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PROGNOSTIC SIGNIFICANCE OF CD56 EXPRESSION IN ACUTE LEUKEMIAS

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Background. *CD56 expression was extensively investigated in cases of acute leukemia. Many studies associated it with short overall survival, unfavorable outcome, lower rates or short complete remission, however the results remain controversial.*

Objectives. *The aim of this study was to investigate the frequency and prognostic relevance of CD56 expression in patients with acute leukemia and to compare its value with other standard prognostic factors, such as age, gender, leukocytosis, morphologic subtypes, extramedullary invasion, cytogenetic abnormalities and performance status.*

Methods. *Forty cases of acute leukemia treated at Ain Shmas University hospitals were investigated. They were classified by the French-American-British group (FAB) criteria, flow cytometry, and cytogenetics data. They included twenty cases of acute myeloid leukemia (AML) and twenty cases of acute lymphoblastic leukemia (ALL).*

Results. *CD56 positive expression was detected in nine cases of AML (45 %), and only in two patients with ALL (10 %). The highest incidence of CD56 positivity was in FAB subtypes M1 (35 %) and M2 (35 %).Association studies between CD56 expression and other prognostic factors in AML cases showed no significant association with age, gender, clinical presentation, hematological data or cytogenetic risk groups. Incidence of relapse was higher in AML patients expressing CD56 than those who did not (66.7 % vs 10 %, P=0.01). Higher death rates were encountered in AML cases with CD56 expression than those without (55.6 % vs 10 %, P=0.032).*

Conclusions*. CD56 antigenic expression in AML cases represents an adverse prognostic factor. It should be regularly investigated in cases of AML for better prognostic stratification and assessment.*

KEY WORDS: **CD56; leukemia, myeloid; prognosis**

Introduction

Acute leukemia is a heterogeneous group of disorders. They have various morphological, immunophenotypic and cytogenetic patterns. Identifying these characteristics is useful for prediction of therapy responses and prognosis of the disease [1]. Several phenotypic markers demonstrated to have clinical significance including detection of minimal residual disease [2, 3] rate and duration of complete remission (CR), disease-free survival, and overall survival (OS) [3].

CD56, a neural cell adhesion molecule (NCAM), is an early described natural killer cell-associated antigen. It mediates cell-to-cell interaction and is possibly involved in cell-mediated cytotoxicity. This antigen is also found in a subset of CD3+ cytotoxic T-cells and a small population of CD4+ T-cells and monocytes [4]. It is expressed in various hematopoietic neoplasms, including acute myeloid leukemia(AML) [5], acute lymphoblastic leukemia (ALL) [6], lymphoma [7], and myeloma cells [8]. Being a cell adhesion molecule, CD56 expression on tumor cells is believed to play a role in their localization with involvement of extramedullary metastasis [9].

The prognostic value of CD56 expression in cases of acute leukemia has been extensively investigated but with few consistent results [3]. Some investigators associated CD56 expression with short OS [5, 10–12], and lower CR rates [10] in AML patient. Although Ferrara et al.[12] reported short OS in AML cases expressing CD56; they could not detect association of this marker with the rate of CR in M3 AML cases. Moreover, Chang et al. studied 379 cases of AML including all subtypes except M3 and reported that the CR rate was not associated with CD56 expression, but with CD34 and HLA-DR expression [13].

The aim of this study is to evaluate the prognostic role of CD56 expression in newly diagnosed acute

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leukemia including AML and ALL cases and correlate the results with other prognostic factors.

Methods

Patients

This study was carried out on 40 newly diagnosed cases of acute leukemia. It included 20 AML and 20 ALL patients presented at the Hematology/ Oncology Clinics in the Internal Medicine and Pediatric Hospitals, Ain Shams University, Cairo, Egypt.

Diagnosis and classification of acute leukemia was based on WHO (2008) [14] and FAB [15] criteria. Bone marrow and peripheral blood samples obtained at presentation were examined for morphology, immunophenotyping and complementary cytogenetics. Another bone marrow samples were taken on the 28th day to evaluate response to induction therapy. Response to treatment was considered ineffective if more than 5 % blasts were detected in BM on the 28th day.

Immunophenotyping

Flow-cytometric analyses were performed as previously described [16]. The reactivity for the following markers was analyzed: a panel of fluorescein isothiocyanate (FITC)/phycoerythrin (PE) conjugated monoclonal antibodies to B-lineage markers (CD19, CD10, CD20, CD79a), T-lineage markers (CD2, CD3, CD5, CD7, cytCD3), myeloid markers (CD13, CD33, CD15, MPO, CD61, glycophorin, CD117), monocytic markers (CD14), and common progenitors markers (CD34, HLA-DR), supplied by Beckman Coulter, France. In addition, MoAb NCAM-PE (clone NCAM) (MiltenyiBiotec, Germany) for detection of CD56 was used. Cells were considered positive for a certain marker when ≥20 % of blasts expressed it, except for CD56, CD34 and intracellular MPO, where expression of ≥10 % of blasts was reported as positive.

Cytogenetic analysis

Leukemic cells were cultured, and the chromosomes were banded. Cytogenetic abnormalities were determined according to the International System for Human Cytogenetic Nomenclature [17]. Cytogenetic results were categorized into favorable, intermediate and unfavorable risk group.

Statistical analysis

Statistical analysis of the data was performed by using SPSS 15 software package and Windows 7® operating system. Categorical data parameters were presented in terms of frequency and percent age. Comparisons and associations that involve categorical variables were done by chi square test or Fisher exact test depending on the nature of the data. Continuous data parameters were described as middle, standard deviation (SD), median and interquartile range (IQR).

Results

Forty acute leukemia patients (20 AML and 20 ALL) were enrolled in this study. Table 1 summarizes age, gender, and clinical findings in the studied AML and ALL cases.

According to FAB criteria, AML patients were classified into: 7 (35 %) M1, 7 (35 %) M2, 4 (20 %) M3, one (5 %) M4 and one (5 %) M5 case. ALL were classified into 17 (85 %) B-ALL and 3 (15 %) T-ALL cases.

Successful mitosis was encountered in 18/20 (90 %) AML cases. Ten of these cases (55 %) were categorized as favorable [t(8:21), inv(16),t(15:17)], 6 (33.3 %) were intermediate (+8, normal) and 2 (11 %) cases were poor risk group [t(9:22), 11q23]. Successful mitosis was obtained in 12(60 %) of ALL cases. Three ALL cases (25 %) were classified as favorable risk (del 6q, hyperdiploidy>50), 5(41 %) were intermediate risk (normal), and 4(33 %) were poor risk group (t(9:22), hypodyploidy<45).

Our follow up of AML cases during induction period showed that 12 (63.2 %) AML cases showed good response to chemotherapy and achieved complete remission, while 7 patients (36.8 %) relapsed, and one case was missed. Six of the relapsed patients died. Meanwhile, 14 (70 %) ALL patients showed good response to chemotherapy and achieved complete remission, while five cases (25 %) relapsed, 3 of them died.

CD56 expression and association studies:

Nine AML cases (45 %) were positive for CD56, while 11 (55 %) were negative. CD56 and CD34 coexpression was found in 2 cases (10 %). None of our AML cases co-expressed CD56 and CD7. Only 2 ALL cases (10 %) expressed CD56. One ALL case co-expressed CD56 and CD34. There was a statistically significant positive association between CD56 positive expression and CD117 in AML ($p<0.05$). No significant association was found between CD56 positive expression and immuno-

Table 1. Demographic and clinical findings in AML and ALL cases

	AML n=20	ALL n=20
Age (years)		
Median	30.5	20
Range	13-65	10-50
Male (M) %(n)	55 (11)	55(11)
Female (F) %(n)	45 (9)	45 (9)
M:F ratio	1.2:1	1.2:1
Hepatomegaly %(n)	15% (3)	60 (12)
Splenomegaly %(n)	35% (7)	45% (9)
Lymphadenopathy %(n)	20% (3)	50% (10)
Pallor %(n)	60% (12)	40% (8)
Fever %(n)	40% (8)	50% (10)
Bleeding % (n)	25% (5)	30% (6)

phenotype profile of ALL (*P*>0.05). Because of the small ALL sample, expressing CD56, the analysis of results of these cases questions its statistical reliability.

No significant association was detected between CD56 positive expression and age (*P*=0.806) (Table 2), gender, clinical or hematological data in AML patients (Table 3). Similarly, we could not associate this marker expression with cytogenetics risk groups *(P*=0.118) (Table 4).

AML cases showed a statistically significant association between CD56 positivity and poor outcome. We missed one case and only 19 patients were evaluated including nine CD56 positive and

Table 2. Association studies between CD56 and age in AML patients

	Negative CD56 n=11	Positive CD56 n=9	X^2	*P* value	Significance
Mean age (years)	37.3	30.44	0.06	0.806f	NS

n = number of cases, NS: non-significant.

Table 3. Association studies between CD56 expression and gender, clinical and hematological data in AML patients

		Negative CD56 (n=11)		Positive CD56 (n=9)		x^2	*P*	Sig
		n	%	n	%			
Sex	M	6	54.55	5	55.56	0.002	1.000f	NS
	F	5	45.45	4	44.44			
Liver	-	10	90.91	7	77.78	0.669	0.566f	NS
	+	1	9.09	2	22.22			
Spleen	-	9	81.82	4	44.44	3.039	0.160f	NS
	+	2	18.18	5	55.56			
LNs	-	8	72.73	8	88.89	0.808	0.591f	NS
	+	3	27.27	1	11.11			
Pallor	-	5	45.45	3	33.33	0.303	0.670f	NS
	+	6	54.55	6	66.67			
Fever	-	7	63.64	5	55.56	0.135	1.000f	NS
	+	4	36.36	4	44.44			
Bleeding	-	9	81.82	6	66.67	0.606	0.617f	NS
	+	2	18.18	3	33.33			
Hb	<10	9	81.82	8	88.89	0.194	1.000f	NS
	≥10	2	18.18	1	11.11			
WBC	<50	8	72.73	4	44.44	1.650	0.362	NS
	≥50	3	27.27	5	55.56			
PLT	<100	9	81.82	7	77.78	0.051	1.000f	NS
	≥100	2	18.18	2	22.22			
PB Blasts	<60	5	45.45	4	44.44	0.002	1.000f	NS
	≥60	6	54.55	5	55.56			
BM Blasts	<70	6	54.55	4	44.44	0.202	1.000f	NS
	≥70	5	45.45	5	55.56			

n: number of cases, Hb: hemoglobin, WBC: white blood counts, PLT: platelets count, PB: peripheral blood, BM: bone marrow
Sig: significant, NS: non-significant.

Table 4.Association between cytogenetics risk groups and CD56 expression in AML patients

		Negative CD56 (n=9)*		Positive CD56 (n=9)		x^2	*P*	Sig
		n	%	n	%			
Cytogenetic Risk Group	Good	3	27.27	7	77.78	4.267	0.118f	NS
	Intermediate	4	36.36	2	22.22			
	Poor	2	18.18	0	0			

*2 cultures failed, n: number, Sig: significant, NS: non-significant

10 negative cases. Six patients out of the 9 positive CD56 cases (66.7 %) relapsed and only 3 (33.7 %) developed remission. Five (55.6%) of the CD56 expressing patients died. On the other hand, the CD56 negative patients group showed one (10 %) case relapse and death, while nine (90 %) patients developed remission.

Statistical comparison between those patient with CD56 expression and those without showed significant increased incidence of relapse (*P*=0.01) (Table 5, Figure 1) and deaths (*P*=0.032) among patients expressing CD56 (Table 5, Figure 2).

Discussion

Acute leukemia comprises a heterogeneous group of diseases that differ in their etiology, pathogenesis, and prognosis. Our study investigated the prognostic significance of CD56 expression in these cases to evaluate its association with other prognostic factors, and its influence on the outcome during induction therapy.

CD56 positivity was observed in 45 % of AML cases, and 10 % ALL cases. These results are in concordance with Fischer et al. [18] who reported that CD56 expression was not restricted to AML samples and could be detected in both B-cell and T-cell ALLs (14 %) as well. They concluded that it is not reliable for lineage distinction between AML and ALL. However, Montero et al. [19] reported expression of this marker in only 4 patients (2 %) out of 200 ALL cases. These differences could be explained by lower number of cases in our study as compared to 200 cases studies, or due to methodology variation. The study of Fischer et al. [18] investigated CD56 in 452 newly diagnosed T-ALL patients included in the GMALL trial. The marker was expressed in 13.9 % of patients, predominating in the non-thymic subtypes, whereas thymic T-ALL was most common in the CD56 negative group. In addition, the authors reported that CD56 expression was associated with higher resistance to therapy.

Our statistical analysis showed that CD56 expression in AML cases was not associated with age (Table 2), sex, or any laboratory variables including blasts counts, WBC, hemoglobin concentration or platelets counts (Table 3). Similarly Yang et al. [20] could not associate CD56 expression with any laboratory variables in AML cases. However, other investigators [1] reported a higher proportion of CD56 expression in men.

The presence of lymphadenopathy, hepatomegaly, and splenomegaly provide an indirect measurement of leukemic cell burden. We could not detect significant association of positive CD56 and presence of any of these clinical conditions in AML cases. Also, no significant association was found with other clinical features as presence of fever, pallor or bleeding tendency (Table 3). These findings are compatible with other published data (Table 18, 21).

Our work detected only two cases of ALL expressing CD56, these were of B-ALL subtype and were not characterised by hepatomegaly or splenomegaly. Although Ravandiet al. [6] considered that

Table 5. Association between treatment outcome, fate and CD56 expression in AML patients

		Negative CD56 n=10*		Positive CD56 n=9		X^2	*P*	Significance
		n	%	n	%			
Outcome	Remission	9	90	3	33.3	6.5369	0.010f	Significant
	Relapse	1	10	6	66.6			
Fate	Alive	9	90	4	44.4	4.5497	0.032f	Significant
	Died	1	10	5	55.6			

n = number of cases, *= one case was missed.

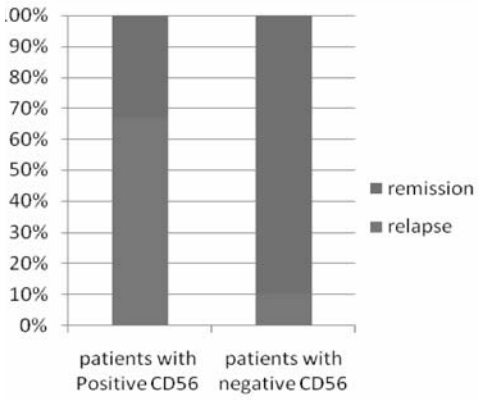

Fig. 1: Association between CD56 expression and treatment outcome in AML patients.

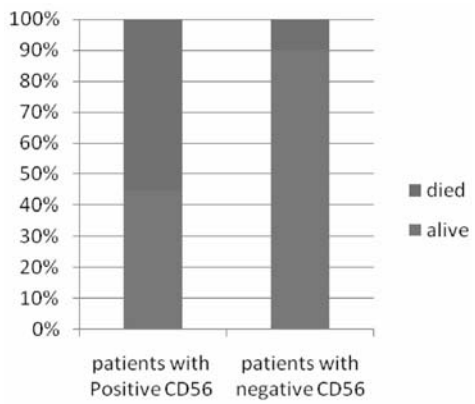

Fig. 2. Association between CD56 expression and mortalityin AML patients

CD56 expression predicts occurrence of CNS disease in ALL, none of our positive CD56 ALL cases had CNS involvement. In addition, no association was found between CD56 expression and demographic, clinical presentation or laboratory tests (P>0.05). However, the low number of ALL cases expressing CD56 incapacitated our statistical and association analysis and doubts these results.

CD56 expression was heterogeneous in different FAB subtypes. The more frequent CD56 expression was observed in M1 (35 %) and M2 (35 %). Allegrettiet al. [1] detected highest incidence of CD56 positivity among FAB subtypes M4 and M5, while Di Bona et al. [22] found more CD56 expression in M5 patients. These differences could be attributed to different number of patients in sample.

To elucidate the prognostic value of CD56, its expression was studied in relation to treatment response in our AML patients. CD56 expression was shown to be significantly related to response to chemotherapy with higher relapse (66.6 % vs 10 %, P=0.010) and death rate (55.5 % vs 10 %, P=0.32) among patients with positive CD56 expression as compared to patients without it. The investigation [1] in a single center in Brazil that investigated cohort of 48 AML patients supported our results and documented the association of CD56 expression with worse prognosis. The authors observed higher death rate during induction in the CD56 positive cases. Their study detected short OS among cases with positive CD56 expression compared to CD56 negative patients. Similarly, Baer et al. stated that CD56 expression was significantly correlated with a short complete remission (CR) period and low OS [21].On the contrary, Ferrara et al. reported that there was no association between CD56 expression and the rate of CR in patients with AML [12]. Moreover, Di Bona et al. failed to demonstrate the influence of CD56 positivity on CR duration or OS in 171 studied cases of AML [22].

AML with t(8;21) is considered a group with favorable outcome, usually marked by high CR rate and prolonged disease-free survival. We encountered five cases with this subtype (25 %), three of these patients (60 %) expressed CD56 and they relapsed and died. Although the small number of our cases (n=5) questions the significance of these results, the fatal outcome is too striking to be ignored. A previous large-scale studies investigated 144 AML patients with t(8;21) in the JALSGAML97 study. Univariate analysis showed that increased white blood cell counts (WBC$\geq 20\times 10^9$/L),CD19 negativity, and CD56 positivity were critical adverse factors for relapse after CR. Multivariate analysis showed that WBC count and CD56 expression were independent adverse risk factors. The authors concluded that CD56 expression has a possible role in risks tratification for patients with AML with t(8;21) [23].

Our study included only four cases of promyelocytic leukemia (APL), three of these patients expressed CD56 (75%). Relapses were evident in two (50%) of those cases expressing this marker. The clinical significance of CD56 expression was studied in a large series of patients with APL, treated with all-trans retinoic acid and anthracycline-based protocols. The authors documented that expression of CD56 is an independent adverse prognostic factor for relapse in these patients and suggested implementing this marker as a risk-adapted therapeutic strategies in APL [24].

Conclusions

The association between CD56 expression and the poor response of AML to current treatments is not fully understood. Raspadori et al. [25] hypothesized that $CD56^+$ AML blasts might overexpress p-glycoprotein (PGP), a multidrug-resistance (MDR) related protein, and reduce responsiveness to chemotherapy. Their data underlined the independent negative prognostic role of CD56 and PGP expression in cases of acute myeloid leukemia. In contrast, other investigators [26] showed that CD56 expression did not correlate with PGP expression, function, or with expression of the other MDR proteins. Other authors [27] have shown that CD56 expression by AML cells is positively regulated by RUNX1 p48 and is negatively regulated by other splice variants. Their findings suggest that p48 and RUNX1-driven NF-B and bcl2 pathways are new elements for targeted treatments in high-risk CD56AMLs.

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