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Prognostic Value of Insulin-Like Growth Factor 1 in Hodgkin Lymphoma

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ABSTRACT

Background: Hodgkin's lymphoma (HL) (formerly, Hodgkin disease) is a potentially curable lymphoma with distinct histology, biologic behavior, and clinical characteristics. The disease is defined in terms of its microscopic appearance (histology) and the expression of cell surface markers (immunophenotype).

Objective: In this study we aim to evaluate the serum level of IGF-1 as prognostic factor in patients with Hodgkin lymphoma and its impact in outcome of treatment.

Patients and methods: This study was conducted in the Internal Medicine Department of Al-Azhar University, during the period from January 2018 to December 2018. It was carried on 60 patients diagnosed with HL. All patients had a confirmed histopathological examination as HL before inclusion in the study. Patients were classified into (3 equal groups) according to (Ann Arbor staging classification scheme): Group -1: 20 patients with HL in stage I &II. Group -2: 20 patients with HL in stage III. Group -3: 20 patients with HL in stage IV. An approval of the study was obtained from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Results: In our study, patients with HL had significantly higher levels of IGF-1 in advanced stages than limited stages. Since serum levels of IGF-1 is a potent proliferative agent affecting almost every cell type and a powerful antiapoptotic agent affecting apoptotic responses to a variety of agents of numerous cell types. These two effects result in a state of hyperproliferation. Such an imbalance between cell proliferation and death. Also, our study showed the higher level of IGF-1, the good response to aggressive chemotherapy.

Conclusion: IGF-1 may be a prognostic factor in HL and may be useful for the identification of a subgroup of patients who may benefit from aggressive chemotherapy.

Keywords: Insulin-Like Growth Factor 1, Hodgkin Lymphoma.

INTRODUCTION

Hodgkin's lymphoma (HL) is characterized by the disruption of the normal lymph node architecture by the presence of Hodgkin/Reed–Sternberg (HRS) cells, which are usually in a minority within a background of reactive by stander cells that are mainly composed of T and B lymphocytes and other cell types [(1)]. Although there have been important advances in treatment, approximately 20% of patients do not respond, or relapse after receiving the optimal initial therapeutic strategy, and may require adapted first-line treatment [(2)].

The International Prognostic Score (IPS) has been the gold standard for predicting prognosis of the patient with HL [(3)]. However, the prognostic value of the IPS is limited to advanced stage HL and does not fully reflect the biological spectrum of HL. Several biologic factors have been suggested as predictors of prognosis in patients with HL, including those identified by gene expression profiling [(4)] or immunohistochemistry-based detection [(5, 6)]. However, whether they have prognostic value for patients with HL remains to be determined.

Insulin produced by the pancreas and insulin-like growth factors (IGFs) produced mainly by the liver regulate cellular growth and metabolism. There are two IGFs, namely IGF-1and IGF-2, which each bind insulin-like growth factor-1receptor (IGF-1R) and insulin-like growth factor-2 receptor [(7)].

The IGF-1/IGF-1R signaling pathway, which is a subfamily of receptor tyrosine kinases, has shown in previous studies to have an association with tumor cell proliferation, transformation, survival and resistance to chemotherapy [(8)]. This association has been noted to influence the incidence and prognosis of prostate, breast and colorectal cancers [(8, 9)].

The IGF-1/IGF-1R signaling pathway is closely associated with proliferation and survival in the hematological malignancies of multiple myeloma [(10)] and mantle cell lymphoma [(11)]. Furthermore, studies of IGF-1R-targeted therapy in IGF-1R-expressing pulmonary non-small cell carcinoma are currently underway [(12, 13)].

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Whether, the IGF-1 can be a prognostic factor for HL is not yet established, in this study we aim at exploring the value of Insulin-Like Growth Factor-1 as a prognostic factor in Hodgkin Lymphoma.

AIM OF THE WORK

In this study we aim to evaluate the serum level of IGF-1 as prognostic factor in patients with Hodgkin lymphoma and its impact in outcome of treatment.

PATIENTS AND METHODS

This study was conducted in the Internal Medicine Department of Al-Azhar University, during the period from January 2018 to December 2018.

Patients:

This study was carried on **60** patients diagnosed with HL.

All patients were having a confirmed histopathological examination as HL before inclusion in the study. Patients were **classified into (3 equal groups)** according to (Ann Arbor staging classification scheme):

- **Group -1**: 20 patients with HL in stage I &II.
- **Group -2**: 20 patients with HL in stage III.
- **Group -3**: 20 patients with HL in stage IV.
- All patients were undergoing complete evaluation before and after therapeutic intervention.

Inclusion criteria:

All patients were having a confirmed histopathological examination as HL without previous treatment and history of malignancy.

Exclusion criteria:

- Patients with HL and previous treatment.
- Patients with other hematological malignancies.
- Patients with history of any other malignancy.

Ethical approval and written informed consent:

An approval of the study was obtained from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Methods:

All patients were subjected to:

- Full history taking especially symptoms and signs of HL.
- Full clinical assessment and performance status through Eastern Cooperative Oncology Group (ECOG).
- Routine laboratory evaluation; complete blood counts, Random blood sugar, renal functions. Liver function tests (including coagulation profile, ALT, AST, total and direct bilirubin, albumin and total protein) and serum lactic dehydrogenase level.
- Lymph node biopsy for histopathological assessment and immunophenotyping.
- Bone marrow aspiration and biopsy to confirm or exclude infiltration.
- Imaging (computed tomography scan for staging).
- IGF-1 assessment by ELISA in different stages of HL, before and after therapy.

Estimation of the serum level of IGF-1 in the two groups was carried out using the DRG IGF-1 600 ELISA kit on the Sunrise Remote/Touch ELISA analyzer.

Specimens: A total of 3 ml of blood was collected by venipuncture and allowed to clot. The serum was then separated by centrifugation at room temperature. Serum samples were frozen at -20°C until the time of assay.

Principle of the test: The DRG IGF-1 600 ELISA kit is a solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding. Patient samples were acidified and neutralized prior to the assay procedure. Microtiter wells were coated with a monoclonal antibody directed towards an antigenic site on the IGF-1 molecule. The pre-treated sample was incubated at room temperature with conjugate (biotinylated IGF-1). The wells were washed and incubated with an enzyme complex (streptavidin-HRP-complex). After addition of the substrate solution, the intensity of the developed color was reverse proportional to the concentration of IGF-1 in the patient sample.

Statement of ethics: The present study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2000, and was approved by our local ethics committee. Informed consent was obtained from the study participants or their guardians.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.

- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.
  - P-value >0.05 was considered insignificant.

RESULTS

Table (1): Comparison between studied groups as regard personal data.

Variables		Group I (n = 20)		Group II (n = 20)		Group III (n = 20)		P-value
Age (years)	**Mean**	35.10		44.30		55.80		P1 < 0.001 P2 < 0.001
	±SD	5.67		3.77		5.91		P3 < 0.001 P4 < 0.001
Sex (n, %)	**Male**	13	65%	12	60%	13	65%	0.931
	Female	7	35%	8	40%	7	35%	
BMI (K/m²)	**Mean**	26.29		21.99		22.65		P1 < 0.001 P2 < 0.001
	±SD	2.75		2.83		4.21		P3 = 0.001 P4 = 0.534

This table shows:

- **As regard age:**
  - Highly statistically significant difference **(p-value < 0.001)** between all studied groups.
- **As regard sex:**
  - No statistically significant difference **(p-value > 0.05)** between all studied groups.
- **As regard BM:**
  - Highly statistically significant difference **(p1 < 0.001)** between all studied groups:
    - Highly statistically significant difference **(p2 < 0.001)** between (group I vs group II).
    - Statistically significant difference **(p3 = 0.001)** between (group I vs group III).
    - No statistically significant difference **(p4 = 0.534)** between (group II vs group III).

Table (2): Comparison between studied groups as regard IGF-1.

Variables		Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	P-value
IGF-1	**Mean**	115.30	238.90	407.35	P1 < 0.001 P2 < 0.001
	±SD	19.74	47.08	74.74	P3 < 0.001 P4 < 0.001

This table shows highly statistically significant difference **(p-value < 0.001)** between all studied groups as regard IGF-1.

Table (3): Comparison of liver function tests before and after therapy in group I.

Variables / Group I		Before (n = 20)	After (n = 20)	P-value
AST (U/L)	**Mean**	31.55	22.60	**< 0.001**
	±SD	7.54	5.62	
ALT (U/L)	**Mean**	31.10	20.75	**< 0.001**
	±SD	8.51	5.87	
PT (sec)	**Mean**	13.40	13.15	0.320
	±SD	0.68	0.88	
T.P (g/dl)	**Mean**	6.75	7.21	**< 0.001**
	±SD	0.38	0.25	
ALB (g/dl)	**Mean**	4.03	4.42	**0.001**
	±SD	0.33	0.34	
T. Bil (mg/dl)	**Mean**	0.59	0.57	0.531
	±SD	0.16	0.11	
D. Bil (mg/dl)	**Mean**	0.14	0.16	0.297
	±SD	0.05	0.07	

This table shows:

- Highly statistically significant difference **(p-value < 0.001)** between AST, ALT & T.P before and after therapy in group I.
- Statistically significant difference **(p-value < 0.05)** between ALB before and after therapy in group I.
- No statistically significant difference **(p-value > 0.05)** between PT before and after therapy in group I.

Table (4): Comparison of liver function tests before and after therapy in group II.

Variables / Group II		Before (n = 20)	After (n = 20)	P-value
AST (U/L)	**Mean**	32.95	23.60	**< 0.001**
	±SD	6.91	4.84	
ALT (U/L)	**Mean**	33.45	23.85	**< 0.001**
	±SD	5.71	4.64	
PT (sec)	**Mean**	13.15	13.10	0.856
	±SD	0.81	0.91	
T.P (g/dl)	**Mean**	6.54	7.09	**< 0.001**
	±SD	0.33	0.16	
ALB (g/dl)	**Mean**	3.23	4.63	**< 0.001**
	±SD	0.22	0.52	
T. Bil (mg/dl)	**Mean**	0.93	0.66	**< 0.001**
	±SD	0.24	0.15	
D. Bil (mg/dl)	**Mean**	0.28	0.19	**0.006**
	±SD	0.12	0.08	

This table shows:

- Highly statistically significant difference **(p-value < 0.001)** between AST, ALT, T.P, ALB & T. Bil before and after therapy in group II.
- Statistically significant difference **(p-value < 0.05)** between D. Bil before and after therapy in group II.
- No statistically significant difference **(p-value > 0.05)** between PT before and after therapy in group II.

Table (5): Comparison of liver function tests before and after therapy in group III.

Variables / Group III		Before (n = 20)	After (n = 20)	P-value
AST (U/L)	**Mean**	46.35	34.95	**0.001**
	±SD	12.70	5.17	
ALT (U/L)	**Mean**	44.45	36.00	**0.038**
	±SD	16.28	5.63	
PT (sec)	**Mean**	16.05	13.70	**< 0.001**
	±SD	1.88	1.22	
T. P (g/dl)	**Mean**	6.29	6.85	**< 0.001**
	±SD	0.32	0.21	
Albumin (g/dl)	**Mean**	2.71	3.72	**< 0.001**
	±SD	0.22	0.28	
T. Bilirubin (mg/dl)	**Mean**	1.06	0.84	**0.049**
	±SD	0.42	0.20	
D. Bilirubin (mg/dl)	**Mean**	0.31	0.20	**0.044**
	±SD	0.20	0.09	

This table shows:

- Highly statistically significant difference **(p-value < 0.001)** between PT, T.P & Albumin before and after therapy in group III.
- Statistically significant difference **(p-value < 0.05)** between AST, ALT, Total & Direct bilirubin before and after therapy in group III.

Table (6): Comparison between studied groups as regard IGF-1 after therapy.

Variables / After therapy		Group I (n = 20)	Group II (n = 20)	Group III (n = 20)	P-value
IGF-1	**Mean**	104.25	115.85	122.55	**P1 = 0.016**
					P2 = 0.066
	±SD	15.85	18.03	23.98	**P3 = 0.005**
					P4 = 0.284

This table shows statistically significant difference **(p1 = 0.016)** between all studied groups as regard IGF-1 after therapy:

- No statistically significant difference **(p2 = 0.066)** between (group I vs group II).
- Statistically significant difference **(p3 = 0.005)** between (group I vs group III).
- No statistically significant difference **(p4 = 0.284)** between (group II vs group III).

Table (7): Diagnostic performance of IGF-1 in discrimination of early stages (group I) and late stages (group II & III).

Cut off	Area under the curve	Sensitivity	Specificity	PPV	NPV	p-value
> 144.5	**0.99**	**100 %**	**95 %**	**95.2 %**	**100 %**	**< 0.001**

PPV: positive predictive value. NPV: negative predictive value.

Using roc curve, it was shown that IGF-1 can be used to discriminate between early stages (group I) and late stages (group II & III) at a cutoff level of > 144.5, with 100% sensitivity, 95% specificity, 95.2% PPV and 100% NPV.

DISCUSSION

Hodgkin's lymphoma (HL) (formerly, Hodgkin disease) is a potentially curable lymphoma with distinct histology, biologic behavior, and clinical characteristics. The disease is defined in terms of its microscopic appearance (histology) and the expression of cell surface markers (immunophenotype). HL is an uncommon hematologic malignancy that forms less than 1% of all de novo neoplasms occurring every year worldwide [14].

The International Prognostic Score (IPS) has been the gold standard for predicting prognosis of the patient with HL [3]**.** However, the prognostic value of the IPS is limited to advanced stage HL and does not fully reflect the biological spectrum of HL.

In current study, patients with HL had significantly higher levels of IGF-1 in advanced stages than limited stages. Since serum levels of IGF-1 is a potent proliferative agent affecting almost every cell type and also a powerful antiapoptotic agent affecting apoptotic responses to a variety of agents of numerous cell types. These two effects result in a state of hyperproliferation. Such an imbalance between cell proliferation and death**.**

Our results are similar to A study by **Ma *et al.*** [15] who showed an association between colorectal cancer risk in men and elevated plasma levels of IGF-1 by using plasma samples drawn over a long period of time prior to the clinical appearance of the tumours.

Hakam *et al.* [16] showed a stepwise increase in the expression of IGF-1R during the progression from colonic adenomas towards primary colorectal adenocarcinomas and metastases.

In contrast to our study, Low serum levels of IGF-1 are common features in patients with diseased liver compared to healthy people and in liver cirrhosis [17, 18]. Advanced-stage liver cirrhosis (CHILD B/C) showed lower levels of IGF-1 compared to patients without liver cirrhosis or in CHILD A stage. Furthermore, serum IGF-1 levels were significantly lower in patients with HCC developing in cirrhosis compared with non-cirrhotic HCC. Recent studies recommended IGF -1 as a "surrogate marker for assessment of liver dysfunction" [17]**.**

Hodgkin's lymphoma has yielded conflicting results. Although IGF-1R expression was found to have a significant negative effect on prognosis in oral squamous cell carcinoma and colorectal carcinoma [19], other studies, in breast cancer [20] and non-small cell lung cancer [21]**,** found it was associated with lower risk [22]**.**

Liang *et al.* [23] reported that IGF-1R expression was strong in the mitotic cHL cells and that inhibition of IGF-1R decreased proliferation and induced a G2/M cell-cycle arrest in cHL cell lines. As tumors with a high proliferation rate tend to respond better to chemotherapy [5, 24], it is plausible that the superior survival rate of IGF-1R-positive patients with cHL is associated with this increased sensitivity to chemotherapy.

The most common approach to blocking IGF-1R downstream signaling is to use monoclonal antibodies against the receptor; they both inhibit ligand binding and down-regulate the receptor. Small molecule kinase inhibitors are a valid alternative. Anti-IGF-1R monoclonal antibodies have shown significant anti-tumor activity in Ewing's sarcoma, adrenocortical carcinoma [25], multiple myeloma [26] and pancreatic cancer [27]**.** The cyclolignan picropodophyllin, a small molecule kinase inhibitor, has been identified as an IGF-1R inhibitor [28]**.** It specifically blocks the phosphorylation of the Tyr1136 residue in IGF-1R and thus reduces kinase activity of the receptor [28]. Picropodophyllin inhibits the PI3K/AKT pathway, leading to apoptosis **Stromberg *et al.*** [10] and growth suppression of multiple myeloma cells **Menu *et al.*** [29], **Liang *et al.*** [23] also found that it inhibits tumor proliferation in cHL cell lines.

CONCLUSION

IGF-1 may be a prognostic factor in HL and may be useful for the identification of a subgroup of patients who may benefit from aggressive chemotherapy.

RECOMMENDATIONS

Our recommendations are addition of serum IGF-1 level to IPS to determine severity and progression of HL. Further studies, including prospective clinical trials, are needed to confirm the present findings and to investigate the effects of Anti-IGF-1R monoclonal antibodies on clinical outcomes which have significant anti-tumor activity.

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