in ethnicities and also the freshness of PB or BM sample used.[4, 7-9, 13] With regard to the clinical profile, splenomegaly was mainly present in the aberrant Ly+ AML while the opposite was detected in My+ B-ALL where splenomegaly was more often present in the conventional group which is probably due to that the majority of cases with B-ALL present with splenomegaly unlike AML cases[32] and a Chinese study on ALL was in accordance with our study results. [33]

The hematological parameters between aberrant and conventional groups of subtypes of AL showed that Hb level in the PB had higher values in the aberrant Ly+ AML group suggesting less chances of anemia and in turn less severe clinical manifestation, while between My+ and My- B-ALL, T-ALL cases no significant difference was detected. In contrary to our study, a Brazilian study by Lopes et al. found out that the platelet count in the PB was significantly higher in My+ B-ALL while the other hematological parameters showed no significant association in agreement with our study.[10] Ahuja and Malviya reported that My+ B-ALL had significantly lower WBC count and blast count in PB than My- B-ALL; our study also had same differences but did not reach the level of significance because of the smaller sample size, while Ly+ AML had higher Hb value in PB and this was in accordance with our study.[16] Remission status post induction chemotherapy between aberrant and conventional phenotype in our study showed no significant difference and many studies agreed with ours.[10, 28, 24, 15]

Conclusion

The study concluded that aberrant phenotype of a reasonable frequency exists among cases of AL and that some differences among clinical and hematological profile between aberrant and conventional phenotypes are present and that no significant difference in achievement of CR exists between the aberrant and conventional phenotype groups. Further studies with larger sample sizes are advised to find out the association with specific cytogenetic and molecular abnormalities.

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Competing interests

The authors declare that they have no competing interests.

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