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BETA-2 MICROGLOBULIN: A NOVEL BIO-MARKER ASSISTING IN THE DIAGNOSIS OF LYMPHOMA: A STUDY OF 669 NEWLY DIAGNOSED LYMPHOMA CASES IN THE SOUTH OF IRAQ

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Abbreviations

B2MG: beta-2 microglobulin, HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, LP: lymphocytic predominant, NS: nodular sclerosis, MC: mixed cellularity, LD: lymphocytic depletion, LG: low grade, IG: intermediate grade, HG: high grade, Msc: miscellaneous, FMCL: follicular mixed cell lymphoma, FSCL: follicular small cell lymphoma, SLL: small lymphocytic lymphoma, DLCL: diffuse large cell lymphoma, DMCL: diffuse mixed cell lymphoma, DSCL: diffuse small cell lymphoma, FLCL: follicular large cell lymphoma, BL: Burkitt lymphoma, IL: immunoblastic lymphoma, LL: lymphoblastic lymphoma, Malt: mucosa-associated lymphoid tissue lymphoma, MF: mycosis fungoides, SLVL: splenic lymphoma with villous lymphocytes, LDH : lactate dehydrogenase, CEA; carcino-embryonic antigen, TPS : tissue polypeptide specific antigen, IPI: international prognostic index. ELFA: enzyme-linked fluorescent antibody.

Abstract

Beta 2 microglobulin is a known marker used in the follow up and monitoring therapy of patients with hematological malignancies. However, its assistant role in the diagnosis of some of them, like lymphomas is less highlighted. Thus, this study was designed as a part of a larger, wide scale study, to clarify the help of B2MG in the support of the diagnosis of different types of lymphoma. A total of 669 newly diagnosed, pre-treated lymphoma cases were investigated for B2MG using the ELFA/mini VIDAS system and the results showed an elevated level of B2MG among both Hodgkin & non-Hodgkin, adults and childhood and nodal and extranodal lymphomas, with a significant increase among non-Hodgkin and extranodal type of lymphomas, a finding that may make its use as a diagnostic marker is helpful. Those results were comparable to some and contradicting to other studies. Further future studies are in need to consolidate this.

Introduction

Beta 2 microglobulin (B2MG), is a low molecular weight polypeptide (11.8 KD) synthesized by most nucleated cells (with the exception of red cells)[1]. Its turnover corresponds to a production of approximately 150 mg/24 hrs. it is encoded in the sixth chromosome. It is composed of 99 amino acids and belongs to the immunoglobulin superfamily with a primary and secondary structure simulating IgG's[2]. It is the light chain protein of HLA class I and is located on the cell membranes of all cells containing nuclei[3].

Half of the plasma B2MG originates daily from lymphocytes. Circulating B2MG is filtered through renal glomeruli, then reabsorbed and catabolized by the proximal tubules[2,4,5].

Elevated plasma B2MG is a result of decreased glomerular filtration or increased synthesis. It is the most effective test for the detection of proximal tubular dysfunction. The determination of urinary B2MG is useful for monitoring renal transplant patients[6-8]. It is elevated in auto-immune diseases like SLE, RA, Sjogren's syndrome[9]. It is a sensitive indicator for monitoring therapy and disease course in patients with malignant diseases like multiple myeloma[10], lymphoma (Hodgkin and non-Hodgkin), ronic lymphocytic and chronic myelocytic leukemias[10-15].

Materials and methods

During the period of June 2008-February 2012, 669 newly diagnosed, pre-treated lymphoma patients, from different Governorates of the South of Iraq were studied. They were of two types: 480 adults (>15 years old) and 189 children (≤15 years old). They were, then, segregated to Hodgkin and non-Hodgkin, adult and childhood, nodal and extranodal lymphomas. Of the latter, lymphomas with bone marrow involvement, gastrointestinal tract (GIT), bone & musculo-skeletal system, respiratory tract and central nervous system (CNS) lymphomas were taken.

Hodgkin lymphomas were classified according the original Rye classification for simplicity, easiness of use, and the lack of immunophenotypic studies[16,17] while the non-Hodgkin lymphomas were classified using the International Working Formulation because of the lack of cytogenetic, immunological and molecular studies that prevent the adoption of the WHO classification[18,19].

Beta 2 microglobulin was estimated once the diagnosis had been established, depending on a two-step enzyme immunoassay sandwich method with a final enzyme-linked fluorescent antibody (ELFA) detection, using the bioMerieux mini VIDAS system, in which at the end of the assay, results were automatically calculated by the machine in relation to the calibration curve stored in the memory and then printed out. Normal value was considered between 0.0-3.0 mg/L[20] and cases were segregated into those with normal and those with elevated levels.

Statistical analysis was done using the descriptive data while correlations were done using the Chi square and ANOVA tests[21].

Results

Table I, shows that B2MG was elevated among 54.6% of HL, ranging between 1.23-4.99 with a mean of 2.91 mg/L while its range in NHL was between 1.65-12.30 with a mean of 4.0 mg/L and it was elevated in 86.1 % of NHL cases. There was a statistically significant difference between the frequencies and means in both HL & NHL. It was also elevated among 75 % of childhood and 82 % of adult lymphoma cases with no significant differences (Table II).

Table I: Values of B2MG, range, mean and SD among both HL and NHL cases.

B2MG level(mg/L)	Range	HL		NHL	
	0.0-3.0	N	%	N	%
		88	45.4	66	13.9
	>3.0	106	54.6	409	86.1*
	Total	194	100	475	100**
Minimum		1.23		1.65	
Maximum		4.99		12.30	
Mean	T test	2.91		4.0	
SD		0.90		1.27	

*X2=76.962, df=1, P=<0.001 **Analysis of variance: F=86.707, df=1, P=<0.001

Table II: The values of B2MG among both adult and childhood lymphomas

Age of onset	B2MG(mg/L)	N	%
Adult lymphomas	0.0-3.0	120	25.0
	>3.0	360	75.0
	Total	480	100.0
Childhood lymphomas	0.0-3.0	34	18.0
	>3.0	155	82.0*
	Total	189	100.0

*X2= 3.961, df=1, P= 0.053

Among HL cases, there was a striking elevation of B2MG among lymphocytic depletion (LD) type (94.1 %), followed by the nodular sclerosis (NS) (60.8 %), while only 31.8 % of lymphocytic predominance (LP) cases had B2MG elevation.

Table III: The values of B2MG among pathological types of Hodgkin lymphomas.

Pathological type	B2MG(mg/L)	N	%
LP	0.0-3.0	15	68.2
	>3.0	7	31.8
	Total	22	100.0
NS	0.0-3.0	20	39.2
	>3.0	31	60.8
	Total	51	100.0
MC	0.0-3.0	52	50.0
	>3.0	52	50.0
	Total	104	100.0
LD	0.0-3.0	1	5.9
	>3.0	16	94.1
	Total	17	100.0

Table IV shows that all histopathological types of NHL were associated with elevated B2MG in more than 3/4th of patients with a noticeable marked elevation among the high grade types (Burkitt, lymphoblastic & immunoblastic lymphomas) as well as the small lymphocytic lymphoma (SLL) of the low grade.

Table IV: The values of B2MG among different pathological types of NHL

IWF Grading of NHL	lymphoma histological type	B2MG (mg/L)	N	%
LG	FMCL	0.0-3.0	8	19.0
		>3.0	34	81.0
		Total	42	100.0
	FSCL	0.0-3.0	13	20.0
		>3.0	52	80.0
		Total	65	100.0
	SLL	>3.0	24	100.0
IG	DLCL	0.0-3.0	30	24.2
		>3.0	94	75.8
		Total	124	100.0
	DMCL	0.0-3.0	7	16.3
		>3.0	36	83.7
		Total	43	100.0
	DSCL	0.0-3.0	1	3.2
		>3.0	30	96.8
		Total	31	100.0
	FLCL	0.0-3.0	3	17.6
		>3.0	14	82.4
		Total	17	100.0
HG	BL	0.0-3.0	3	6.0
		>3.0	47	94.0
		Total	50	100.0
	IL	>3.0	11	100.0
	LL	>3.0	41	100.0
Msc	Malt	>3.0	18	100.0
	MF	0.0-3.0	1	16.7
		>3.0	5	83.3
		Total	6	100.0
	SLVL	>3.0	3	100.0

Table V shows the great and statistically significant increase of B2MG among extranodal lymphomas, compared to nodal ones.

Table V: Values o B2MG among both extranodal and nodal lymphomas

Pattern of involvement	B2MG(mg/L)	N	%
Extra nodal	0.0-3.0	8	2.3
	>3.0	339	97.7*
	Total	347	100.0
Nodal	0.0-3.0	146	45.3
	>3.0	176	54.7
	Total	322	100.0

*X2 = 174.562, df =1, P = < 0.001

Table VI shows that B2MG is elevated among all types of extranodal lymphomas studied with a minor elevation of the means among CNS lymphomas and lymphomas with bone marrow involvement than other types.

Table VI: Range, mean & SD of B2MG values among different extranodal lymphomas.

Type of ENL	M2MG level (mg/L)			
	Min	Max	Mean	SD
Lymphomas with BM involvement	3.10	12.30	4.49	1.52
GIT lymphomas	1.76	7.43	4.05	0.87
Bone and musculo-skeletal lymphomas	3.11	10.40	4.31	1.22
Resp T lymphomas	3.11	9.32	4.19	1.16
CNS lymphomas	3.01	10.90	4.72	2.03

Table VII: The values of B2MG among different types of extranodal lymphomas.

Type of ENL	B2MG level(mg/L)					
	0.0-3.0		>3.0		Total	
	N	%	N	%	N	%
Lymphomas with BM involvement	0	0	169	100	169	100
GIT lymphomas	4	3.6	108	96.4	112	100
Bone and musculo-skeletal lymphomas	0	0	43	100	43	100
Resp T lymphomas	0	0	29	100	29	100
CNS lymphomas	0	0	21	100	21	100

Discussion

Among HL, serum B2MG was elevated in 54.6% of cases. This was higher than that reported by Dimopoulos et al 1993 and Vassilakopoulos et al 2005 who reported an elevation of B2MG in 29% and 36% of pre-treated HL, respectively[22,23]. This difference can be explained by the possibility of racial/ethnic differences, besides to the large number of cases taken in this study compared to the smaller number of cases of the 2 above. Chronowski, et al 2002, on the other hand, concluded that elevation of the serum B2MG level is an independent adverse prognostic factor for overall survival[24].

Nakajima Y et al 2014, also found that serum β2MG level elevation at diagnosis is a useful prognostic marker in patients with HL[25].

Among NHL cases, serum B2MG was elevated in 86.1%. This is higher than that reported by Duan et al 2012 who found that 67.24% of NHL cases had significant β2MG elevation, compared to control group,[26]. Chen, et al, 2006, also, found that in patients with NHL, the levels of 4 tumor markers [B2MG, LDH, CEA and TPS] were significantly higher in NHL patients than in the healthy control subjects (P<0.05)[27]. Toth DF et al 2013, on the contrary, concluded on a study of

180 patients of newly diagnosed NHL, that β2M had a low sensitivity and specificity of 49% and 52% for all types and settings and thus, it cannot be used in the clinical routine as a diagnostic marker for the diagnosis of NHL[28]. Yoo C et al, 2104, in a study on relatively large numbers of patients with specific histologic subtypes showed that serum β2MG is a potent prognostic marker in malignant lymphomas, and in follicular lymphoma, they did suggest the incorporation of serum B2MG as an indicator in a new prognostic model[29].

Wu L et al 2014 concluded that due to the strong association between serum β2MG and NHL prognosis, combining β2MG with IPI may help to improve the prognostic accuracy of NHL[30].

The significant increase of B2MG among extranodal lymphomas, compared to that of nodal ones is comparable to that found by Li ZM et al 2014, who concluded that patients with high serum β2MG level at diagnosis seemed to have more adverse clinical features and was a novel predictor of prognosis in patients with upper aerodigestive tract NK/T-cell lymphoma (UNKTL)[31], and also to that concluded by Yoo C et al, 2014 who stated that in patients with nasal extranodal natural killer/T cell lymphoma (ENKTL), baseline serum B2MG is a powerful prognostic factor[32].

Avilés A and Narváez BR 1998, found that the use B2MG and LDH can define different groups at risk and develop a prognostic system to define the best therapeutic approach in primary gastric lymphoma[33] while Avilés A et al 1991 stated that serum B2MG should be included in the initial staging of patients with primary extranodal NHL and patients with high levels should be treated more aggressively[34].

Conclusions and recommendations

Serum B2MG is a good bio-marker aiding in the initial diagnosis of lymphomas, both HL & NHL. It shows a significant increase among NHL than HL, with the more aggressive types among both and with extranodal more than nodal lymphomas.

Researches concentrating on the impact of prognostic values of B2MG among lymphomas are recommended in the future as this study was done on newly diagnosed, pre-treated cases only.

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