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Clinicopathological, immunohistochemical charachtaristic and the outcome of Hodghkin lymphoma patients in Erbil city, Iraq

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Abstract:

BACKGROUND: Hodgkin lymphoma (HL) has unique epidemiological features with diversified pathologies and exhibits considerable clinicopathological variations in different parts of the world.

OBJECTIVES: We aimed in this study to assess clinic-pathological features, immunohistochemistry and outcome of HL patients treated in Erbil, northren Iraq.

PATIENTS AND METHODS: This was a retrospective study conducted in Nanakaly Hospital for blood diseases and oncology in Erbil, North Iraq; a total of 125 patients diagnosed between January 2012 and December 2016 were involved; they were assessed for their clinical characteristics and histopathology and immunophenotyping findings and their outcome was evaluated as well.

RESULTS: The median age was 28 years (range: 18–71 years); 55% were male and 41% had Stage II disease; common histological type is nodular sclerosis (51.2%) followed by mixed cellularity (43.2%); CD30 was positive in nearly all cases of classical HL, and CD15 was positive in 98.7% and CD20 was positive in 75% in nodular lymphocyte predominant subtype. Most of the patients received adriamycin, bleomycin, vinblastine, and dacarbazine chemotherapy, and the 5-year overall survival in our study is 70%. Advanced stage (IV), high lactate dehydrogenase level, low hemoglobin, and splenomegaly are significant predictors for poor survival.

CONCLUSION: Our patient exhibited outcomes that were lower to those reported in developed countries.

Keywords:

Erbil, Hodgkin lymphoma, immunohistochemistry

Introduction

Hodgkin lymphoma (HL) is a B-cell-derived malignancy mostly affecting young adults. More than 80% of patients are cured after stage-adapted first-line treatment with chemotherapy and/or radiotherapy.[1] It is an uncommon disorder with an annual incidence of 2–3/100,000 in Europe and the USA. In industrialized countries, the onset of HL shows a bimodal distribution with a first peak in the third decade and a second peak after the age of 50. Men are affected by HL slightly more often than women among all subtypes, except for the nodular sclerosing subtype that occurs slightly more often in young females than in male patients.[2]

The usual presentation of HL is with painless lymph node (LN) enlargement. Constitutional symptoms may be present: "B" symptoms: fever above 38°C, drenching night sweats, and weight loss of more than 10% of baseline body weight. Detection

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of an unusual mass or swelling in the superficial, supradiaphragmatic LNs (60%–70% cervical and supraclavicular, 15%–20% axillary) is the most common presentation. There are two main types of HL, first is classical HL (cHL) which is further subdivided to (nodular sclerosis, mixed cellularity, lymphocyte predominant, and lymphocyte depleted) and second is nodular lymphocyte predominant HL (NLPHL). The immunophenotype and genetic features of both cHL and NLPHL have been defined. These are useful in the subclassification of HL and in distinguishing HL from two recently described, aggressive lymphomas that were in the past often diagnosed as HL: anaplastic large-cell lymphoma, T-cell type, and T-cell/histiocyte-rich large B-cell lymphoma.[3]

Antibodies against CD15, CD30, and CD20 are often used to support morphological diagnosis of HL. The cHL is CD15+, CD30+, and CD20− in general and the NLPHL type is CD20+.[4]

The staging system that is used in patients with HL is the Ann Arbor staging system. It divided HL into four stages (I–IV). Designations applicable to any stage (A) no symptoms, (B) fever (38°C), night sweats, and unexplained loss of 10% body weight in previous 6 months, (X) bulky disease, and (E) involvement of a single extranodal site that is contiguous or proximal to the known nodal site.[5]

The prognostic scoring system was developed for patients with HL by the international prognostic score on advanced HL[6] which includes anemia, lymphopenia, male sex, high erythrocyte sedimentation rate (ESR), age, and Stage III–IV. HL is a curable disease with 82%–90% of newly diagnosed patients achieving a durable remission with first-line therapy; however, 15%–20% of patients will be resistant to therapy (primary refractory) or relapse after treatment.[7,8] A common treatment strategy for early-stage cHL is combined modality therapy with doxorubicin, adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by consolidative radiation therapy.[9]

The aims of this study were to clinical presentation and stage of disease at presentation, histopathology and immunohistochemistry findings of LN biopsy, and finally, the outcome of the enrolled patients.

Patients and Methods

This is a retrospective study conducted in Nanakaly Hospital for blood diseases and oncology in Erbil city, Kurdistan Region of Iraq, on 125 patients diagnosed between January 2012 and December 2016. Patients aged ≥18 years diagnosed with HL biopsy and admitted to the hospital were included in this study; all patients aged below 18 years or those with missing data in the hospital were excluded from this study. Informed consent was obtained from included patients before accessing their files, and the study was approved by the Ethical Committee of the Kurdistan Board for Medical Specialties. Patients are mostly Kurds (second most ethnic groups in Iraq following Arab). All patients were diagnosed according to the WHO classification by tissue biopsy and confirmed by immunohistochemistry. Positron emission tomography–computed tomography (CT) or CT scan was performed to stage all patients according to the Ann Arbor staging system. The data were collected by reviewing their hospital file for age, sex, baseline hematological and biochemical investigations, organomegaly, type of HL, presence or absence of surface marker (CD15, CD30, CD20, and CD3), and bone marrow examination. Most of the patients in this study took adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD*6) or ABVD*8 as a treatment, and the 5-year overall survival (OS) was 70%.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Science (SPSS 22, IBM, Armnok, NY, United State Of America). Chi-square test of association was used to compare proportions. Fisher's exact test was used when the expected count of more than 20% of the cells of the table was <5. Survival curves were plotted using the Kaplan–Meier method, and the log-rank test (by Mantel–Cox) was used to show whether there was a significant difference or not in the survival time of the study groups. $P \leq 0.05$ was considered as statistically significant.

Results

The mean age (± standard deviation [SD]) of the patients was 32.57 ± 14.17 years (range: 18–71 years). The median was 28 years. More than half (53.6%) aged <30 years, and 55.2% of them were male with male-to-female ratio of 1:0.8.

The most commonly involved LNs were in the neck, mediastinum, and abdomen (80.8%, 68.8%, and 36%, respectively) as shown in Table 1.

The mean hemoglobin (Hb) value ± SD was 12.01 ± 2.14 g/dl; 22.4% of the patients had low Hb. The mean white blood cell (WBC) counts were 11.46 ± 7.1315 × 10^9/l; 80.8% of patients had WBC count of <15 × 10^9/L. The mean lymphocyte count was 2.05 ± 1.11 × 10^9/L; 92.8% had lymphocyte count more than 0.6 × 10^9/L; the detail laboratory and bone marrow finding showed in Table 2.

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The CD expression was as follows: CD30 (96.8%), CD15 (95.2%), CD20 (3.2%), and CD3 (3.2%).

The CD15 expression was low (25%) in the nodular lymphocyte predominant, while it was more than 95% in the other types ($P = 0.001$) as presented in Table 3. The same pattern is observed in the same table regarding CD30 ($P < 0.001$). CD20 mostly expressed in the nodular lymphocyte predominant (75%), while it was 1.6% in the nodular sclerosis and 0% in the other types ($P < 0.001$). Nearly, the same pattern was observed regarding CD3 ($P = 0.013$).

Table 4 shows that the more advance the stage of HL, the more the death rate within the period of 5 years, reaching to 30.4% in Stage 4 ($P = 0.007$). No significant difference was detected between the death rates of different types of HL ($P = 0.433$). The death rate (20.2%) was significantly higher among those with B symptom than the death rate (0%) among those with no B symptoms ($P = 0.002$). It was also higher among those with splenomegaly (32.3%) compared with 7.4% among those with no splenomegaly ($P = 0.001$). No significant association was detected between death rate and hepatomegaly ($P = 0.123$). The death rate was significantly ($P < 0.001$) high among those with Hb ≤10.5 (35.7%) than those with high Hb >10.5 (7.2%). No significant association was detected between death rate and WBCs > or < 15 × 10^9 ($P > 0.99$), lymphocytes ≤ or >0.6 × 10^9 ($P > 0.99$), and ESR equal > or <30 ($P = 0.391$). The death rate was significantly ($P = 0.001$) high among those with lactate dehydrogenase (LDH) ≥450 (33.3%) compared with 7.4% among those with LDH <450. Death rate was not associated with bone marrow involvement ($P = 0.137$).

This study shows that 103 out of 125 patients (82.4%) got remission, while 14 out of 125 patients (11.2%) had relapse. Most common treatment regimen used was ×6 ABVD, whether alone (54.4%) or in combination with ×6 Bleomycin, Etoposide, Doxorubicin,

Table 1: Patients' characteristics on presentation (*n*=125)

	n (%)
Ag (years)	
<30	67 (53.6)
30-39	30 (24.0)
40-49	10 (8.0)
≥50	18 (14.4)
Gender	
Male	69 (55.2)
Female	56 (44.8)
Loss of weight, fever, and night sweat	84 (67.2)
Bulky disease	11 (8.8)
Stage	
I	15 (12.0)
II	52 (41.6)
III	35 (28.0)
IV	23 (18.4)
Type of HL	
Nodular sclerosis	64 (51.2)
Mixed cellularity	54 (43.2)
lymphocyte predominant	2 (1.6)
lymphocyte depleted	1 (0.8)
Nodular lymphocyte predominant	4 (3.2)

HL=Hodgkin lymphoma

Table 2: Laboratory findings

	n (%)	Mean±SD	Median	Minimum	Maximum
Hb (g/dl)					
≤10.5	28 (22.4)	12.01±2.14	12.00	6.1	18.4
>10.5	97 (77.6)				
WBC (×10^9)					
<15	101 (80.8)	11.46±7.13	10.00	1.9	36.4
≥15	24 (19.2)				
Lymphocyte (×10^9/L)					
≤0.6	9 (7.2)	2.05±1.11	2.00	0.10	7.00
>0.6	116 (92.8)				
ESR (mm/h)					
<30	36 (28.8)	58.68±37.68	55.00	3	142
≥30	89 (71.2)				
LDH (mg/dl)					
<450	95 (76)	372.00±153.68	356.00	105	1025
≥450	30 (24)				
Bone marrow involvement					
No	115 (92.0)				
Yes	10 (8.0)				
Total	125 (100)				

Hb=Hemoglobin, WBC=White blood cell, ESR=Erythrocyte sedimentation rate, LDH=Lactate dehydrogenase, SD=Standard deviation

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Table 3: CD expression by type of lymphoma

	Type of HL					Total (*n*=125), *n* (%)	*P*
	Nodular sclerosis (*n*=64), *n* (%)	Mixed cellularity (*n*=54), *n* (%)	Lymphocyte predominant (*n*=2), *n* (%)	Lymphocyte depleted (*n*=1), *n* (%)	Nodular lymphocyte predominant (*n*=4), *n* (%)		
CD15	62 (96.9)	53 (98.1)	2 (100.0)	1 (100.0)	1 (25.0)	119 (95.2)	0.001*
CD30	63 (98.4)	54 (100.0)	2 (100.0)	1 (100.0)	1 (25.0)	121 (96.8)	<0.001*
CD20	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (75.0)	4 (3.2)	<0.001*
CD3	1 (1.6)	1 (1.9)	0 (0.0)	0 (0.0)	2 (50.0)	4 (3.2)	0.013*

*By Fisher's exact test. HL=Hodgkin lymphoma

Table 4: Death rate according to clinical and laboratory characteristics

	n	Death, *n* (%)	*P*
Stage			
1	15	0 (0.0)	0.007*
2	52	3 (5.8)	
3	35	7 (20.0)	
4	23	7 (30.4)	
Type of HL			
Nodular sclerosis	64	6 (9.4)	0.433*
Mixed cellularity	54	10 (18.5)	
lymphocyte predominant	2	0 (0.0)	
lymphocyte depleted	1	0 (0.0)	
Nodular lymphocyte predominant	4	1 (25.0)	
B symptom			
No	41	0 (0.0)	0.002
Yes	84	17 (20.2)	
Splenomegaly			
No	94	7 (7.4)	0.001*
Hepatomegaly			
No	110	13 (11.8)	0.123*
Hb			
≤10.5	28	10 (35.7)	<0.001*
>10.5	97	7 (7.2)	
WBC			
<15	101	14 (13.9)	> 0.99*
≥15	24	3 (12.5)	
Lymphocyte			
≤0.6	9	1 (11.1)	> 0.99*
>0.6	116	16 (13.8)	
ESR			
<30	36	3 (8.3)	0.391*
≥30	89	14 (15.7)	
LDH			
<450	95	7 (7.4)	0.001*
≥450	30	10 (33.3)	
Bone marrow involvement			
No	115	14 (12.2)	0.137*
Yes	10	3 (30.0)	

*By Fisher's exact test. Hb=Hemoglobin, WBC=White blood cell, ESR=Erythrocyte sedimentation rate, LDH=Lactate dehydrogenase, HL=Hodgkin lymphoma

Cyclophosphamide, Vincristine, Procarbazine, Prednisone (BEACOPP) (5.6%), and only 8 patients underwent autologous stem cell transplant due to relapse Table 5, due to relapse refractory disease.

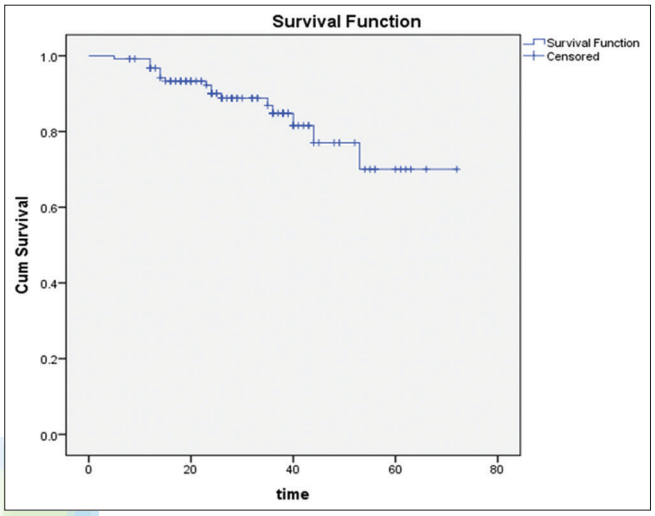

Figure 1: Mean overall survival time

Figure 1 shows that mean OS time ± standard error was 60.76 ± 2.61 months. Table 6 and Figure 2 show that the mean survival time of males (58.25 months) does not significantly (P = 0.347) differ from that of females (56.67 months). Figure 3 shows that the least survival time was in Stage 4 (P = 0.028).

Discussion

The distribution of disease was found to be more common in male, and the most common subtype of HL in our study was nodular sclerosis followed by mixed cellularity (51%,43% respectively), close figure were reported in study done in Dahouk and Sulaimanya in North part of iraq, and neighboring countries like Jordan, United Arab Emirate and Saudi Arabia, also close to our result were found in study done in USA.[10-14]

In our study, NLPHL type, which is now considered as a distinct entity of HL according to the recent WHO classification system, was diagnosed in only 4 patients (3.2%); similar to this, 5% was also reported in study conducted in number of European and American center.[15]

The median age at time of diagnosis was 28 years, 41.6% were in Stage II, and 28% of them were in Stage III; in

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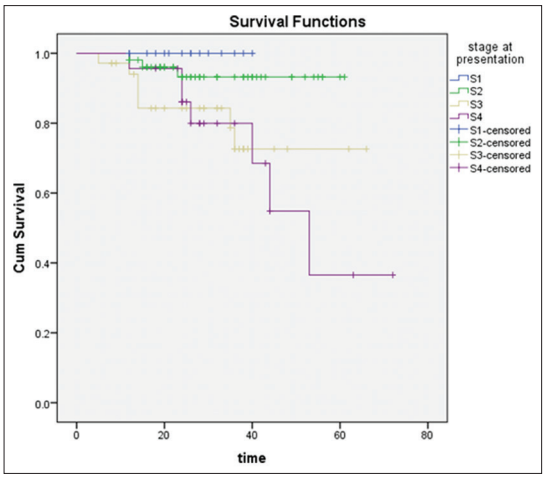

Figure 2: Mean overall survival time (months) by gender. Mean survival time ± standard error: 60.76 ± 2.61 month

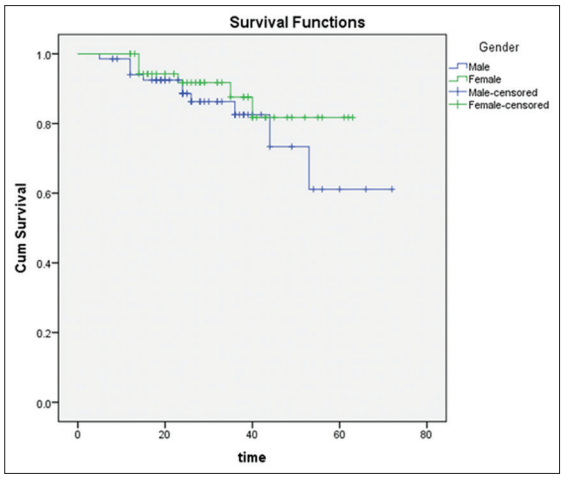

Figure 3: Mean overall survival time (months) by stage of the disease. Log rank (Mantel–Cox): *P* =0.028. Note: The detailed table can't be computed because all cases in Stage 1 were censored

Table 5: Patients' follow-up and lines of treatment (*n*=125)

	n (%)
Remission+relapse	117 (93.6)
Refractory disease	18 (14.4)
Treatment	
6 × ABVD	68 (54.4)
8 × ABVD	10 (8.0)
4 × ABVD	15 (12.0)
6 × BEACOPP	2 (1.6)
6 × esc-BEACOPP	2 (1.6)
6 × ABVD + 6 × BEACOPP*	7 (5.6)
8 × ABVD + 4 × BEACOPP*	2 (1.6)
8 × AVBD + salvage*	15 (12.0)
6 × BEACOPP + salvage*	2 (1.6)
6 × R-CHOP	2 (1.6)
ASCT	8 (6.4)

*It means those patient received first-line treatment ABVD then BEACOPP, or salvage such as DHAPP or ESHAP. ABVD=Adriamycin, bleomycin, vincristine, and dacarbazine, ASCT=Autologous stem cell transplant, R-CHOP=Rituximab, Cyclophosphamide, Doxorubicin, vincristine, prednisone, BEACOPP=Bleomycin,Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone

Table 6: Mean overall survival time by gender

Gender	Mean overall survival time by months				*P* (log rank mantel-cox)
	Estimate	SE	95% CI		
			Lower bound	Upper bound	
Male	58.259	3.868	50.677	65.841	0.347
Female	56.671	2.413	51.942	61.399	
Overall	60.763	2.616	55.635	65.891	

SE=Standard error, CI=Confidence interval

comparison to the study done in USA, most of patients at the time of diagnosis were in stage II (40%) while (23%) were in stage I and this due to the fact of the availability of advanced facilities and imaging study for early detection and diagnosis of the disease.[16]

Similar to our figures were reported in developing country like Nigeria and India which most of their patients were in stage III, IV at time of diagnosis.[17,18]

Most common nodal involvement in our study was in the neck (80%) followed by mediastinum (68%) (Saudi Arabia 65% in the neck followed by 7% mediastinum)[19] and splenomegaly (24%) similar to a study done in Poland in which splenomegaly was found in 24%.[20] B symptoms are present in 67% which is similar to other study (Egypt 61% and Saudi Arabia 82%).[19,21]

In the current study, CD30 was positive in nearly all cases of HL (96.8%), and this is similar to study done in North of Iraq, Egypt, and China (100%, 100%, and 100%, respectively),[22-24] while CD15 was positive in 95% lower than other study, and this may be due to the properties of different antibodies, variation in the technique of incubation, and antigen retrieval.[22]

CD20 was positive only in one case of cHL (1.6%) which is also lower than that reported in Egypt, China, and Austria (15%, 30%, and 20%, respectively),[23-25] while three out of four cases of NLPHL were positive for CD20.

The 5-year OS in our study is 70% which somewhat similar to the study done in Mediterranean basin in Turkey (69%), Libya (59%) but our result showed to be lower when compared to studies done in France,Spain and USA which showed 5-year OS are (83%,86%, 85.2% respectively),[26,27] this difference in OS curve with the developed country may be due to first: delay at diagnosis which most of our patient seeking medical attention late, second: may be difference in modality of treatment and radiotherapy and third: may be due to short follow-up period in this study.

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In the present study, advanced stage (IV), high LDH level, low Hb, and splenomegaly are significant predictors for poor survival. Other variables such as total leukocyte count, absolute lymphocyte count, and bulk disease were not predictors for survival, and this was similar to multivariate analysis of single institution.[20] Most common cause of death in this study was due to the disease progression.

No statistical difference was found in OS between males and females which is similar to study published in 2011 on European patients with HL.[28]

Conclusion

In this study, we have discussed in detailed the various clinical and histopathological parameters of HL; the most common type was nodular sclerosis, most of them were in Stage II–III, and most common LN involved was in the neck; 60% of patients had B symptom. Almost all patients had CD30 and CD15 positive by immunophenotyping.

In this study, advanced stage (IV), high LDH level, low Hb, and splenomegaly are significant predictors for poor survival, and the 5-year OS was 70%, which is lower than the developed country.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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