Original article

Inducing of Interleukins-10 and 8 by Epstein Barr Virus in Chronic Lymphocytic Leukemia

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Abstract:

Background: Many newer studies reported that Epstein- Barr virus (EBV) has association with chronic lymphocytic leukemia (CLL). The average age of presentation is of patients with CLL is between 65 and 70 years with male to female ratio is 2:1. Notably, several studies have reported that expression of Epstein Barr encoding RNA (EBERs) is associated with progressive or accelerated clinical courses. This type of RNA increases the level of IL-8 and IL-10 in serum of newly diagnosis of CLL patients.

Objectives: the aims of study were to determine the interleukins 10 and 8 level in newly diagnosed CLL patients and determine the incidence of EBV infection in patient of CLL.

Materials and Methods: A prospective study conducted at department of clinical hematology in the national center of hematology in Baghdad, Iraq from January 2013 to January 2014. It included thirty samples of formalin-fixed, paraffin-embedded tissue of bone marrow aspirates samples and blood from newly diagnosis B-CLL. They were diagnosed with CLL according to Binet criteria. The detection of EBV encoded RNAs (EBER1, EBER2) and also detection for the level of Interleukin (8 and 10) in the serum of CLL patients were done by in situ hybridization technique.

Results: Histopathological study revealed that all the controls were negative for EBERs and 46.7% were found to be EBERs positive. There was a correlation between positive EBERs and tumors stage and also EBERs and IL-10 and with IL-8.

Conclusion: The highest incidence of CLL occurs in the age group 40-80 years old and males are more liable than females (male/female: 70/30).In situ hybridization technique is successful method to detect of EBV and positive EBERs. IL-8 is highly significant in CLL patients and correlates with EBERs and LMP1. There is a correlation between IL-10 EBERs and LMP1 in CLL patients.

Keywords: Epstein-Barr virus, CLL, EBERs, IL-8, IL-10

Introduction

Chronic lymphocytic leukemia (CLL) results from neoplastic proliferation of a mature B by the accumulation of non-dividing Small lymphocytes. It is characterized by a persistent lymphocytosis of more than 10 x 10^9/ liter and lymphoid intrusion of the bone marrow of at least 40% [1,2]

With the use of immunological markers, it is likely to establish the diagnosis of CLL by B cell clonality, even with lymphocyte counts of less than 5 x 10^9/liter. CLL is documented as a disease entity in the WHO organization and as the leukemic counterpart of small lymphocytic lymphoma and CLL the most common type of adult leukemia in the United States and Western Europe.[3]

The mutation status of the immunoglobulin heavy chain variable region (Ig VH) genes can differentiate between these two groups: CLL patients with unmutated immunoglobulin high variable (Ig VH) genes have a negative prognosis with rapid progression of the disease.[3]

Epstein- Barr virus (EBV) infection is only occasionally detected in CLL by conventional diagnostic approaches. This is consistent with in vitro results suggesting that CLL cells do not regularly become activated or immortalized after exposure to EBV, although this can be achieved after cytokine activation.[4]

Epstein-Barr virus is the first virus described to be linked with the human pathogenesis of tumor. The topographical distribution of Burkitt lymphoma were related to areas endemic with falciparum malaria is supposed to cause chronic excitement or suppression of the immune system, making children more susceptible to the oncogenicity of EBV.[5,6]

In 1968, EBV was recognized to be the etiological factor of infectious mononucleosis. At the same time, EBV was reported to alter infected B cells to uncontrolled proliferation.[7] A large study in 2009 determined around one in every ten stomach cancers contained EBV. Studies are ongoing to decode what role the virus is playing in this type of cancer and how it weaves together with other risk factors like nutrition, genetics, and infection of H. pylori.[8]

Initiation of EBV lytic program occurs in memory B cells recirculating during the lymphoid tissue related with the oropharyngeal mucosa. Host

immunosuppression may also generate viral reactivation in lately infected B cells, which leads to creative infection. Nevertheless, the original mechanism of viral reactivation in vivo is not clearly understood.[9]

EBV alters B-lymphocyte growth, causing permanent growth transformation by regulated expression of multiple viral genes. These genes comprise three integral membrane proteins, latent membrane proteins 1, 2A, and 2B (LMP), 6 EBV nuclear antigens (EBNA1, 2, 3A, 3B, 3C, and EBNA-LP), then two small, non-coding nuclear RNAs (EBERs). The gene linked products relate with or present homology to various antiapoptotic molecules, cytokines, and signal transducers, endorsing EBV infection, immortalization, and alteration.[10]

There are two types of EBV viruses , EBV-1 and EBV-2, which vary depend on the EBV nuclear antigen (EBNA) genes.[11] .EBV-1 is more common in most populations and is more competent in transforming B cells *in vitro*. EBV-2 is mainly found in parts of Africa and is related endemic Burkitt lymphoma.[12]

Material and Methods:

This study was designed as a prospective (case-control) study conducted on the following main groups during the period from January 2013 to January 2014. Thirty formalin-fixed, paraffin embedded tissue blocks were obtained from Bone marrow biopsies and blood samples of B-CLL patients.

The age of the patients ranged between 40-80 years, and the samples were collected directly from patients in Baghdad Teaching Hospital, from the National Center of Hematology and Twenty Bone marrow biopsies and blood sera of 20 patients who have hematological problem other than CLL as control.

We use In situ hybridization to detected EBERs in Bone marrow samples In situ hybridization detection kit from abcam lot-S01_M61, REF _ WB. 005.50: Hybridization / detection system for EBV was purchased from ZytoFast /Germany Cat. Numbers (T-1070-40) and ELISA kit for detection Human IL-10 and Il-8 by (abcam46059 lot:GR162207- 4) and (abcam46032 the lot: GR151489-6) .

Results:

The distribution of age in the studied group ranged between 40 - 80 years with a mean of (60.4) year (table 4.1). Males constituted 70% of cases and female 30%. The ages of control groups ranged between 42 - 70 years with a mean of (55.8) year. Males constituted 76.2% of control groups and female constituted 23.8%. (Table 1).

As shown in table (2), all controls were negative for EBERs. Although the median score and intensity for EBERs was negative for cases group, the mean rank for EBERs score, intensity and composite score (a score resulting from multiplying the score by intensity) was significantly higher among cases compared to controls, figure (1),(2) ,(3) and Figure(4) show the result of In situ hybridization. As shown in table (3), the median IL8 was significantly higher in CLL cases group (33.1 pg/ml) compared to control group (22.1 pg/ml),also in figure (5). A similar pattern was applicable to IL10. The median IL10 was also significantly higher in CLL cases group (29.1 pg/ml) compared to control group (0 pg/ml), figure (6) . As shown in table (4), the positive test for EBERs had no obvious or statistically significant association with IL8 concentration. IL10 concentration also failed to show any noticeable linear correlation with similarly measured IL8 concentration.

Table (1): CLL patients distribution according the age and gender

		CLL		Control	
		No	%	No	%
Age (years)	<50	5	16.7	4	19.0
	50---	7	23.3	9	42.9
	60---	14	46.7	7	33.3
	=>70	4	13.3	1	4.8
	Mean±SD(Range)	60.4±9.2 (40-80)		55.8±8.1 (42-70)	
	P value	0.392			
Gender	Male	21	70.0	16	76.2
	Female	9	30.0	5	23.8
	P value	0.626			

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*Significant difference between proportions using Pearson Chi-square test at 0.05 level

Table 2 : The case-control difference in median score and intensity and composite score for EBERs viral marker.

		Study group				
		Controls		Cases (CLL)		
		N	%	N	%	P
1.	EBERs-score					
	Negative	20	100.0	16	53.3	
	+	0	0.0	11	36.7	
	++	0	0.0	3	10.0	
	Total	20	100.0	30	100.0	
	Range	(Negative to Negative)		(Negative to ++)		<0.001
	Median	Negative		Negative		
	Inter-quartile range	(Negative to Negative)		(Negative to +)		
	Mean rank	18.5		30.2		
2.	EBERs-intensity					<0.001
	Negative	20	100.0	16	53.3	
	Weak	0	0.0	8	26.7	
	Moderate	0	0.0	5	16.7	
	High	0	0.0	1	3.3	
	Total	20	100.0	30	100.0	
	Range	(Negative to Negative)		(Negative to High)		
	Median	Negative		Negative		
	Inter-quartile range	(Negative to Negative)		(Negative to weak)		
	Mean rank	18.5		30.2		
3.	EBERs-composite score (score x intensity)					<0.001
	Range	(Negative to Negative)		(Negative to 6)		
	Median	Negative		Negative		
	Inter-quartile range	(Negative to Negative)		(Negative to 1)		
	Mean rank	18.5		30.2		

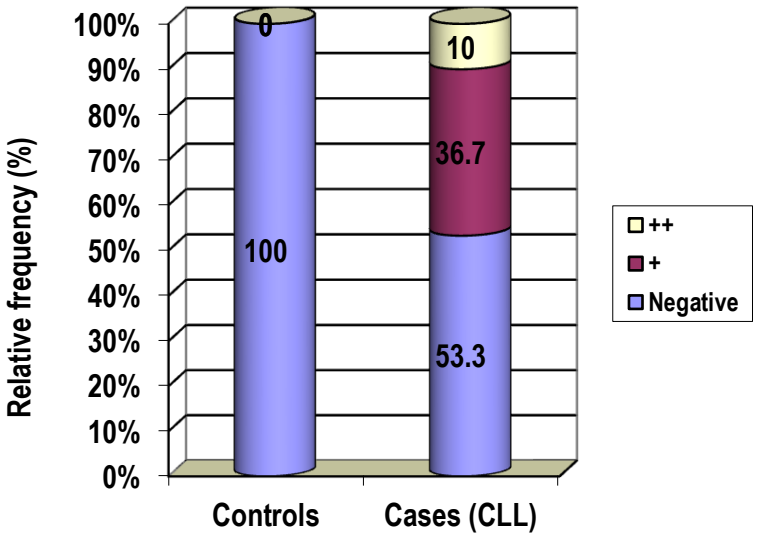

Figure 1: Component bar chart showing the case-control difference in EBERs-score.

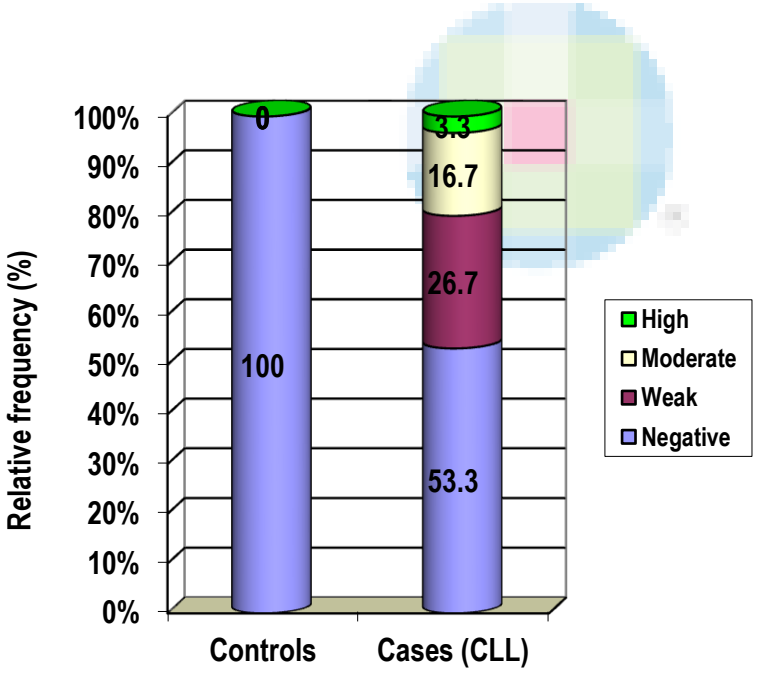

Figure 2: Component bar chart showing the case-control difference in EBERs-intensity.

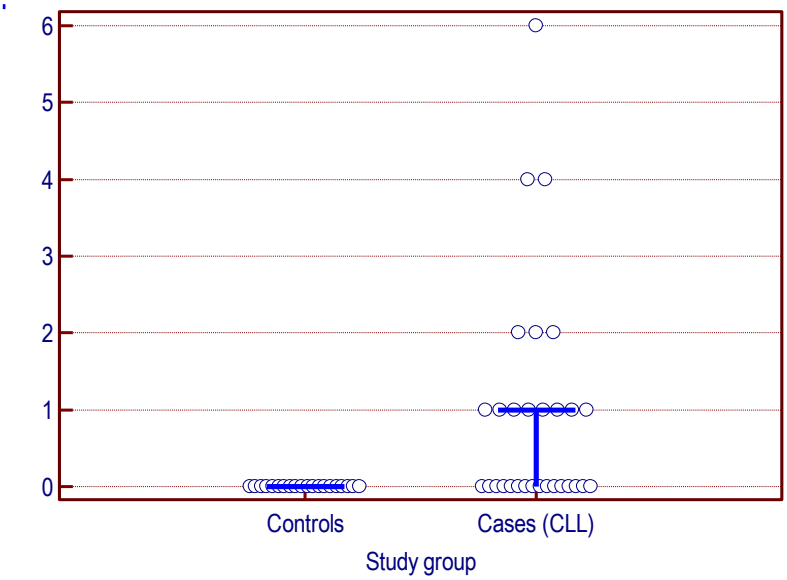

Figure 3 : Dot diagram with error bars showing the median (with its inter-quartile range) EBERSs in cases with CLL compared to controls.

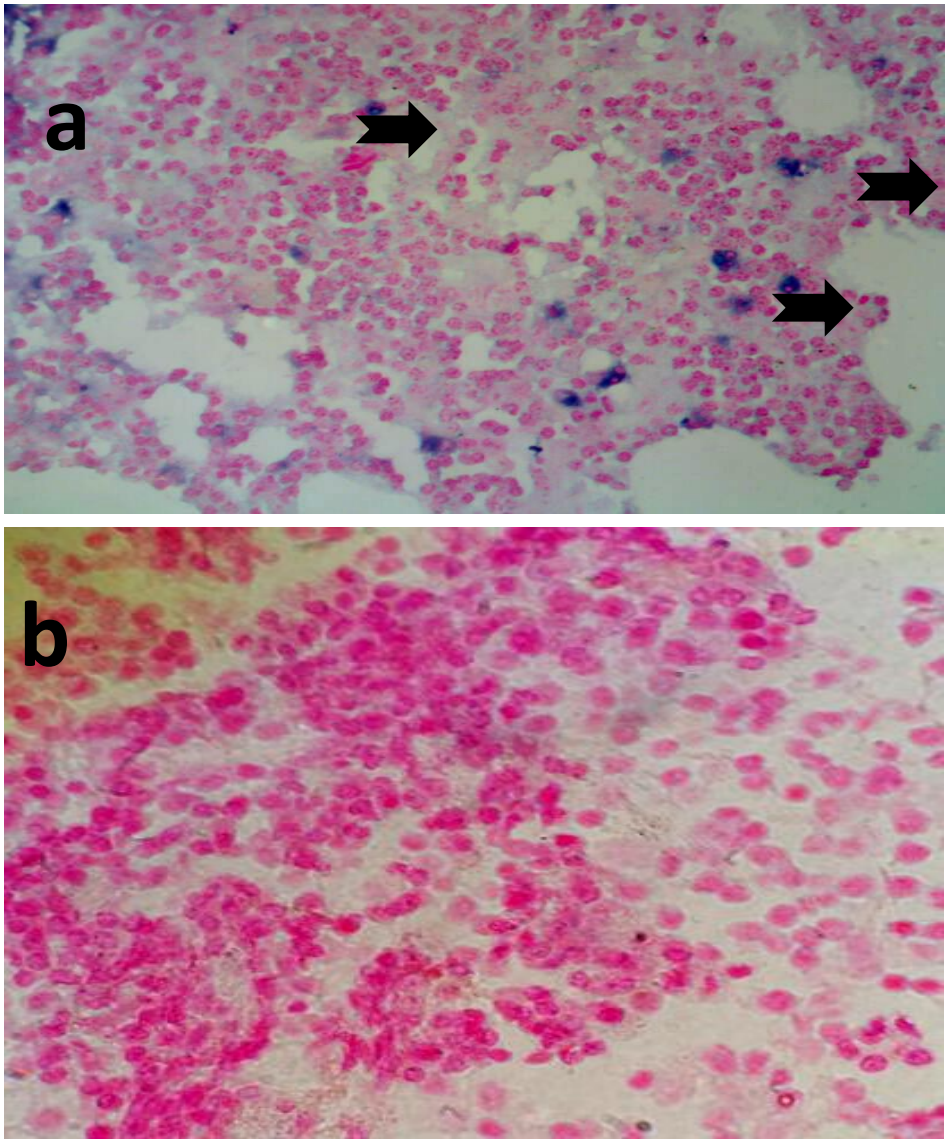

Figure 4 : Representative expression of EBV-encoded small nuclear early region (EBERs) in Bone Marrow of CLL patients d . **a** : **positive result show the** Nuclear localization of the EBERs in neoplastic cells by ISH **. b : Negative result.**

Table 3 : The case-control difference in median interleukin concentration.

	Study group		
	Controls	**Cases (CLL)**	**P**
IL8 (pg/ml)			0.03
Range	(12.2 - 55.3)	(7.8 - 1215)	
Median	22.1	33.1	
Inter-quartile range	(17.9 - 35.4)	(21.9 - 70.1)	
N	41	30	
Mean rank	20.6	29.8	
IL10 (pg/ml)			<0.001
Range	(0 - 24.9)	(0.9 - 43)	
Median	0	29.1	
Inter-quartile range	(0 - 0)	(7.7 - 33.9)	
N	41	30	
Mean rank	12	35.8	

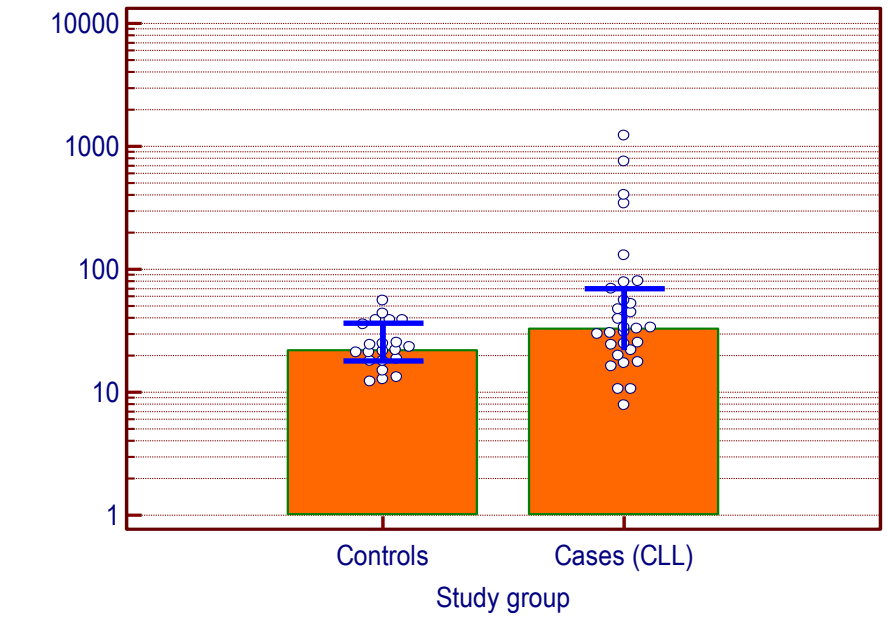

Figure 5 : Dot diagram with error bars showing the median (with its inter-quartile range) IL8 (pg/ml) in cases with CLL compared to controls. (Logarithmic scale was used)

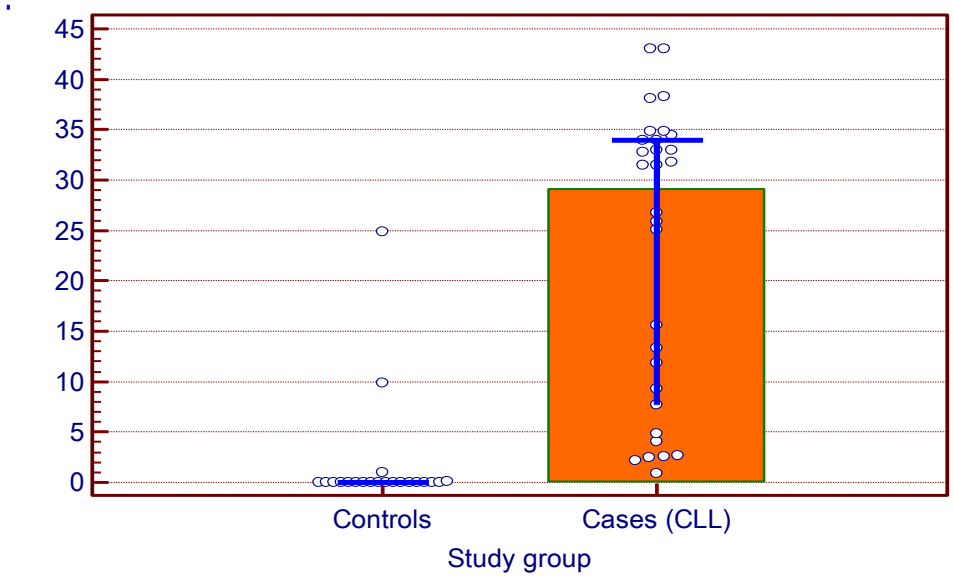

Figure 6 : Dot diagram with error bars showing the median (with its inter-quartile range) IL10 (pg/ml) in cases with CLL compared to controls.

Table 4 : The median IL8 concentration (pg/ml) by selected explanatory variables among cases with CLL.

	Range	Median	IL8 Interquartile range	N	Mean Rank	P
Age group (years)						0.6[NS]
<60	(10.6 to 79.4)	31.9	(22.2 to 61.3)	12	14.5	
60+	(7.8 to 1215)	36	(21.9 to 130.3)	18	16.2	
Gender						0.5[NS]
Female	(7.8 to 1215)	55.6	(20 to 401.5)	9	17.2	
Male	(10.6 to 346.2)	32.8	(24.3 to 46.9)	21	14.8	
Positive EBERs						0.1[NS]
Negative	(10.6 to 1215)	43.1	(25.3 to 104.9)	16	18	
Positive	(7.8 to 401.5)	30.4	(17.7 to 44.4)	14	12.7	

Table 5 : The median IL10 concentration (pg/ml) by selected explanatory variables among cases with CLL.

	IL10					
	Range	**Median**	**Interquartile range**	**N**	**Mean Rank**	**P**
Age group (years)						0.18[NS]
<60	(0.9 to 38.3)	20.35	(6.25 to 29.85)	12	12.9	
60+	(2.5 to 43)	32.3	(9.3 to 34.8)	18	17.3	
Positive EBERs						0.63[NS]
Negative	(0.9 to 43)	20.75	(8.5 to 33.9)	16	14.8	
Positive	(2.2 to 43)	32.3	(4 to 33.9)	14	16.3	

Discussion :

Epstein- Barr virus has strong association with variety in B-cell tumors including Burkitt's lymphoma, Hodgkin lymphoma, human immunodeficiency virus, post transplantation lymphoma disorder and chronic lymphocytic leukemia. Many studies reported that CLL patient had evidence of EBV infection by In situ hybridization for EBERs and detection of EBV-encoded EBER transcripts is considered the gold standard for localizing latent EBV in tissue samples, as EBER transcripts are universally expressed in all EBV associated tumors.[13,14]

The presence of EBERs has been shown to correlate with progressive or accelerated clinical course including transformation to Richter's large cell lymphoma.[15,16]

However EBERs is also found in quiescent EBV latency where no protein is produced and that may be a suboptimal marker for proliferation or transformation capability.

In this study all controls showed negative result EBERs but in patients the result show that 14 (46%) out of 30 CLL patients were positive with EBERs.

Results obtained are nearly compatible to previous study who reported that (38%) of CLL patients had evidence of EBV infection proved by EBERs positively in tumor cells [16].

Result demonstrated in this study were in accordance with 16) Tsimberidou *et al* who stated that 12 out of 32 CLL patients has appositive result.[16]

On the other hand another study found that 8 of 75 (10.7%) cases showed EBERs expression restricted to 5–10% of tumor cells.[17]

This controversy in the above results may be related to that ISH process depends on the RNA staining and the concentration of RNA in the cell .this method affected by many factors, including the RNA present in the cell and concentration of RNA. This technique is very sensitive. Interleukins-8 and it's receptor increased in cancer cells, infiltrating neutrophils, endothelial cells, and tumor-associated macrophages [18]

There is no evidence of IL-8 production by normal B cells but many studies showed that the natural cellular source of IL-8 production have been described to be monocyte/macrophages, T cells, large granular lymphocytes, fibroblasts, endothelial cells, mesothelial cells, keratinocytes, neutrophils ,hepatocytes and chondrocytes.[19,20,21]

A study which has been done by Celle et al showed that elevated IL-8 levels may be founds in the serum of untreated B cell patient which may be release by B cells and superannuated of purified B-CLL cells contain IL8 released chemotactic activity for neutrophils.[22]

In our study we found that IL-8 was significantly higher in CLL cases group the compared with control group. This result is compatible with other study published [23,24] which found that plasma IL-8 level enhances in CLL patients. The same result was studied by Yoshizaki et al who found that IL-8 increased in CLL patients .[25] On the other hand another study found that serum IL-8 level was not increased in significant level in patient with CLL when she compared with healthy control.[26]

The association of EBERs and IL-8 did not reach the level of statistical significance. This result is not compatible with study done by William et al who found that the stages were associated with significantly higher plasma IL-8 levels ($P < 0.0001$) but There were no significant difference between IL-8 production and gender. [27] While another study found compatible result with this study where IL8 level in CLL patients not correlated with CLL stages. [24]

Notably, serum IL-10 levels are increased in CLL patients and correlate with adverse disease features and short survival.[28,29]

Results obtained in this study revealed that the IL-10 was significantly higher in CLL cases group median rang (29.1 pg.

/ml) compared to control group (0 pg/ml) and the mean rank 35.8 with p<0.001 figure (6)

This result is compatible with other study[30],Which found that IL-10 levels were higher in CLL patients (median, 5.04 pg/mL; range, undetectable to 74 pg/mL) than in normal volunteers (median, undetectable; range, undetectable to 13.68 pg/mL) (P < .00001) ,and another study found that IL-10 levels increased in CLL patient of Iraq and significantly than control group P<0.05 same study was studied by [31] who found that Serum levels IL-10 in 20 CLL patient severely dropped in untreated group (27±11.47 and 0.65±0.23 pg/mL respectively) and differed significantly healthy in 20 control group (1715.66±1014 pg/mL respectively)[26] and David at al who found that Serum IL-10 levels were also significantly elevated in CLL patients. [18]

Other explanations for the increase in the level of IL-10 in patient with CLL was demonstrated in other researches which found that IL-10 is increased in production by culture of CLL and that serum IL-10 levels were elevated in five of the eleven B-CLL patients. These findings suggest that IL-10 acts as an autocrine growth factor for B-CLL cells and cytokine-based therapy might be a new approach for the treatment of B-CLL.[33,34]

IL-10 was derived from EBV infected tumor cells and demonstrated in serum of CLL and Hodgkin lymphoma patients. [30,34] . Several studies have reported an association between EBERs, LMP1and IL10 stimulation. EBV infection enhanced production of viral IL-10 and may also contribute to a local immune suppression by production of hydrophobic peptides derived from the first transmembrane domain of LMP-1 [35] In contract EBERs induce the transcription of various cytokines depending on cell type, such as interleukin-10 (IL-10).

Conclusion: The highest incidence of CLL occurs in the age group 40-80 years old and males are more liable than females (male/female: 70/30).In situ hybridization technique is successful method to detect of EBV and positive EBERs. IL-8 is highly significant in CLL patients and correlates with EBERs and LMP1. There is a correlation between IL-10 EBERs and LMP1 in CLL patients.

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تحفير الانترلوكين-10 و 8 بواسطة فيروس ابشتاين بار في سرطان الدم الليمفاوي المزمن

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الملخص:

الخلفية: اثبت الدراسات ان الابيشتاين بار فايرس له علاقة ويعتبر احد المسببات لمرضى سرطان الدم اللمفاوي المزمن في هذه الدراسة كان معدل عمر المرضى يتراوح بين (65-70) عام وكانت نسبة الذكور الى الاناث تتراوح بين 1/2 % في مرضى سرطان الدم اللمفاوي المزمن وكما اثبت هذه الدراسة ان EBERs يزيد من افراز IL-10 وIL-8 في مصول المرضى .

المواد والطرق: دراسة مستقبلية أجريت في قسم علم أمراض الدم السريري في المركز الوطني للأمراض الدم في بغداد، العراق خلال الفترة من يناير 2013 إلى يناير 2014. وشملت ثلاثين عينات من والأنسجة الثابتة بالفورمالين جزءا لا يتجزأ من البارافين من عينات نخاع العظام والدم من حديثي التشخيص ب سرطان الدم اللمفاوي المزمن .. وقد أجريت للكشف عن الرنا EBV المشفرة (EBER1، EBER2)، وكذلك الكشف عن مستوى انترلوكين (8 و 10) في مصل مرضى سرطان الدم اللمفاوي المزمن بتقنية التهجين الموقعي.
النتائج : كشفت الدراسة النسيجية أن جميع الضوابط كانت سلبية EBERs ووجد 46.7٪ إيجابية من EBERs في سرطان الدم اللمفاوي المزمن . كان هناك ارتباط بين EBERs الإيجابية ومرحلة الأورام وأيضا EBERs و IL-10 و مع IL-8.
الاستنتاج: يحدث أعلى معدل لانتشار سرطان الدم اللمفاوي المزمن في الفئة العمرية 40-80 سنة والذكور أكثر عرضة من الإناث (ذكور / إناث: 30/70) . تقنية التهجين الموقي هي طريقة ناجحة للكشف عن EBV وEBERs الإيجابية. IL-8 مهم للغاية في المرضى الذين يعانون من سرطان الدم اللمفاوي المزمن ويرتبط EBERs وLMP1. هناك علاقة بين IL-10 EBERs وLMP1 في مرضى سرطان الدم اللمفاوي المزمن.
كلمات البحث: فيروس ابشتاين بار، سرطان الدم اللمفاوي المزمن ، IL-8، IL-10