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Assessment of soluble syndecan-1 level in adult patients with *de novo* acute myeloid leukemia and its correlation with hematological parameters and treatment response

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Abstract:

BACKGROUND: Syndecan-1 (CD138) is a member of the transmembrane proteoglycans family that is expressed in various normal and malignant tissues. It attracted the attention because of its possible prognostic role when expressed in different tumors as well as its role as a target for therapy by the monoclonal antibody indatuximab coupled with other cytotoxic agents. In acute myeloid leukemia (AML), syndecan-1 was found to be significantly increased either inside leukocytes or as a soluble form in the plasma and it was correlated with overall survival of AML patients and with more bleeding manifestations and impaired platelet function.

AIMS: The aims of this study were to assess the level of soluble syndecan-1 (or CD 138) in adult patients with *de novo* AML compared to the control group and to explore any possible correlation between the level of syndecan-1 with hematological parameters and response to remission induction therapy.

PATIENTS AND METHODS: Cross-sectional study recruited 60 newly diagnosed adult AML patients. Moreover, 25 healthy individuals were included as the control group. The peripheral blood and bone marrow smears were examined at presentation for establishing the diagnosis and after remission induction for assessing the treatment response. Plasma syndecan-1 assay was done by sandwich enzyme-linked immunosorbent assay, which was done to patients at time of diagnosis.

RESULTS: Plasma syndecan-1 (SDC-1) level of AML patients at presentation was much higher than that in the control group ($P < 0.001$); there was also a statistically significant difference in plasma level of syndecan-1 between male and female patients ($P = 0.002$). There was no significant difference for plasma (SDC-1) level between different AML French American British (FAB) subtypes; however, the highest level was seen among patients with the M3 subtype. No significant difference for plasma (SDC-1) level was seen between the patients who achieved remission status and patients who failed to achieve remission after chemotherapy and also between patients alive and deceased after 6 months of follow-up. Insignificant correlations were demonstrated between soluble (SDC-1) and the presenting complete blood count (CBC) parameters.

CONCLUSIONS: Although the high level of plasma syndecan-1 was demonstrated in patients with AML compared to the control group, there was no significant difference with respect to age, FAB subtype, and type of response to treatment nor with the patient outcome, and also no significant association was established with any of the hematological parameters.

Keywords:

Acute myeloid leukemia, FAB subtype, remission induction, SDC-1

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Introduction

Acute myeloid leukemia (AML) is a malignant, aggressive disorder in which malignant transformation occurs at the level of hemopoietic stem cells or early progenitors. The underlying genetic defect is believed to occur at more than one key biochemical step ultimately result in the accumulation of early hemopoietic cells known as blast cells. Clinical features of acute leukemia result from bone marrow (BM) failure and organ infiltration, both resulting from the accumulation of blast cells. If untreated, acute leukemias are usually rapidly fatal.[1] The diagnosis of AML requires the presence of 20% or more blast cells in the peripheral blood (PB) and/or BM at clinical presentation. However, it can be diagnosed with less than this percentage if specific leukemia-associated cytogenetic or molecular genetic abnormalities are present.[2] The lineage of the blast cells is determined by morphology, immunophenotypic, cytogenetic, and molecular analysis with different schemes being applied for subtyping.[3] The clinical outcome of AML is variable with many factors being involved in prognosis and in determining treatment outcomes. SDC1 is a heparan sulfate proteoglycan that is predominantly expressed on the basolateral surface of epithelial cells; it is also found at certain stages of differentiation of normal lymphoid cells (pre-B) and mesenchymal cells during the development of mature plasma B-cells.[4] It functions as an extracellular matrix receptor that participates in regulating cell proliferation, migration, adhesion, matrix interactions, and morphogenesis.[5] Through the process of synthesis, syndecans undergo a regulated proteolytic cleavage, usually near the plasma membrane, in a process known as shedding and this is the source of the plasma soluble forms.[6] Under physiological conditions, the shedding is rather limited; however, the rate of shedding can be substantially increased in response to external stimuli.[6] Syndecan ectodomain shedding is mediated by various matrix metalloproteinases (MMP) such as MMP2, MMP7, and MMP9. Furthermore, plasmin and thrombin have also been shown to participate in syndecans shedding.[7] Inside the BM, syndecan-1 is detected on the surface of the B-lymphocyte cell lineage, and its expression varies with specific stages of differentiation.[8] Moreover, hematopoietic stem cells and leukemic stem cells express numerous adhesive molecules, including syndecan-1.[9] The soluble forms of syndecan-1 were found to be increased in graft versus host disease, multiple myeloma, and AML.[10,11] Different studies attempted to examine the impact of syndecan-1 in different neoplasms and concluded that its expression may be altered and this may lead to malignant neoplasms.[12]

Patients and Methods

This cross-sectional study included 60 newly diagnosed adult AML patients (25 females and 35 males), and their age range was 15–80 years. Moreover, 25 normal healthy people as a control group their age range were 15–65 years. The patients received the remission induction therapy for medically fit patients younger than 65-year protocols of "3+7," ATRA and ATO or ATRA and anthracycline (idarubicin or daunorubicin) for patients with acute promyelocytic leukemia. The treatment for medically less-fit patients older than age 65 received decitabine (dacogen) and venetoclax. The diagnosis and FAB subtyping was done by PB and BM smears examination and confirmed by immunophenotyping. Patients with a diagnosis of secondary or relapsed AML, patients with previous solid malignancy, previous exposure to chemotherapy and/or radiation, patients with other hematological malignancies, and AML patients who deceased before assessing remission were all excluded from this study. For all AML patients, examination of PB and BM aspirate samples was done at the appropriate time for remission assessment according to the type of chemotherapy, and patients were divided into two groups, those who achieved complete remission (CR) or CR with partial hematological recovery (CR) and the patient who failed to achieve those two types of no response (NR). Follow-up for AML patients was done for 6 months from the diagnosis to assess the disease outcome (whether the patient is still alive or deceased). Plasma syndecan-1 level assay was done at presentation for AML patients and control by sandwich enzyme-linked immunosorbent assay using the human syndecan-1/(SDC1) (Cusabio/China)[13] and microplate reader (Bio RAD, USA).

Ethical consideration

This study was reviewed and approved by ethical committee of scientific council of pathology in Iraqi council for medical specializations . All patients were signed written informed consent prior to enrollment in the study.

Statistical analysis

Microsoft Excel 2019 and IBM Corporation in Armonk, New York, USA, SPSS (Statistical Package for the Social Sciences) version 26 Ink were used as software for the statistical analysis. The data were irregularly distributed, so displayed as median, range, and interquartile range (IQR), and comparison between variables of the study groups was done using the Mann–Whitney U-test and Kruskal–Wallis test for independent samples. Spearman correlation was done to show the relation between plasma SDC-1 and different hematological parameters. $P < 0.05$ was considered statistically significant.

Results

The median age of the patients group was 49.00 years and IQR was 36.75. AML was observed more in patients between the age of 15 and 60 years (71.7%, 43/60) than in

patients between the age of 61–80 years (28.3%, 17/60). AML was observed more in males 58.3% (35/60) than in females 41.7% (25/60), with a male: female ratio of 1.39:1. The median, range value and interquartile range (IQR) for white blood cells (WBC), platelets, peripheral blood and bone marrow blast percentage are all summarized in [Table 1]. According to FAB classification of the 60 AML cases studied 5 (8.3%) were M0, 4 (6.7%) were M1, 26 (43.3%) were M2, 11 (18.3%) were M3, 5 (8.3%) were M4, and 9 (15%) were M5. Fever was the most common presentation of the patient's group 78.3% (47/60), followed by pallor 75% (45/60), then extramedullary disease 51.6% including organomegaly, lymphadenopathy, gingival hypertrophy, skin infiltration, and central nervous system involvement, and then bleeding 38.3% (23/60).

Mann–Whitney U-test was utilized, and there was a statistically significant difference for SDC-1 level between the two groups (AML patients and control groups) with a $P < 0.001$ [Table 2].

There was also a statistically significant difference in plasma SDC-1 level between males and females with $P = 0.002$ [Table 3].

There was an insignificant difference for plasma syndecan-1 level between different AML FAB subtypes, and the $P = 0.215$, however, the highest level was seen among patients with M3 subtype, as shown in Figure 1.

According to response criteria, 33 patients achieved CR group while 27 failed (NR group). Using Mann–Whitney U test, there was no significant difference for plasma syndecan-1 level between the two groups with a $P = 0.795$, as shown in Table 4.

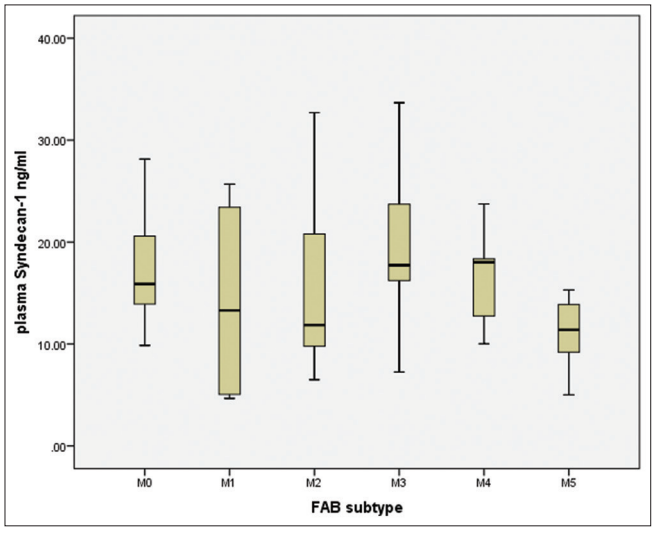

Figure 1: Comparison of SDC-1 level in AML patients according to FAB classification. AML = Acute myeloid leukemia, FAB = French American British

All AML patients were followed up for 6 months' duration after the remission induction therapy, where 13 patients deceased during the follow-up period and 47 patients were still alive, and Mann–Whitney U test was utilized and the difference did not prove to be statistically significant ($P = 0.713$), as shown in Table 5.

A positive nonsignificant correlation was demonstrated between plasma syndecan-1 level and white blood count count, age, and percentage of blasts in PB and in BM,

Table 1: Laboratory parameters of the patient's group

Parameters for patients	Median	IQR	Range
WBC (×10^9/L)	17.65	43.50	0.80–284.00
PLT (×10^9/L)	41.50	40.50	5.00–353.00
PB blasts (%)	62.00	46.25	8.00–98.00
BM blasts (%)	73.50	73.00	23.00–96.00
Parameters for patients	**Mean**	**SD**	**Range**
Hb (g/dL)	7.87	1.65	3.60–11.00

WBC=White blood cell, PLT=Platelet, PB=Peripheral blood, BM=Bone marrow, Hb=Hemoglobin, IQR=Interquartile range, SD=Standard deviation

Table 2: Comparison between the median syndecan-1 levels in acute myeloid leukemia patients group and control group

Parameter SCD-1 (ng/mL)	Patients (*n*=60)	Control (*n*=25)
Median	14.10	4.23
IQR	10.58	1.60
Range	4.66–37.01	2.70–9.99

SCD-1=Syndecan-1, IQR=Interquartile range

Table 3: Comparison of syndecan-1 level at presentation with sex

Sex of patients SCD-1 (ng/mL)	Median	IQR	Range
Male	17.18	9.94	8.36–37.01
Female	10.42	8.10	4.66–30.77

SCD-1=Syndecan-1, IQR=Interquartile range

Table 4: Comparison of syndecan-1 level in acute myeloid leukemia patients according to response to treatment

Response to treatment SCD-1 (ng/mL)	Median	IQR	Range
CR group (33/60)	13.90	12.72	4.66–34.63
NR group (27/60)	14.30	7.56	5.21–37.01

SCD-1=Syndecan-1, IQR=Interquartile range, CR=Complete remission, NR=No response

Table 5: Comparison of syndecan-1 level in acute myeloid leukemia patients according to outcome after 6 months

Outcome of patients SCD-1 (ng/mL)	Median	IQR	Range
Alive	15.29	10.81	4.6634.63
Deceased	12.75	7.28	5.21–37.01

SCD-1=Syndecan-1, IQR=Interquartile range

Table 6: Correlation of syndecan-1 at presentation with other parameters in acute myeloid leukemia group

Parameter	SDC-1	
	r	*P**
WBC ($\times 10^9$/L)	0.076	0.566
Hb (g/dL)	−0.160	0.221
PLT ($\times 10^9$/L)	−0.167	0.203
Age (years)	0.019	0.883
Blast in PB (%)	0.182	0.165
Blast in BM (%)	0.203	0.120

*Spearman's rho correlation test. WBC=White blood cell, PLT=Platelet, PB=Peripheral blood, BM=Bone marrow, Hb=Hemoglobin, SCD-1=Syndecan-1

while a negative nonsignificant correlation was seen between syndecan-1 and hemoglobin level and platelets count, as shown in Table 6.

Discussion

Syndecan-1 is a member of a large family of transmembrane heparan sulfates proteoglycans expressed by epithelial cells, B cells, and plasma cells.[5] It is believed to be involved in many biological processes, including cell adhesion and differentiation.[14]

The expression of syndecan-1 and its shedding has been involved in a variety of neoplasms and in multiple myeloma.[10,12]

In the current study, a high level of soluble plasma syndecan-1 was demonstrated in newly diagnosed patients with *de novo* AML as compared to the control group, and this finding was consistent with previous studies by Larsen *et al.*,[15] Alghandour *et al.*,[16] as well as other studies that addressed the level of membranous expression of syndecan-1 in BM of patients with AML, and[17] this increment may be linked to disease development and progression.

There was no significant association between the plasma level of syndecan-1 and the FAB subtype of leukemia, although the highest level was demonstrated in patients with acute promyelocytic leukemia (AML-M3), patients with M3 are more likely to develop disseminated intravascular coagulation and endothelial injury which might be a contributing factor as an increase in syndecan-1 level has been seen in other diseases with endothelial perturbation and disfunction as patients with COVID-19 and patients with hemodialysis.[18,19]

Unlike the study of Alghandour *et al.*,[16] no significant association was seen between patients who achieved remission and patients who failed to achieve remission; furthermore, no significant difference was seen after 6 months of follow-up between patients who were alive or deceased after the follow-up period. This lack of consistency may be attributed to the difference in the number of cases and also to the method of assessment of syndecan-1. However, the current study results were consistent with Larsen *et al.*'s[15] study, which also did not establish an association between disease outcome and plasma syndecan-1 level. Although the high level of syndecan-1 was linked to treatment resistance in patients with MM and patients with pancreatic cancer, this was not established in this study. Daunorubicin (chemotherapeutic agent used in the treatment of AML) has been shown to enhance syndecan-1 shedding.

Finally, an interesting finding was the demonstration of a significant difference in plasma syndecan-1 level between male and female patients, and for our knowledge, no previous study was addressed this issue to compare with higher level of syndecan-1 in males compared to females might be attributed to hormonal differences that might affect epithelial and endothelial shedding.

Conclusions

High levels of syndecan-1 were seen in patients with *de novo* AML at presentation compared to the control group, and no significant difference was established with respect to treatment response nor disease outcome after 6 months of follow-up.

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Conflicts of interest
There are no conflicts of interest.

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