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ORIGINAL ARTICLE

CD19 gene Polymorphism in Chronic Myeloid Leukemia Patients Infected with Varicella Zoster Virus

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ABSTRACT

Background: *Chronic myeloid leukemia (CML), driven by the BCR-ABL1 oncogene, is associated with immune dysregulation and increased susceptibility to reactivation of viruses such as Varicella Zoster Virus (VZV). CD19, a critical B cell receptor co-regulator, may influence the immune response in CML.* ***Objective:*** *This study investigates CD19 polymorphisms and their potential link to VZV reactivation in patients with CML.* ***Methodology****: Blood samples from 120 CML patients and 100 age-and sex-matched healthy controls (AHC) were analyzed. CD19 serum levels were quantified using ELISA. CD19 genotyping (AA, AG, and GG) and VZV-DNA detection were performed by PCR and sequencing in both CML patients and healthy controls. Statistical analyses included Chi-square, Hardy-Weinberg equilibrium, and Spearman's correlation (SPSS v24).* ***Results****: CD19 levels were significantly lower in CML patients (27.45 ± 16.23 pg/mL) versus controls (37.47 ± 40.43 pg/mL; p=0.02). Genotyping revealed a higher GG genotype frequency in CML (30% vs. 10% in controls), although no significant association was found (p=0.21). VZV DNA was not detected in any of the samples. CD19 levels and polymorphisms were correlated with patient age (r=0.647, p=0.04; r=0.722, p=0.03). No significant differences in biochemical parameters were observed, except for elevated creatinine levels in the relapsed patients (p=0.01).* ***Conclusions:*** *Reduced CD19 levels in patients with CML suggest immune dysregulation, potentially impairing B-cell function. The absence of VZV reactivation contrasts with previous studies, possibly because of effective antiviral management or limited sample diversity. CD19 polymorphisms, particularly the GG genotype, may warrant further investigation as biomarkers of immune status in CML. These findings underscore the need for larger studies to clarify CD19's role in viral susceptibility and therapeutic outcome.*

INTRODUCTION

Chronic myeloid leukemia is a clonal myeloproliferative condition that is classified as a triphasic hematological malignancy. The production of the Philadelphia chromosome, an aberrant chromosome, ultimately leads to the development of this condition. This abnormal chromosome is primarily associated with changes in the microenvironment of the bone marrow and peripheral blood, in addition to uncontrolled proliferation of myeloid cells [1]. The Philadelphia (Ph) chromosome arises from reciprocal translocation between chromosome 9 and 22 long arms, which results from the fusion of the breakpoint cluster region (BCR) on chromosome 22q1 with the abelson oncogene (ABL1) on chromosome 9q34 to form the BCR-ABL1 oncogene that is responsible for the disease pathology [2]. Subsequently, the BCR-ABL1 hybrid gene encodes the 210 kD oncoprotein. By stimulating the tyrosine kinase pathway, this oncoprotein contributes to leukemogenesis, which occurs in chronic myelogenous leukemia (CML). Through this activation, the signal transduction of unregulated downstream carcinogenic pathways, such as JAK/STAT, PI3K/AKT, RAF, MYC, and RAS/MEK, is initiated. These pathways are responsible for the development of cancer. These routes include those that contribute to cell survival, proliferation, and apoptosis prevention [3].

On a yearly basis, there are two cases of chronic myelogenous leukemia for every 100,000 people, accounting for approximately 15% of newly diagnosed cases of adult leukemia [4] with a median age of almost 50 years[5]. Viral infections, particularly the reactivation of latent viruses, such as Varicella Zoster Virus (VZV), are more common in patients with CML [6]. Tyrosine kinase inhibitors, such as imatinib, have been shown to be an extremely effective treatment for individuals who have been diagnosed with CML according to recent research evidence. However, the utilization of these inhibitors is linked to an elevated risk of a variety of diseases, notably reactivation of viral infections [7].

The cluster of differentiation 19 (CD19) gene encodes a transmembrane glycoprotein of 95kd which belongs to the immunoglobulin superfamily. In light of

the fact that it is expressed during the whole process of B cell development, it is frequently used as a biomarker for the diagnosis of lymphoma and immunotherapy for leukemia [8]. The CD19 function as a co-receptor for BCR signaling, which is essential for controls downstream signaling pathways responsible for the proliferation and differentiation of B cells as well as the differentiation of their functions [9]. The proportion of lymphocytes expressing T cell antigen and CD19 was lower in patients with CML than in normal controls [10]. Previous studies have indicated that tyrosine kinase inhibitors (TKIs) in CML therapy increase viral reactivation risks, such VZV. However, this study found no VZV-DNA in CML patients, contradicting existing evidence. Additionally, although CD19 gene polymorphisms and reduced CD19 levels are linked to B-cell dysfunction in CML, their specific roles in disease susceptibility, immune dysregulation, and viral reactivation remain unclear. This study aimed to investigate CD19 gene polymorphisms, serum CD19 levels, and their association with VZV infection in CML patients, addressing gaps in the understanding of immune mechanisms and viral reactivation risks in TKI-treated populations to guide targeted therapeutic strategies.

METHODOLOGY

Study Population

The case-control study, conducted at the University of Babylon, Iraq, enrolled 220 participants: 120 consecutively recruited CML patients from the Iraqi Hematology Center (Baghdad) and 100 age- and sex-matched apparently healthy controls (AHC) from Al-Hillah City, Babylon Province, between October and December 2024. The ages of both the AHC and patient groups ranged between 20 and 60 years.

Estimation of CD19

Around (3 ml) of venous blood was placed into a gel tube and centrifuged to obtain serum, which was instantly stored at freezing (-20) until use. CD19 levels in the serum of both patients and AHC groups were evaluated using an ELISA Kit (BT LAB/China).

DNA extraction

A. Total DNA Extraction:

Total DNA was extracted to investigate the polymorphism of CD19 genes. Approximately (2 ml) of venous blood was placed into an EDTA tube that was collected from patients with CML and AHC groups**,** then stored it immediately at -20 °C until total DNA was extracted. For total DNA extraction, a G-SpinTM Total DNA Extraction Mini Kit (iNtRON Biotechnology Co., Korea) was used, which was optimized to extract (20-30kb) DNA fragments that were also able to extract up to 50kb fragments.

B. Viral Genome Extraction:

The viral genome was extracted as follows: 3 ml of venous blood from patients that already had CML as well as AHC were put into an EDTA tube using the Patho Gene-spinTM DNA/RNA Extraction kit (iNtRON Biotechnology Co., Korea), which was designed to isolate high-quality nucleic acids from a variety of pathogens and specimens using low elution volumes that allow sensitive downstream analysis. The viral genome was extracted and stored at (-20˚C).

Primer selection

Primer pairs for the CD19 gene (forward: "TCTAGTGGTGAAGGTGGAAGGT," reverse: "CCATCTGTTGAGAGACGTTGAA") and VZV (forward: "CCTCTGGACCACCGATAGAA," reverse: "CAACGCAAAAATTGATGTGG" CAACGCAAAAATTGATGTGG') were designed and utilized for amplification. Polymerase chain reaction (PCR) was performed using a conventional thermal cycler (Biometra, Germany) with a 25 µL reaction mixture comprising 12.5 µL master mix, 1 µL each of forward and reverse primers, 5.5 µL nuclease-free water, and 5 µL of extracted DNA template. This standardized protocol ensured the efficient amplification of target sequences under optimized cycling conditions.

DNA genotyping and Sequencing

The reactions were ultimately placed in a thermal cycler (Biometra, Germany), which was preheated to 94°C and set up with the proper cycle settings described in Table (2). The target regions of VZV and CD19 polymorphisms were amplified using specific primers. Next, the PCR products were electrophoresed using a 1.5% agarose gel, which was then visualized using the gel documentation system. The thermal conditions used for CD19 and VZV amplification were as follows: initial denaturation (95 °C/5 min), denaturation (95 °C/1 min), annealing (59 °C/45 s for CD19 and 56 °C/45 s for VZV), extension (72 °C/2 min), final extension (72 °C/5 min), and No. of cycles (35). Next, the forward (F) PCR primer was used as the sequencing primer for CD19 to automatically sequence the PCR results. Sequencing was carried out at the Macrogen Company in Geumcheon, Seoul, South Korea, and the sequences were examined using the NCBI reference database's DNA sequences and Geneious Bioinformatics software version 2 for sequence data processing and alignment.

Ethical certification

This study adhered to the principles of the Declaration of Helsinki. Before sample collection, verbal and written consent was obtained from all patients. This study was conducted at the University of Babylon, Iraq. A local ethics commission reviewed and approved the study protocol, consent form, and subject information on September 10, 2024, under project number M240903.

Statistical analysis

To assess the significance of the variables examined in this study, the chi-square test was used. All statistical analyses were conducted using SPSS program version 24. Statistical significance was set at p <0.05. Hardy-Weinberg equilibrium was used to analyze CD19 gene polymorphism.

RESULTS

For age, the patient groups were matched with the control group (p = 0.57). The sex ratio among the new diagnosis and treated group was 1.5 and 1.08, respectively, which matched the control group ratio of 1.5(p = 0.59), as shown in Table (1)

According to the results of the serum levels of biochemical parameters, including urea creatinine, ALT, AST, and LDH, there were non-significant differences among newly diagnosed CML, treated patients who responded to treatment, and the relapse group, except for the serum level of creatinine between the newly diagnosed CML group and the relapse group; there were statistically significant differences at a p value (0.01), as shown in Table (2).

Table 1: Age and sex distribution between patients with CML and AHC group

Parameters		Patients (n=120)		Controls (n=100)	p-value
		New diagnosis (n=20)	Treated (n=100)		
Age ±SD		43±13.3	49±12.43	46±12.9	0.57
Sex	**Male**	12(60%)	52(52%)	56(56%)	0.59
	Female	8(40%)	48(48%)	44 (44%)	
Sex	**Ratio**	1.5:1	1.08	1.5	

Table 2: Estimation the levels of some biochemical parameters for new diagnosis CML, treated patients respond to treatment and relapse groups.

Parameters	New diagnosis (n=20) Mean±SD	Treated (n=100) Mean±SD		p-value
		Response to treatment (n=69)	Relapse (n=31)	
Urea (mg/dl)	31.5±7.8	33.3±18.2	30.3±12.1	*0.615 **0.69 ***0.399
Creatinine(mg/dl)	0.71±0.51	1.0±0.73	0.9±0.33	*0.059 **0.01 ***0.329
ALT (IU/L)	29.5±10.9	30.5±10.79	28.3±12.3	*0.73 **742 ***418
AST (IU/L)	33.6±12.6	32.2±12.7	33.2±15.6	*0.671 **931 ***733
LDH (IU/L)	478±201	485±278	438±20.4	*0.909 **0.49 ***0.39

***** Comparison between newly diagnosed CML and response to treatment patients. ** Comparison between newly diagnosed CML patients and relapse patients. *** Response to treatment and relapse patients.

The mean level of CD19 was significantly decreased in patients (27.45 ± 16.23pg/ml) compared to AHC (37.47 ± 40.43pg/ml) groups, with a Sig 0.02 OR 0.276 According to CD19 serum level, there are NON OR statistically significant differences among patients with CML and AHC groups,

In this study, CD19 genetic sequences located on chromosome 16 were targeted. The 463 bp amplicon analyzed in this study represents part of the exon region of the CD19 molecule, which plays a key role in B cell development and activation (Figure 1). When analyzed using the NCBI BLASTn engine, the obtained sequence showed approximately 99% similarity to the human CD19 reference sequence (GenBank accession No. NC_000016.10). As shown in figure (1).

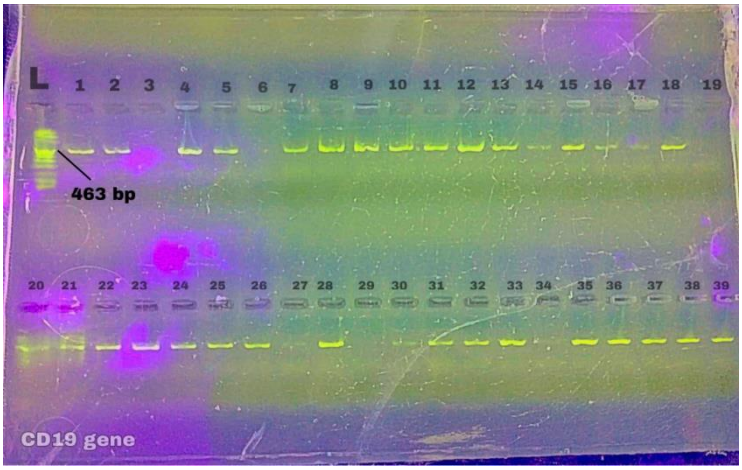

Fig. 1: Agarose gel electrophoresis result showing PCR-amplified CD19 gene fragments. distinctive bands at the expected size demonstrating the presence of this gene in studies sample.

The present results showed that the DNA polymorphism distribution was according to AA; AG and GG were 40%, 30%, and 30%, respectively, in patients with CML and 60%, 30%, and 10%, respectively, in the control group. There were no statistically significant differences ($p< 0.05$) between the different groups according to the genotyping of CD19. Although the GG genotype seems to be more common in patients (30%) than in controls (10%), the statistical analysis exhibited no significant relationship between genotype and disease (P=0.21, OR=0.22; 95% CI: 0.02–2.36). Likewise, the AG genotype was slightly more frequent in patients (30%) than in controls (30%) but also showed no significant association (P=0.64, OR=0.66; 95% CI: 0.11–3.81). With regard to allele frequency, the A allele was more common in both patient and AHC groups (55% and 75%, respectively), compared to the G allele in 45% of patients and only 25% in the AHC group. Although the G allele was significantly higher in the patient group, the statistical analysis indicated no significant difference (P=0.13, OR=0.40; 95% CI: 0.12–1.33, as illustrated in Table (3).

Table 3: Genotyping of CD19 (NC_000016.10) gene in CML patients and AHC groups

Genotype CD19	Patients No. no. (%)	Control no. (%)	z- statics	Sig.	OR (95%)
AA [a]	8	6	References		
AG	6	3	0.45	0.64	0.66(0.11-3.81)
GG	6	1	1.24	0.21	0.22(0.02-2.36)
Total number	20	10			
A allele	22	15	References		
G allele	18	5	1.48	0.13	0.40(0.12-1.33)

A novel partial sequence of the CD19 gene was identified, covering 463 bp and located on chromosome 16. The samples were collected from blood-derived leukocytes and submitted to the DDBJ/EMBL/GenBank databases under accession numbers LC867677, LC867678, and LC867679. In the current study, the genetic sequence of CD19 was analyzed. For the currently investigated 463 bp gene amplicon, BLASTn analysis revealed a high similarity with the reference human CD19 gene sequences available in NCBI, including coding and adjacent regulatory regions, according to human genome annotation (GenBank version: LC867677.1, LC867678.1, LC867679.1).

VZV -DNA was not found in any of the blood samples of patients in the CML or AHC groups, as shown in Table (4) and figure (2).

Table 4: The results of PCR for VZV-DNA-infection in patients with CML.

VZV	No.	%	P value
Positive	**0**	**O.OO%**	**P=0.03 Sign >0.05**
Negative	**120**	**73%**	
Total	**100**	**100%**	

A significant correlation was found between the CD19 polymorphism and age of patients with CML (r=0.722, p= 0.03). In addition, a significant correlation was found between CD19 levels and the age of patients with CML (r=0.647, p= 0.04). In addition, a non-significant correlation was observed between the CD-19 polymorphism**s,** as shown in Table (5)

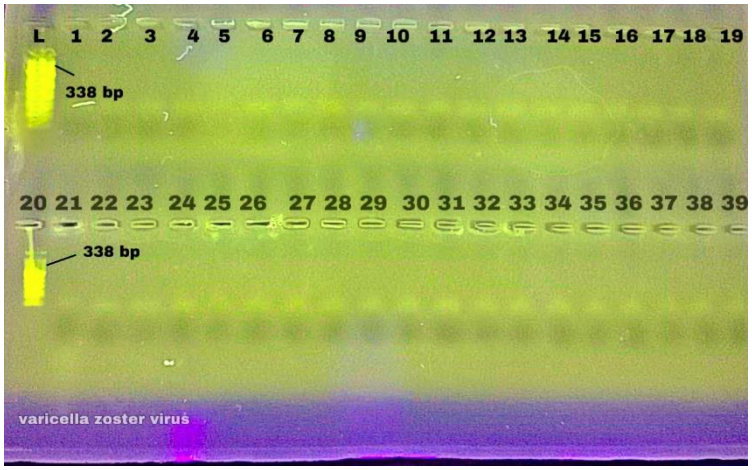

Fig. 2: NO-PCR detection of the VZV gene; in CML patients. M: A 100–1100 bp DNA ladder. After migrating into 2% agarose at 75V and 20 mA for 120 minutes, the PCR-amplified products were stained with ethidium bromide and placed in 15 µl per well.

Table 5: Spearman's Rho statistical testing of age, sex, VZV-DNA-PCR and CD19 SNP to evaluate the studied markers in patients with CML.

Spearman's rho		Age	CD19 polymorphism	CD19 level	Sex
CD19 Polymorphism	r	**0.722**			0.342
	p	**0.03**			0.6
CD19 Levels	r	0.647			**0.235**
	p	0.04			**0.3**

DISCUSSION

Chronic myeloid leukemia is described as a condition of the clonal progenitor of the hemopoietic tissue in which the production of new myeloid blast cells is accelerated while the rate of apoptosis is decreased [2]. In this study, the average age of newly diagnosed patients was 35 years, while that of the control group was 43 years. The difference in age between the groups was not statistically significant (p=0.57). The sick group had a slightly higher percentage of men than the control group, but the difference was not statistically significant. The median age of CML patients at analysis was 52–64 years, which is consistent with epidemiological data [11]. In another study, Asians appeared to have CML at a median age of 35–45 years, with a global incidence rate of 15/1,000,000 per year, and a male-to-female ratio of 1.34 [12, 13]. According to the accessible Indian literature, a significant portion of the sick population is under 60. This study found no statistically significant difference in clinical parameters among older CML patients [14, 15].

Our study found that pretreatment AST and ALT enzyme levels increased significantly in patients aged 12 (20%) and 6 years (10%). These increases were statistically significant compared to the pretreatment values. The p-values for AST, ALT, and ALP were 0.000, 0.001, and 0.03, respectively. In addition, both groups had higher mean ALP enzyme levels than the typical reference values. This observation concerns tumor metabolism and physiology. Mupepe et al. studied uricemia and fasting blood sugar and serum creatinine levels in Kinshasa. Serum creatinine, uricemia, and fasting blood sugar varied from 1.2 to 4.7 mg/Dl, 60 to 108 mg/L, and 50 to 172 g/dL, respectively [16].

Imatinib, dasatinib, and nilotinib are typical CML medications with side effects. Although these drugs are effective for treating CML, they may cause hepatotoxicity and nephrotoxicity. Drug-induced liver and kidney damage may result in elevated ALT and AST [17].

The study found that patients with CML (30%) had a higher frequency of the GG CD19 genotype than the AHC group (10%), with a non-significant association (p = 0.21), as shown in Table (4), which also includes A and G alleles. The CD19 exon 2 mutation replaces serine with isoleucine, altering protein structure and reducing gene expression. These data support previous studies showing that CD19 (MIM 107265) mutations diminish serum immunoglobulin (Ig), memory B cell counts, and antibody responses to vaccinations [18, 19]. Patients with hypogammaglobulinemia from two families exhibited deficient CD19 expression due to gene mutations. This shows a new CD19 deficiency with two CD19 gene mutations[18].

Van Zelm et al.[18] and Kanegane et al.[19] Documentation was performed on a patient who had a CD19 deficiency, and it was discovered that the patient was compound heterozygous for two distinct mutations. As a consequence of these mutations, the absence of CD19 membrane expression is the final result, which ultimately results in antibody deficiency syndrome. Recurrent infections, primarily caused by bacteria, are the defining features of this illness. When a mutation occurs in the splice acceptor site of exon 6 (IVS5-1G4T), an early stop codon is produced at the intracellular amino acid level. This occurred because of the mutation. This mutation causes exon 6 to be skipped, which in turn causes exon 7 to be out of frame following exon 5. No evidence of membrane CD19 expression was observed in all patients. Furthermore, any protein that is made is rendered ineffective because it does not contain all the intracellular domains necessary for signal transduction[20].

The results of CD19 levels demonstrated that the mean serum level of CD19 was significantly decreased in patients with CML compared with the AHC group. This statistically significant difference suggests a possible involvement of humoral immune dysregulation in CML patients, and the decrease in CD19 levels is consistent with that reported by Kim et al.[10] who observed a low expression of CD19 in patients compared to normal controls. As CD19 acts as a co-receptor for B-cell this downregulation may be related to humoral immunodeficiency characterized by defective B cell development, impaired germinal center formation, and reduced immunoglobulin production, as indicated by Sermer et al.[9]

With respect to viral reactivation, all samples were negative for VZV-DNA, as shown in Table (6). This result was inconsistent with a previous study that suggested that VZV is more frequent in CML patients with longer duration as a result of the use of tyrosine kinase inhibitors (TKIs) that may inhibit the proliferation of CD4+ T cells in a dose-dependent manner [21]. Considering that there was no indication of nosocomial transmission among our patients, it appears that the reactivation of dormant viral infection not a contributing factor to the illness observed in these individual. Immediately after the first infection, VZV enters a dormant condition and has the potential to reactivate, particularly in situations where the cell-mediated immune system is impaired (including a low number of CD4-positive cells; Refs.[22, 23].

Patients with chronic myelogenous leukemia receiving imatinib appear to have a significantly lower incidence and severity of VZV infection than those receiving alternative immunosuppressive treatments for CML. This is the case even when antiviral prophylaxis is not used (for example allogeneic SCT; Refs.[24]. It is important to note that interferon- may provide protection against infections caused by the herpes virus[25-27] and that hydroxyurea, frequently employed in the treatment of CML, may potentially possess antiviral characteristics [28-30]. The widespread application of antiviral medications in patients with CML may explain the previously noted low frequency of VZV infection in this population. While the majority of VZV cases were noted in patients with a history of substantial therapy, our initial observations in untreated individuals indicated that VZV infection may still arise in such circumstances.

The standard prophylaxis for VZV infection is not indicated in this particular case because the danger of VZV infection in CML patients who are being treated with imatinib is extremely low, the severity of the illness is low, and the patient has an exceptional response to the medicine. Despite this, it is strongly recommended that infections of this type be recognized and treated as quickly as possible. This occurs because of the high occurrence of postherpetic neuralgia, as well as the danger of a fatal infection if treatment is delayed. Patients who are taking imatinib and who have a history of VZV infection or who have had extensive exposure to people who have developed this illness in the past are advised to receive antiviral prophylaxis while they are taking imatinib. It is possible that in the future, when we have a better understanding of the factors that put people at risk for VZV infection in this setting, we will be able to develop more effective tools (such as CD4 count) to guide prophylaxis against this lethal virus.

However, the significantly lower serum levels of CD19 in CML patients compared to those in the AHC group may reflect underlying immune changes, such as B-cell impairment associated with this disease. Furthermore, the lack of VZV-DNA in all samples indicated that viral reactivation was limited in this population. Despite the lack of a direct relationship, CD19 levels may serve as biomarkers for immunological dysregulation in CML.

CONCLUSIONS

This study highlights the altered CD19 expression and genotype distribution in patients with CML, indicative of underlying B-cell dysfunction. Despite the theoretical risks of VZV reactivation with tyrosine kinase inhibitors, no viral DNA was detected, suggesting the need for effective clinical management such as regular immune status monitoring or preventive antiviral strategies and consideration of population specific factors, including age, diseases phase, or treatment duration. The correlation between CD19 levels and age implies age-related immune changes in CML patients. Future research should explore longitudinal CD19 dynamics and broader viral screening to refine the risk stratification and therapeutic strategies.

Ethical approval
The present study followed the principles of the Declaration of Helsinki. Before sample collection, verbal and written consent was obtained from the patients. A local ethics commission reviewed and approved the study protocol, consent form, and subject information on September 10, 2024, under project number M240903.

Competing interests The author declare that they have no competing interests
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Author Contribution The authors were contributed equally in conceptualized the research, collected data, participated in data analysis and write-up, editing and review.

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