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Soluble HLA-G as a Novel Biomarker for the Diagnosis of Acute Lymphoblastic Leukemia

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Abstract

Objective: Acute lymphoblastic leukemia (ALL) is a malignant proliferation of immature lymphocytes in the bone marrow and blood. Cancer cells utilize soluble human leukocyte antigen G (sHLA-G) as a key component of their immune evasion strategy. This study aimed to assess sHLA-G levels in patients with ALL, as it may serve as a diagnostic marker for tumors.

Materials and Methods: Children diagnosed with ALL were compared with healthy children in a control group. Participants in both groups were between 1 and 14 years of age. Patient samples were categorized into three subgroups based on disease duration and treatment. Serum sHLA-G levels were measured using enzyme-linked immunosorbent assay (ELISA).

Results: The patient group consisted of 80 participants, while the control group included 40 individuals. The findings indicated that sHLA-G levels were significantly higher in patients (mean ± standard deviation [SD]= 42.08 ± 21.62 ng/mL) in contrast to control subjects (mean ± SD=23.20 ± 21.54 ng/mL; p=0.001). While no significant differences were found in sHLA-G levels across the three patient subgroups compared with Duncan's test (p=0.213), all patient groups had a considerable elevation in sHLA-G levels compared to the control group.

Conclusions: sHLA-G acts as an immune checkpoint used by tumor cells to spread and evade immunity. Therefore, it can be used as an indicator for diagnosing and monitoring tumor development and treatment response.

Keywords: Acute lymphoblastic leukemia, biomarker, cancer, children, diagnosis, sHLA-G

Introduction

Acute lymphoblastic leukemia (ALL) is an uncontrolled proliferation of immature lymphocytes that are precursors to either B-cells or T-cells, and their rapid proliferation leads to their collection in the blood, bone marrow, and other organs (1). ALL is one of the most common types of tumors among children, and the incidence rate peaks between the ages of 1-4 years (2, 3). It also constitutes

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about 20% of leukemia among adults (4, 5). Following the bone marrow, leukemia cells spread to the brain, spinal cord, and other extramedullary locations, such as the spleen, liver, mediastinum, and lymph nodes. In pediatric ALL patients, B cells constitute 85%, and T cells account for 15% (5-7).

Human leukocyte antigen G (HLA-G) is primarily derived from the non-classical major histocompatibility complex class I molecule. It is a molecule associated with autoimmune illnesses and susceptibility to viral infections, resulting in an imbalanced and pathological environment (8). First identified in fetal cytotrophoblasts through gestation, HLA is believed to contribute to a phenomenon known as fetal-maternal tolerance, which shields the fetus from immune system destruction (9). Also, HLA-G is observed in tumors (10). In both normal and abnormal circumstances, HLA-G is located on the membrane of various cell types, and it can also be found in soluble form in cerebrospinal fluid, bodily plasma, and even extracellular vesicles (11).

sHLA-G serves as an immune checkpoint and is a promising candidate for disease monitoring and cancer outcome prediction due to (i) its restricted expression pattern in physiological tissues, (ii) minimal polymorphism in the coding region, and (iii) diverse immunomodulatory properties. Under pathological circumstances, Nonetheless, HLA-G is present in several primary tumor types and metastases with differing frequencies, and it is significantly associated with elevated tumor grade and a bad prognosis for cancer patients (12).

sHLA-G plays a critical role in the clinical context of ALL, particularly regarding prognosis and immunological response, as a biomarker for forecasting outcomes in ALL patients. sHLA-G expression in ALL facilitates immune evasion by down-regulating natural killer (NK) cells and compromising both innate and adaptive immunological responses (13). The engagement of sHLA-G with immune cells results in a suppressive tumor microenvironment, hence facilitating tumor survival and growth (14).

Functioning through its receptors on immune cells, such as immunoglobulin-like transcript receptor 4 (ILT-4), immunoglobulin-like transcript receptor 2 (ILT-2), killer inhibitory receptor (KIR), CD160 receptor, and CD8 receptor, sHLA-G functionally impacts both non-specific and specific immune by compromising anti-tumor immune responses (15-17).

This study aimed to quantify sHLA-G concentrations in patients with ALL since it serves as a significant and promising immunological marker for diagnosis and disease progression while assessing its use in monitoring tumor growth.

Materials and Methods

Study Area

ALL patient samples were collected under the supervision of a haematology specialist from the Al-Hadbaa Specialized Hospital in Mosul, Iraq, from March to July 2024. The samples of ALL patients were collected under the supervision of a hematology specialist. The study was approved by the Iraqi Ministry of Health and the ethical and scientific board of Mosul University in Mosul, Iraq. All procedures followed the Declaration of Helsinki. Informed consent was obtained from all participants. Participants were assured confidentiality and received blood testing free of charge.

Study Subject

Blood samples were collected from children diagnosed with ALL and healthy controls. All participants were aged 1 and 14 years. Demographic information, including age, sex, disease duration, treatment type, and family medical history, was recorded. The samples of ALL patients were divided into three subgroups based on disease duration and treatment type:

Group 1: <1 year
Group 2: 1–2 years
Group 3: >2 years

Clinical features of the patients are summarized in Table 1, and the FAB (French-American-British) classification is presented in Table 2. Chemotherapy regimens included vincristine, methotrexate, and prednisone, following international pediatric oncology protocols. The response to chemotherapy was complete and within the standard risk category.

Serum Collection

A 3 mL venous blood sample was collected from each participant and placed in a gel tube. Samples were centrifuged at 3000 rpm for 15 minutes. The separated serum was transferred to Eppendorf tubes to prepare for analysis and stored at -20°C.

Table 1. The clinical characteristics of ALL patients.

Clinical characteristics of ALL patients
Fever
Extreme fatigue
Feeling of exhaustion
Anaemia
Bone pain
Easy bruising

Table 2. The FAB (French-American-British) classification of ALL patients.

Subtype of ALL	Description	%
L1	Blast cells that are uniformly tiny and have a high nuclear-to-cytoplasm ratio	90
L2	Larger blasts that have nucleoli, a more-varied cytoplasm, and an uneven nuclear structure	10

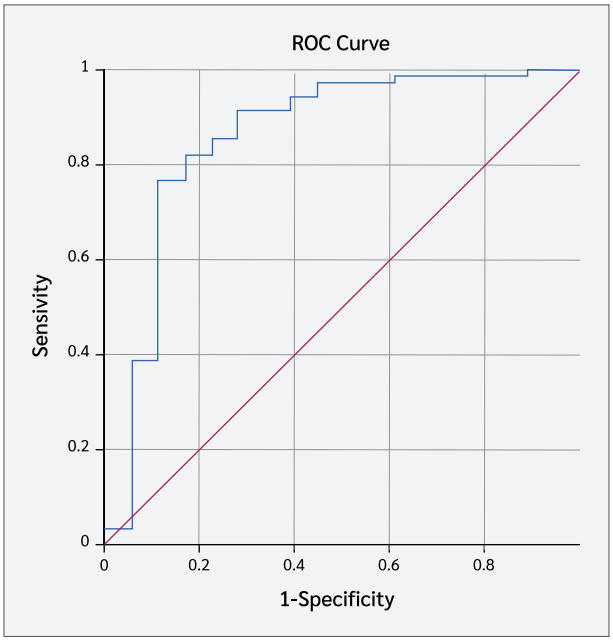

Figure 5. ROC curve of the variable sHLA-G.

Complete Blood Count (CBC)

Hematological parameters were measured using the Mythic™ 18 automated hematology analyzer (Orphée S.A., Switzerland).

Measurement of sHLA-G Concentration by ELISA

The principle of the assay is based on the reaction of sHLA-G present in serum samples with antibodies previously fixed on the surface of a polystyrene plate. A biotin-labeled antibody is added, which binds to the Ag-AB complex. After incubation, washing is done, streptavidin-horseradish peroxidase (HRP) enzyme and substrate solution are added in order, and the color develops according to the amount of sHLA-G. After stopping the reaction with an acid-stop solution, the absorbance is read at 450 nm.

Procedure

1. The ELISA kit (Fine Test Company, China) was used. 100 µL of the standard solution was added to the first twelve wells, and 100 µL of the sample was introduced to the remaining wells; the plate was covered and incubated at 37°C for 90 minutes. Subsequent to incubation, the plate was rinsed three times and immersed in the wash solution for one minute.
2. Added 100 µL of biotin-labeled antibody to each well and incubated the plate at 37°C for 60 minutes. After incubation, the plate was washed twice with wash solution.
3. Added 100 µL of HRP-streptavidin conjugate solution to each well and incubated at 37°C for 30 minutes.
4. Added 90 µL of TMB solution to each well. Incubation was carried out at 37°C for 10-20 minutes in the dark.
5. 50µL of stop solution was added to each well, and the optical density was read at 450 nm within 10 minutes using a microplate reader model Rt-2100c.

Statistical Analysis

Duncan's test was used to compare the means, and the probability level was set as $p \leq 0.05$. Statistical analyses, including the receiver operating characteristic (ROC) curve, were performed using the Statistical Package for the Social Sciences (SPSS), version 24.0.

Results

A total of 80 blood samples from the patient group were compared to 40 samples from the control group. The patient group consisted of 60 males and 20 females; while the control group included 20 males and 20 females. The results of Duncan's test for paired comparisons and

Table 3. Duncan's test for pairs of comparisons and to test the significance level of the variable WBC count.

Variable	Groups	n	Mean ± SD	Duncan test	
				Subset for alpha = 0.05	
				1	2
WBC cell/µL	1-2 years	25	3211.50 ± 1948.29	3211.50	
	Less than 1 year	30	3482.52 ± 2095.82	3482.52	
	More than 2 years	25	3705.50 ± 1772.09	3705.50	
	Control	40	8013.22 ± 2165.74		8013.22
			p-value	0.460	1.000

WBC: White blood cell count, **SD:** Standard deviation.

Table 4. Comparison of sHLA-G concentrations in ALL patients and control group.

Parameter	Groups	Number	Mean ± SD	Extreme value	*T*-test	*p*-value
sHLA-G ng/mL	Patients	80	42.08 ± 21.62	10.85-132.09	3.292	0.001*
	Control	40	23.20 ± 21.54	6.16-102.55		

sHLA-G: Soluble human leukocyte antigen-G, **SD:** Standard deviation.

Table 5. Duncan's test for pairs of comparisons and to test the significance level of the variable sHLA-G.

Variable	Groups	Number	Mean ± SD	Duncan's test	
				Subset for alpha=0.05	
				1	2
sHLA-G ng/mL	Less than 1 year	30	45.99 ± 28.95		45.99
	1-2 years	25	37.05 ± 13.16		37.05
	More than 2 years	25	41.82 ± 15.99		41.82
	Control	40	23.20 ± 21.54	23.20	
			p-value	1.000	0.213

sHLA-G: Soluble human leukocyte antigen-G, **SD:** Standard deviation.

significance level test for white blood cell (WBC) count showed no significant differences between the three subgroups of the patients (p=0.460). However, all patient groups showed significantly lower WBC counts than the control group (Table 3).

sHLA-G concentrations were significantly elevated in patients with ALL compared to controls (p=0.001) (Table 4). However, sHLA-G demonstrated no significant difference among the subgroups of the patients (p=0.213) (Table 5).

Table 6. ROC curve of the variable sHLA-G.

ROC curve				Max.	Cut-off value
Test result variable	Area	Asymptotic 95% CI			
		Lower bound	Upper bound		
sHLA-G	0.858	0.739	0.978	Sensitivity=0.821	27.4885
				Specificity=0.833	

sHLA-G: Soluble human leukocyte antigen-G, **ROC:** Receiver operating characteristic, **CI:** Confidence interval.

The results of the ROC curve analysis showed the sensitivity as 0.821 and the specificity as 0.833 (Table 6) (Figure 1), indicating that sHLA-G is a valuable tool for diagnosing ALL patients.

Discussion

The total WBC count is a measure of the presence of extramedullary cells in ALL (17). Alghamdi et al. (18) indicated that a decrease in WBC count in patients with ALL undergoing chemotherapy is a common and expected outcome. This decrease is primarily due to the effects of chemotherapeutic agents, which target rapidly dividing cells, including leukemic and normal hematopoietic cells.

The reason for the decrease in the total WBC counts and the absolute number of WBC types in ALL patients compared to the control in Table 3 is that all patients were undergoing chemotherapy. Chemotherapy is designed to target rapidly dividing cells, including cancer cells. It also affects other rapidly dividing cells in the body, such as those in the bone marrow, which produces blood cells. The drugs damage the DNA of dividing cells, leading to cell death. This results in a decrease in the absolute number of cells, which can serve as a prognostic indicator of treatment effectiveness and patient outcomes.

One important immunological checkpoint protein in cancer is sHLA-G (19), a vital biomarker for invasion and metastasis of cancer cells, as it inhibits all stages of the anti-tumor response (12, 21). Elevated sHLA-G in cancer can alter the immune surveillance system and cause tumor escape from the immunity in a number of hematologic malignancies, including acute and chronic leukemia (12).

Excessive levels of sHLA-G in children with ALL are connected to leukemia cells' capacity to elude the immune system, which may result in worse clinical outcomes. sHLA-G often acts as a "disappearance cloak" for tumor cells by inhibiting immune responses, including those from NK and T cells. Consequently, HLA-G appears as a potential tumor biomarker of clinical results, as shown in Table 1 (13, 22).

Our findings support the study by Ribeiro et al. (13), who reported increased sHLA-G levels in patients with leukemia and lymphoma but not in healthy individuals. Moreover, we found sHLA-G levels considerably higher in ALL patients than healthy controls, suggesting it is usable as a prognostic marker. Also, Almeida et al. found that elevated sHLA-G levels in bone marrow were linked to increased blood cell counts in juvenile T-cell ALL, a metric linked to a bad prognosis (24). High HLA-G levels are generally related to adverse outcomes in ALL. As reported by Xu et al. (20), high sHLA-G levels in cancer are connected with poor survival in ALL. Chemotherapy in ALL targets leukemia cells, which may indirectly affect sHLA-G by reducing tumor burden.

Ribeiro et al. (13) indicated that sHLA-G levels decreased after chemotherapy and were associated with improved clinical outcomes. Chemotherapy targets tumor cells, which indirectly affects sHLA-G by reducing tumor burden, in addition to causing significant changes in the cellular metabolism of tumor cells, which may indirectly affect the secretion of sHLA-G, although this has not been directly measured in studies (25). This situation explains what is shown in Table 2. The protein concentration was higher in Group 1 because they were at the beginning of the disease and the beginning of chemotherapy, and the expression of the protein was at its highest levels for use as a means of cancer cell proliferation. Then, the protein

concentration began to decrease somewhat in Group 2 and Group 3 as a result of undergoing chemotherapy for long periods. Therefore, sHLA-G can serve as a prognostic marker for treatment response in ALL.

Physiological tissues have a limited pattern of sHLA-G expression, while a wide range of primary and malignant tumors has shown positivity. There is a significant correlation between elevated tumor grade and worse prognosis in cancer patients (12). This is also attributable to its immunosuppressive properties, which tumor cells use to circumvent the host immune system. Consequently, in recent decades, the expression of sHLA-G and its immunosuppressive effects have emerged as a significant subject of investigation, particularly in cancer research. Multiple studies suggest that sHLA-G may pave the way for its consideration as a novel immune checkpoint in tumor diagnosis, acting as a natural immune signal that prevents the development of an immune response (26, 27).

The interaction of sHLA-G with its receptors causes inhibition of cytotoxic T cells, inhibition of $CD4^+$ T cell proliferation (28) and may also lead to reduced expression of pro-inflammatory cytokines generated by T helper 1 (Th1) cells and enhanced production of anti-inflammatory cytokines produced by T helper 2 (Th2) cells. Therefore, it is believed that abnormal HLA-G/sHLA-G expression enables tumor cells to evade immune responses (29).

Expression of this protein in hematological malignancies, such as leukemia, is linked to immune cell-mediated cytotoxicity resistance and the development of an immunological milieu that supports tumors, including the activation of regulatory T cells and interleukin 10 (IL-10)-producing dendritic cells (13).

Additionally, distinct micro RNAs that differ depending on the leukemia subtype affect the control of sHLA-G expression in leukemia, suggesting a complicated regulatory mechanism that could aid in the course of the disease and immune evasion (21). Therefore, it is possible to view the presence of sHLA-G in leukemic cells as a means of evading immune monitoring, which could result in treatment resistance and lower survival rates in afflicted children (13, 22).

Leukemia patients receiving hematopoietic stem cell transplantation have experienced unfavorable results because of genetic variations in the sHLA-G gene in the 3' untranslated region (3'-UTR) and 5' upstream regulatory region (5'-URR). This suggests a genetic vulnerability to immunological regulation by sHLA-G (30)

Conclusion

We concluded that increased sHLA-G is an immune mechanism that tumor cells utilize to eliminate the immune system response. sHLA-G is one of the most significant contemporary indicators that should be used as a marker for the onset and progression of the tumor condition in patients with lymphocytic leukemia.

Ethics Committee Approval: Prior to the initiation of the clinical study, ethical approval was obtained from the Scientific and Ethical Committee of Mosul University, Mosul, Iraq (Approval No. 476, dated January 21, 2024), and further authorization was granted by the Iraqi Ministry of Health (Approval No. 6428, dated February 12, 2024).

Informed Consent: Ethical approvals for patient data were obtained under the supervision of the Department of Health and the Scientific Committee of the Department of Biology, Faculty of Science, University of Mosul, in accordance with the Declaration of Helsinki..

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