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Clinical significance of aberrant expression of CD56 on newly diagnosed adult acute myeloid leukemia blast cells

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Abstract:

BACKGROUND: Acute myeloid leukemia (AML) is a clonal malignancy affecting hemopoietic immature cells, characterized by uncontrolled proliferation and impaired differentiation of these cells, causing their accumulation in the marrow and ultimately marrow failure. Cluster of differentiation 56 or CD56 antigen is typically found on the majority of healthy natural killer cells, some cytotoxic T-cells, and a number of CD4+ T-cells. However, in around 20%–40% of AML patients, it is aberrantly expressed.

OBJECTIVES: The aims of this study were to determine the frequency of abnormal CD56 expression in adult *de novo* AML blasts and evaluate its correlation with complete blood count (CBC), blast percentages, AML subtypes, extramedullary disease, and induction therapy response.

MATERIALS AND METHODS: Thirty adult cases (>15 years) with *de novo* AML were consequently selected in the period from August 1, 2023, to January 30, 2024. On average, their age was 38.97 years old. Cytomorphology, with the use of flow cytometry in suspected instances, was used to diagnose all AML patients in accordance with the World Health Organization criteria for AML. At the first diagnosis, the blast cell percentage was determined by counting the cells on the peripheral blood (PB) and bone marrow (BM)-stained films, and the CBC was performed using a 5-part automated analyzer. Using an eight-color (BD FACSCanto II USA), aberrant CD56 expression was examined. Extramedullary manifestations were determined at the time of diagnosis and determine its correlation with CD56 expression. Three weeks after the completion of the first chemotherapy cycle, the patients were re-assessed for the accomplishment of complete remission.

RESULTS: Expression of CD56 was observed on blast cells in 26.7% of AML patients. Patients with AML exhibiting positive CD56 expression were older compared to those with negative expression. Furthermore, CD56 expression was more prevalent in males, with the male: female ratio of 7:1. Nevertheless, no statistically significant correlations were identified between either of the aberrant expressions and age or sex. CD56 expression was significantly higher in blasts of AML subtypes with monocytic differentiation. The total white blood cell (WBC) count and the percentage of PB and/or BM blast cells in AML patients exhibiting positive expression were significantly higher compared to those without such expression. Significant correlations were observed between aberrant CD56 expression and extramedullary manifestations and with the nonresponsiveness to the induction therapy.

CONCLUSION: There is evidence of aberrant CD56 expression in around a quarter percent of all instances of AML. It was discovered that neither the age nor the gender of the patient had a significant correlation with this expression. It was shown that monocytic AML subtypes had a higher expression of CD56. It was shown that individuals with AML who had aberrant CD56 expression had considerably higher overall WBC, as well as greater percentages of blast cells in both the PB and BM. There was a substantial association between the abnormal expression of CD56 and the extramedullary symptoms, as well as the nonresponsiveness to the induction treatment.

Keywords:

Aberrant expression, acute myeloid leukemia, CD56, extramedullary manifestations, monocytic AML

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Introduction

Acute myeloid leukemia (AML) is a clonal malignant disorder of immature cells in the hemopoietic hierarchical system. Leukemic transformation is supposed to occur in many cases at, or near, the level of the hemopoietic stem cell before it has been commenced on any lineage commitment. Some cases may originate at a slightly later stage in cells that are committed to lineage differentiation. The proliferative advantage of the leukemic stem cell, coupled with impairments in differentiation and inhibition of apoptosis, leads that immature or blast cells is accumulated in the bone marrow (BM). Eventually, the blasts suppress normal hematopoiesis, leading to marrow failure and infiltrate other organs and tissues.[1-3]

Accurate diagnosis and classification in AML are crucial for treatment decisions and assessment of prognosis. Initial assessment requires a careful history, physical exam, complete blood count (CBC) with peripheral blood (PB) smear, BM examination, flow cytometry (FC), cytogenetics, and selected molecular genetic analyses.[3,4]

FC is the measurement of numerous cell properties as the cells move in a single flow in a fluid column and interrupt a beam of laser light. The method permits the quantitative and qualitative measurement of several properties of cell populations from body fluids. In an AML patient, the role of FC immunophenotyping may be: confirming a diagnosis, identifying prognosis, and detecting an aberrant immunophenotype that can be used for monitoring minimal residual disease, i.e., expression of an antigen inappropriate to a lineage.[5,6]

An example of an aberrant immunophenotype is the CD56 expression in AML blast cells. CD56 antigen is usually naturally expressed on most normal NKCs; it is also found in a subset of cytotoxic T-cells, a small population of CD4+ T-cells. CD56 is expressed aberrantly in 20%–40% of cases of AML. This expression has been found to correlate with unfavorable cytogenetic abnormalities, with a lower complete remission (CR) rate and a worse survival, and an association with extramedullary manifestations at the time of diagnosis. More notably, CD56 expression has also been associated with a worse prognosis when found in two good prognosis categories of AML, those with t(8;21)(q22;q22) and t(15;17)(q22;q12), respectively.[7-10]

The aim of this study is to find out how frequently adult AML blast cells show aberrant CD56 expression when they are initially diagnosed, and to connect this expression with the results of CBC, blast cells percent in PB and BM, the different AML subtypes, extramedullary manifestations at time of diagnosis, and the initial response to induction therapy.

Materials and Methods

Patients

Thirty adult patients with *de novo* AML participated in this prospective cohort from the August 1, 2023, to the January 30, 2024. Participants averaged 38.97 years old, with 18 men and 12 women. The Medical City-based Baghdad Teaching Hospital, Hematology Department, treated the patients. Blood, BM aspirate, and FC samples were analyzed at the Medical City Teaching Laboratories in Baghdad. FC was done using the eight-color (BD FACSCanto II USA) technology.

Each patient's name, age, gender, chief symptoms, and physical signs were recorded, with a focus on the extramedullary manifestations that involve (lymphadenopathy, splenomegaly, hepatomegaly, gingival hypertrophy, cutaneous infiltrates, and CNS involvement).

Therapy and follow-up

Cheson *et al*.[11,12] criteria were used to assess full response 3 weeks following one chemotherapy cycle in all patients. Based on age and white blood cell (WBC) upon presentation, the patients are categorized into high- and low-risk groups to induce remission. Patients aged 60 or older with a WBC of 50×10^9/L or greater were deemed high-risk and got less extensive treatment. For low-risk patients under 60 with a WBC $<50 \times 10^9$/L upon presentation, the "3 + 7" induction treatment strategy was used. After 4 weeks, all AML patients' PB and BMA samples were taken to determine remission. Two patients died during therapy induction.

Laboratory tests

Blood sampling

By a venipuncture from the antecubital fossa or a BM aspirate from the posterior superior iliac crest using an aseptic method, a venous blood sample of 2.5 ml and a BM aspirate sample of 0.5 ml, respectively, were taken from each patient who participated in this study. The samples were collected in K2-EDTA tubes.

Complete blood count, peripheral blood, and bone marrow smears

All suspect patients' blood samples were examined for hemoglobin, WBC and differential, and platelet count using an automated system (XN-1000, Sysmex, Japan). A skilled hematologist analyzed PB and BM smears to assess blast percent and remission following induction therapy. One drop of blood was inserted in the center of a slide, 1 cm from one end, to make blood films. In front of the drop, a

spreader was oriented 30° to the slide. The spreader was withdrawn until it hit the drop, spreading blood down the slide. The films were air-dried and dyed with Leishman's stain. A smooth-edged glass spreader was used to make 3–5 cm BM smears from aspirated marrow. As the spreader moves marrow fragments, it creates a cell trail. After drying, the BM films were stained as the PB films.

Flow cytometric immunophenotyping

Upon confirmation of AML cases, the samples were sent to the FC unit in the Teaching Lab/Medical City. They were examined for abnormal expression of surface marker antigens CD56 using eight-color (BD FACSCanto II USA) within 6 h of sample collection. The SSC/45 gate dictated the cell-specific gate. The software of the device is based on the FACSDiva™ Clinical Software operating system for multiparametric data acquisition, display, data analysis, and instrument control. FC (BD FACSCanto II, USA) is used as a fully-equipped FC with laser excitation in blue, red, and violet; it investigates up to three optical parameters (FSC, Side scatter [SSC], and 8 fluorescence channels).[13]

Assessment of the aberrant phenotype

SSC and CD45 expression parameters were implemented to identify blast cells. Antigen expression was considered to be positive when the percentage of positive blast cells was equal or >20%. Similarly, aberrant phenotypes were defined when at least 20% of the blast cells expressed that particular phenotype.

Statistical analysis

To display, explain, and evaluate the data contained in this research, the SPSS statistical package, version 16, was used. Numerical variables were reported as median, mean, and standard deviation. Numbers and percentages out of totals were used to represent nominal variables. Pearson's Chi-square and Fisher's exact tests were implemented to evaluate the variation in nominal variable frequency between the groups. To compare the means of numerical variables among groups, an independent sample Student's-*t*-test was implemented. The statistical significance level was considered at $P < 0.05$.

Ethical approval

The Medical Ethical Committee of the Medical City, Baghdad, approved this study (Reference no. 410 at May 25, 2024). The committee waived participant consent as only patient files were examined.

Results

Patients with AML who were a part of this research had an age mean of 38.97 years. Fourteen out of thirty instances, or 46.7%, occurred in people aged 17–36. AML cases exhibited a higher prevalence in males, with 18 males (60%) compared to 12 females (40%), yielding a male-to-female ratio of 1.5:1.

In the analysis of FAB subtypes, 30 cases were examined, resulting in 7 classified as M1, 9 as M2, 3 as M3, 2 as M4, 8 as M5, and 1 as M6.

The most common signs and symptoms of patients participating in this study were pallor and fever, reported in 53.3% and 43.3% of cases, respectively. This was followed by easy fatigability, bleeding, and hepatosplenomegaly, which occurred in 40%, 23.3%, and 20% of patients, respectively. Lymphadenopathy and gingival enlargement occurred with a frequency of 10% each, representing the least common findings. Extramedullary manifestations occurred in 8 out of 30 patients, representing 26.7%. among these cases, 5 were classified as M5, 2 as M2, and 1 as M4.

CD56 expression was detected in 8 of 30 patients, accounting for 26.7% of cases. Patients with positive CD56 expression had a mean age of 41.13 ± 22.41 years, slightly exceeding the mean age of 38.18 ± 17.54 years in those with negative expression. There was no significant correlation between this expression and the mean age of the patients.

There was no significant association ($P > 0.05$) between gender and the aberrant CD56; nevertheless, CD56 was more often expressed in men (7:1) among CD56+ patients.

Table 1 indicates that AML patients exhibiting aberrant CD56 expression demonstrated a significantly elevated total WBC, as well as increased percentages of blast cells in PB and BM, in comparison to patients without aberrant CD56 expression ($P < 0.05$). There was no significant correlation observed between aberrant CD56 expression and hemoglobin or platelet counts.

CD56 was expressed in half of the cases of AML subtypes with monocytic differentiation, M5 (4/8, 50%) and M4 (1/2, 50%); it was also expressed in other FAB subtypes, 2/7 for M1, 1/3 for M3. CD56 was not expressed in M2 and M6 subtypes.

There was a significant correlation ($P = 0.016$) between the presence of extramedullary symptoms in 62.5% of CD56+ patients and only 13.6% of CD56 individuals Table 2.

In Table 3, the study showed that 19 of the 30 patients (63.3%) who had conventional treatment had a full response. In a group of patients with abnormal CD56 expression, 6 out of 8 did not respond to induction treatment. Two of these patients died during the

Table 1: Assessment of abnormal CD56 expression in relation to hematological variables

Parameter	CD56 negative			CD56 positive			*P*
	Mean	SD	SE	Mean	SD	SE	
Total WBC (×10^9/L)	41.53	57.00	12.15	146.44	89.14	31.52	0.012
Hb (g/dl)	7.78	2.06	0.44	6.84	1.23	0.44	0.238
Platelet count (×10^9/L)	91.05	113.46	24.19	37.25	21.29	7.53	0.198
PB blast cells (%)	56.86	27.44	5.85	85.25	11.37	4.02	0.009
BM blast cells (%)	64.50	25.82	5.50	85.50	10.84	3.83	0.004

WBC=White blood cell, BM=Bone marrow, Hb=Hemoglobin, SD=Standard deviation, SE=Standard error, PB=Peripheral blood

Table 2: Relationship between extramedullary symptoms and abnormal CD56 expression

Extramedullary manifestations	CD56		Total
	Negative, *n* (%)	Positive, *n* (%)	
Yes	3 (13.6)	5 (62.5)	8 (26.7)
No	19 (86.4)	3 (37.5)	22 (73.3)
Total	22 (100)	8 (100)	30 (100.00)

P=0.016

Table 3: Relationship between abnormal CD56 expression and complete remission accomplishment

CR achievement	CD56		
	Negative, *n* (%)	Positive, *n* (%)	Total
Yes	17 (77.3)	2 (25)	19 (63.3)
No	5 (22.7)	6 (75)	11 (36.7)
Total	22 (100)	8 (100)	30 (100)

P=0.028. CR=Complete remission

induction therapy. There was a significant link between this expression and nonresponse to induction treatment, with a $P = 0.028$.

Discussion

The participants' ages ranged from 17 to 75, with a median of 37 and a mean of 38. Research conducted in Iraq,[14-16] alongside a Jordanian[17] and a Saudi[9] study produced similar findings.

The male-to-female ratio of AML patients was 1.5:1, with men constituting 60% of the cases. This could be due to that the disease pathology could be linked to their exposure to mutants more than females due to work quality. The results are consistent with previous research conducted in Iraq,[18] Oman,[19] and the West.[20,21]

In the analysis of 30 instances, M2 emerged as the most prevalent, succeeded by M5 and M1. This is in agreement with most published data indicate that M2 is the predominant subtype, followed by M5.[22-24]

This research identified that 26.7% of 30 newly diagnosed *de novo* AML cases displayed aberrant expression of the CD56 antigen. This finding is consistent with previous research demonstrating that CD56 is expressed in 27% of AML cases, Dina *et al*.,[25] in 27.5% Abdulateef *et al*.,[26] in 24% Di Bona *et al*.,[27] and in 22% El-Sissy *et al*.[9] This study's findings were higher than the 15% reported by Chang *et al*.[28] and the 37.8% reported by Shen *et al*.[29]

This study found that CD56+ patients had a higher mean age (41.1 ± 22.4 years) than individuals lacking CD56 expression (mean age 38.2 ± 17.5 years). The analysis indicated no significant age difference between the two data sets ($P = 0.709$). The findings are conforming with the research conducted by Alegretti *et al*.[7] and Baer *et al*.[30] Hsiao *et al*.[31] found that the average age of AML patients with CD56 expression is lower compared to those without CD56 expression.

The expression of CD56 was higher in males, exhibiting a male: female ratio of 7:1; nonetheless, this difference did not reach the significance level ($P = 0.099$). Ferrara *et al*.[32] noted an increased prevalence of CD56 in male AML patients, whereas Alegretti *et al*.[7] documented a comparable male-to-female ratio. Elevated CD56 expression was observed in female patients with AML, as reported by Baer *et al*.[30]

This study found that WBC in AML patients with aberrant CD56 expression was significantly elevated compared to those without this expression ($P = 0.012$). Montesinos *et al*.[33] and Olteanu *et al*.[34] found that the total WBC is elevated in AML patients with positive aberrant CD56 expression relative to those with negative expression. In contrast, CD56 expression showed no correlation with total WBC count, as indicated by Wang *et al*.[35]

Significant associations were identified ($P = 0.009$ and 0.004, respectively) between the percentages of PB and BM blast cells in AML patients with aberrant CD56 expression. These results were comparable to that published by Di Bona *et al*.[27] who reported that the median blast cell's count in AML patients with CD56 positivity was higher than those without this expression, but this finding did not reach the level of significance, and the same result was also reported by Hsiao *et al*.[31] Ortolani[36] indicated that a low blast cell count correlates with the coexpression of CD56 and CD7 on M0 blasts.

CD56 was expressed in half of the cases of AML subtypes with monocytic differentiation (M5 cases (4/8, 50%) and M4 (1/2, 50%), in agreement with Graf *et al*.[37] and Di Bona

et al.[27] who published that CD56 was expressed more in monocytic subtypes. This finding could be attributed to the fact that the CD56 antigen is constitutively expressed in normal monocyte and monocyte-derived cells. Furthermore, El-Sissy *et al*.,[9] Wang *et al*.,[35] and Zheng *et al*.[38] reported that CD56 was mainly expressed in M5 cases. However, Raspadori *et al*.[39] found that CD56 expression was detected more in M2 and M5 patients, whereas none of the M2 cases in the present study expressed CD56.

This study found a significant association between aberrant CD56 expression and extramedullary manifestations ($P = 0.016$), corroborates the findings of Chang *et al*.,[28] who examined the expression of CD34, TdT, HLADR, CD7, CD19, and CD56 in leukemic blasts, noting that only CD56 expression correlated with extramedullary infiltrates., with a statistically significant relationship to lymphadenopathy. Because CD56 is a neural cell adhesion molecule isoform that plays an important function in neuronal growth and migration through cell-to-cell adhesion, there is a hypothesis that CD56 expression in leukemic cells could allow infiltration through the adhesion of these cells to tissues that also express this marker.[7] Other study had linked CD56 expression to an increased risk of extramedullary leukemic infiltration, Byrd *et al*.[7,40]

The results demonstrated a statistically significant relationship between CD56 expression and lack of response to induction treatment ($P = 0.028$). Since an increased expression and function of the PGP has been observed in normal CD56+ NK cells, we hypothesize that CD56+ AML blasts might overexpress PGP, a MDR-related protein, which may potentially increase the drug resistance mechanism and this may account for the reduced responsiveness to chemotherapy of CD56 + AML patients.; furthermore, CD56 expression was correlated with the expression of other antigens generally associated with unfavourable outcomes such as CD34, CD7, BCL2 and PGP.[39,41] This result corresponding to that of Raspadori *et al*.[39] and Elyamany *et al*.[42] who suggested that CD56 expression correlates with a decreased rate of CR in AML patients.

Conclusion

One-third of patients with AML exhibit expression of CD56. The analysis revealed no significant correlation between patient age and gender with abnormal expressions of CD56. Monocytic AML subtypes exhibit elevated CD56 expression. Cancer patients exhibiting aberrant CD56 expression demonstrated significantly elevated total WBC, PB, and BM blast cell counts in comparison to those lacking aberrant CD56 expression. A significant correlation exists between extramedullary involvement and aberrant expression of CD56. A significant correlation is observed between aberrant CD56 expression and lack of responsiveness to induction treatment.

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Conflicts of interest
There are no conflicts of interest.

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