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Research Article

Lymphopenia in Hodgkin Lymphoma is the Consequence the Disease Progression or the Cause of the Disease Progression?

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ABSTRACT

Classical Hodgkin Lymphoma (cHL) has many distinctive characters, which could make it the most suitable cancer to investigate the precise role of the immune system in tumor incidence and progression. There are two hypotheses to explain the relationship between lymphopenia and poor prognosis. Knowing the mechanism that links lymphopenia with disease progression could have very important clinical applications. This study includes 84 classical hodgkin lymphoma patients. Patients were followed for 2 years. This period is considered sufficient for assessing progression of hodgkin lymphoma. Lymphopenia was associated with the presence of B symptoms, elevated Lactate Dehydrogenase (LDH) values and higher eosinophil counts. There was a significant difference in progression free survival between high Absolute Lymphocyte Count (ALC) group and low ALC group, and we find that Attributable Risk (AR) was equal to 35.7%. This study supports the hypothesis that the lymphopenia is caused by progression of the disease, mostly by inducing a defect in the secretion of cytokines, which causes an increase in lymphocyte death. We recommend conducting clinical trials to investigate the effectiveness of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or anti-cytokines as effective drugs in Hodgkin's lymphoma.

Keywords: Absolute lymphocyte count; Hodgkin lymphoma; Lymphopenia; Disease progression; Attributable risk

INTRODUCTION

Classical Hodgkin Lymphoma (cHL) has many distinctive characters such as: Incidence decreases with age, tumor cells make up only 1% of a tumor, the cure rate is high (more than 80%) and unlike many hematological malignancies, there is no lymphocytosis in cHL, on the contrary, lymphopenia is present in many patients [1-4]. Lymphopenia in hodgkin lymphoma has several definitions. Hasenclever et al. in Germany defined lymphopenia as Absolute Lymphocyte Count (ALC) of less than 600 cell/mcL or lymphocyte percentage of less than 8 percent [5]. Koh et al. in South Korea defined it as ALC of less than 1100 cell/mcL [6]. Sethi et al. in USA defined it as ALC of less than 1000 cell/mcL. Hancock et al. in UK defined it as ALC of less than 1500 cell/mcL [7]. Reference values for differential leukocyte count vary by ethnicity and geography and the characters of hodgkin lymphoma also differ with the previous differences [8,9]. The foregoing explains differences in the threshold for defining lymphopenia between studies. There are two hypotheses to explain the relationship between lymphopenia and poor prognosis. Some researchers believe that lymphopenia is the cause of a poor prognosis and disease progression. They are based on the proven role of lymphocytes in suppressing tumor cells, and the high incidence of Hodgkin's lymphoma in immunodeficiency patients, AIDS patients and patients taking immunosuppressant such as corticosteroids, cyclosporine and others [10,11]. Other researchers suggest that progression of hodgkin lymphoma is the cause of lymphopenia. There are three mechanisms, one of which may be the cause of lymphopenia. Lymphopenia maybe because of the decrease in the production of lymphocytes by increased expression of PD-1 [12]. Increased expression of PD-1 reduces

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lymphocyte maturation and differentiation. The second proposed mechanism of lymphopenia is lymphocytes leaving the peripheral blood and accumulation in tumor nodes [13]. The last mechanism is an increase in lymphocytes death by defective cytokines releasing [9]. The objective of this study is to know how lymphopenia is associated with progression of hodgkin lymphoma. This will provide a better understanding of the pathophysiology of this disease and it is likely that these findings can be generalized to other cancers. The above may have important applications, such as if we proved that lymphopenia is the cause of progression of hodgkin lymphoma, we can use lymphocytes growth factors like IL-7 and IL-2 for prevention of hodgkin lymphoma in high-risk individuals such as people with a family history of hodgkin's disease or other hematological malignancies, immunosuppressed patients, people with AIDS or Epstein-Barr. In the event that lymphopenia is demonstrated to be caused by decreased production of lymphocytes, we can recommend the use of PD-1 inhibitors more widely not only to treat hodgkin lymphoma but also to prevent serious complications such as septic shock. Finally, if we demonstrate that lymphopenia is the result of increased death of lymphocytes, we could reduce progression of disease by correcting defective cytokine secretion.

MATERIALS AND METHODS

A pilot study was performed to determine the appropriate lymphocyte count's cut-off for local patients participating in this study and to determine an appropriate sample size for our study. This pilot study was retrospective case-control study. It included 136 classical hodgkin lymphoma. We found that a lymphocyte count of 1,500 cell/mcL was the best cut-off point separating patients with good prognosis from poor prognosis. We also found that the sample size of 73 patients gives the study minimal power. Our actual study was prospective cohort that includes 84 classical hodgkin lymphoma patients. Inclusion criteria was: Participants are over 16 years old and have not yet received treatment, they do not have immunodeficiency or history of cancer and they do not have a recent history of taking corticosteroids, cyclosporine, phenytoin, carbamazepine and lithium. Patients participating in this study were divided into two groups: The high Absolute Lymphocyte Count (ALC) group which includes those with ALC equal or greater than 1500 cells/mcL, and the low ALC group in the case of patients with ALC less than 1500 cells/mcL. Propensity Score Matching (PSM) was performed in order to homogenize the two groups in terms of all confounder that could affect the results. Variables that were used to calculate the propensity score index were sex, age, Ann arbor stage, histologic subtype, albumin level, WBC count, hemoglobin level, monocytes count, neutrophils count, eosinophils count, platelets count, ESR, LDH. PSM was carried out using the nearest neighbor 1:1 matching in MatchIt package of "R" version 4.1.0 (the R foundation of statistical computing, Vienna, Austria). As a result of propensity score matching, two patients were excluded from high ALC group because there were not corresponding patients have same prognostic characters. Patients were followed up for 2 years. This period is considered sufficient for assessing progression of hodgkin lymphoma. Cox proportional hazards model was used to estimate the HR and 95% CI.

RESULTS

This study included 84 patients with newly diagnosed Hodgkin's Lymphoma. Patients' characteristics are summed up in Table 1.

Table 1: Patients' characteristics at diagnosis and outcomes, correlation with absolute lymphocyte.

Factor		Total	ALC<1500 cell/mcL	ALC ≥ 1500 cell/mcL	p
		N=84	N=41	N=43	
Age, n (%)	≥ 45	37 (46)	18 (43.9)	19 (44.2)	0.979
	<45	47 (44)	23 (56.1)	24 (55.8)	
Gender, n (%)	Male	43 (51.2)	23 (56.1)	20 (46.5)	0.38
	Female	41 (48.8)	18 (43.9)	23 (53.5)	
B-symptoms, n (%)	Absent	51 (60.7)	23 (56.1)	28 (65.1)	0.398
	Present	33 (39.3)	18 (43.9)	15 (34.9)	
Ann arbor staging, n (%)	I	5 (5.9)	3 (7.3)	2 (4.6)	0.19
	II	36 (42.9)	14 (34.1)	22 (51.2)	
	III	30 (35.7)	19 (46.4)	11 (25.6)	
	IV	13 (15.5)	5 (12.2)	8 (18.6)	
LDH, n (%)	≥ 280	51 (60.7)	26 (63.4)	25 (58.1)	0.621
	<280	33 (39.3)	15 (36.6)	18 (41.9)	
Histology, n (%)	Mixed cellularity	21 (25)	11 (26.8)	10 (23.3)	0.157
	Nodular sclerosis	50 (59.5)	21 (51.3)	29 (67.5)	
	Lymphocytic depleted	3 (3.6)	1 (2.4)	2 (4.6)	
	Lymphocytic rich	10 (11.9)	8 (19.5)	2 (4.6)	
ESR, n (%)	<50	46 (54.8)	25 (61)	21 (48.8)	0.264
	≥ 50	38 (45.2)	16 (39)	22 (51.2)	
Bulky disease	Absent	76 (90.5)	35 (85.4)	41 (95.3)	0.119
	Present	8 (9.5)	6 (14.6)	2 (4.7)	
Hb	≥ 10.5	55 (65.5)	24 (58.5)	31 (72.1)	0.191
	<10.5	29 (34.5)	17 (41.5)	12 (27.9)	
Albumin	≥ 40	-	18	23	0.38
	<40		23	20	
Stage, n (%)	Early stage I,II	41 (48.8)	17 (41.4)	24 (55.8)	0.188
	Advanced stage III,IV	43 (51.2)	24 (58.6)	19 (44.2)	
Response to treatment, n (%)	CR	68 (80.9)	31 (75.6)	37 (86)	0.537
	PR	13 (15.5)	8 (19.6)	5 (11.7)	
	SD	2 (2.4)	1 (2.4)	1 (2.3)	
	PD	1 (1.2)	1 (2.4)	0 (0)	

Note: Hb: Hemoglobin; ALC: Absolute Lymphocyte Count; ESR: Erythrocytic Sedimentation Rate; LDH: Lactate Dehydrogenase; CR: Complete Response; PD: Progressive Disease; PR: Partial Response; SD: Stable Disease; Significant p-value<0.05.

Association between lymphopenia and other prognostic factors are shown in Table 2.

Table 2: Association between lymphopenia and other prognostic factors.

		ALC<1500	ALC ≥ 1500	P value Chi (or Fisher)
		N		
Gender, n (%)	Male	23	20	0.772
	Female	18	23	
Age, n (%)	≥ 45	19	19	0.843
	<45	22	24	
Ann arbor staging, n (%)	I	2	3	0.246
	II	14	22	
	III	19	11	
	IV	6	7	
Histology, n (%)	NS	21	29	0.157
	MC	11	10	
	LR	8	2	
	LD	1	2	
Albumin	≥ 40	18	23	0.38
	<40	23	20	
Hb	≥ 10.5	24	31	0.191
	<10.5	17	12	
WBC	≥ 15000	9	5	0.204
	<15000	32	38	
Bulky disease	Present	5	3	0.415
	Absent	36	40	
B-symptoms, n (%)	Present	34	17	0.00005
	Absent	7	26	
ESR, n (%)	≥ 50 mm/h	19	26	0.194
	<50 mm/h	22	17	
		ALC<1500	ALC ≥ 1500	P value
		Means		T (or Mann Whitney)
LDH (IU/L)		388	311	0.035
ANC (cell/mcL)		8809	7601	0.078
AMC (cell/mcL)		548	490	0.166
AEC (cell/mcL)		210	170	0.001
PLT (cell/mcL)		340	316	0.209

Note: Hb: Hemoglobin; ALC: Absolute Lymphocyte Count; ESR: Erythrocytic Sedimentation Rate; LDH: Lactate Dehydrogenase; CR: Complete Response; PD: Progressive Disease; PR: Partial Response; SD: Stable Disease; Significant p-value<0.05.

Lymphopenia was associated with the presence of B symptoms, elevated LDH values, and higher eosinophil counts. But there was not any association between lymphopenia and other prognostic factors such as presence of bulky mass. As mentioned before, after PSM there were 41 pairs of patients (41 patients with a high lymphocyte count and 41 patients with a low lymphocyte count). The two previous ALC groups were similar in terms of all other prognostic factors cox regression was performed to assess prognostic value of ALC as shown in the Table 3. There was a significant difference in progression free survival between high ALC group and low ALC group. Moreover, the probability of not achieving a two-year progression-free survival in the low ALC group was two and a half times greater than that of the high ALC group. By studying the association between lymphopenia and progression of hodgkin lymphoma, we found the results shown in the Table 4. By calculating the Attributable Risk (AR), we find that it is equal to 35.7%.

Table 3: Cox-regression analysis for ALC in predicting progression-free survival.

	24 months PFS	
	HR (95% CI)	P value
ALC (<1500 *vs.* ≥ 1500)	2.48 (2.13-3.08)	0.021

Note: PFS: Progression Free Survival; HR: Hazard Ratio; ALC: Absolute Lymphocyte Count; Sig: Significance; Significant p-value ≤ 0.05.

Table 4: Association between lymphopenia and progression of hodgkin lymphoma.

	Absence of progression	Presence of progression
ALC<1500 cell/mcL	27	14
ALC ≥ 1500 cell/mcL	32	9

AR is defined as the frequency of progression in the lymphopenia-exposed group that can be attributed to exposure to this lymphopenia.

DISCUSSION

Attributable risk was 35.7%, which means that more than 60% of progression cases were not due to lymphopenia. This is inconsistent with the hypothesis that lymphopenia caused disease progression and this is consistent with the hypothesis that the progression of hodgkin's Lymphoma is the cause of lymphopenia. As previously mentioned, the last hypothesis has three mechanisms to explain this association. For the decreasing of production; the design of our study is not suitable to deny or confirm this hypothesis. The results of this study completely contradict the hypothesis that lymphopenia is the result of its redistribution in the neoplastic lymphatic organs, because we found a prognostic significance for ALC in HL. It is worth noting that there are many researchers who have also found prognostic significance for lymphocyte counts [4,5,7,12,13].

CONCLUSION

If lymphopenia was because the accumulation of lymphocytes in the affected nodes, we would not have found a prognostic importance for lymphopenia, because there is no real lymphopenia and therefore there is no immune deficiency. The second reason that makes our study contradicts the hypothesis of redistribution is that by studying the association between lymphocytopenia and the presence of a bulky mass, we did not find any significant correlation, and therefore it is not possible to attribute lymphopenia in the peripheral blood that it occurred due to its accumulation in the neoplastic lymphoid organs,

and this finding contradicts what Ayoub has found. The results of this study are consistent with the hypothesis that lymphopenia resulted from increased death as a result of a defect in the secretion of cytokines, where a significant statistical correlation was found between lymphopenia and the presence of B symptoms and these B symptoms reflect the disturbance of cytokine secretion, which in turn causes an increase in lymphocyte death.

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DECLARATIONS

Recommendation

We recommend conducting studies that include studying the association of cytokine concentrations with prognosis. We also recommend conducting clinical trials to investigate the effectiveness of NSAIDs or anti-cytokines as effective drugs in hodgkin's Lymphoma.

Ethical approval

Ethical approval was obtained from institutional review board of Tishreen University Hospital Number (2374) and written consents were obtained from all patients before enrolment. The study was performed in accordance with the 1964 declaration of Helsinki and its later amendments.

Competing interests

The authors declare no competing interests.

Authors' contributions

Study design: Hasan Khalil and Firas Hussein. Data collection and analysis: Hasan Khalil. Review and editing: Firas Hussein.

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Availability of data and materials

All the data used to support the findings of this study are included within the article.

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