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Original Article

Hodgkin Lymphoma and Anaplastic Variants of Non-Hodgkin Lymphoma

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ABSTRACT

Background and Objectives: Classic Hodgkin lymphoma (CHL), anaplastic large cell lymphoma (ALCL) and some cases of diffuse large B cell lymphoma (DLBCL) have overlapping morphologic features. Since they all represent distinct clinico-pathologic entities, we explored the differential diagnostic impact of immunophenotyping to discriminate between them.

Materials and Methods: We included 61 cases diagnosed as CHL, ALCL, and anaplastic variant of DLBCL. We reviewed morphologic microscopic findings by conventional staining and immunohistochemistry (IHC) with antibodies against PAX-5, CD30, CD15, CD45, EMA, ALK-1, and LMP-1.

Results: Fifty cases corresponded to CHL (81.97%), 4 cases to ALCL (6.56%), and 4 cases to DLBCL (6.56%) excluding 3 cases, which remained unclassifiable (4.92%). PAX-5 was expressed in 94% of CHL and 100% of DLBCL cases. LMP-1 was expressed in 52% of CHL and 25% of DLBCL cases. EMA was invariably expressed in all 4 cases of ALK^{+}ALCL. It was expressed in 4/50 cases (8%) of CHL and in 2/4 cases (50%) of DLBCL. CD45 was expressed in all cases of ALCL and DLBCL but also in 3/50 cases (6%) of CHL.

Conclusion: The differentiation between ALCL and CHL based on EMA and CD45 is not reliable. Utilization of PAX-5 in combination with other markers such as CD15 and LMP-1 is recommended. CD20 and PAX-5 are not too helpful in the differentiation of CHL and DLBCL, while CD15 and CD79a were found to be quite useful discriminative markers for this purpose.

Keywords: Hodgkins Lymphoma, Non Hodgkin Lymphoma, Diagnosis, Immunohistochemistry ,Iran

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Introduction

Hodgkin lymphoma (HL) is a common malignancy of lymphoid tissue. In Kerman, Iran, malignant lymphomas comprised 8.8% and Hodgkin lymphomas (HL) 4.1% of all malignancies (1). Hashemi *et al.* reported Hodgkin's disease as the major type (28%) among 385 lymphoma cases in Tehran (2). Malignant lymphomas comprise 11.3% and HL 2.8% of all malignant tumors (3).

Classic Hodgkin lymphomas (CHL) are morphologically hall marked by the presence of Hodgkin-cells (HC) and Reed-Sternberg cells (RS) intermingled among numerous reactive non-neoplastic background cells. In 98% of cases, the tumor cells originate from mature B cells of germinal center cell stage and very rarely from peripheral T cells (4-6).
Some subgroups of non-Hodgkin's lymphoma (NHL) mimic morphologically and immunohistologically CHL, most likely anaplastic large cell lymphoma (ALCL) and diffuse large B cell lymphoma (DLBCL) including anaplastic and T-cell/histiocyte rich subtypes (7-11).
Immunophenotyping is crucial to differentiate between CHL and NHL, but there is no discriminative single immunologic marker. Here we suggest a panel of antibodies to resolve the problem. However, a minority of case still needs additional molecular analyses for definite diagnosis (5, 7, 8).
In this study, 61 cases of lymphoma diagnosed in Kerman City in south – east of Iran as CHL, anaplastic variants of DLBCL and ALCL were selected and reevaluated with profound morphologic and immunophenotypic profiling.

Materials and Methods

In this cross-sectional study, patients primarily diagnosed between 2004 and 2008 in the Pathology Department at Kerman Medical University as CHL, ALCL, or as anaplastic variant of DLBCL, were reevaluated. Formalin-fixed, paraffin-embedded biopsy specimens of neoplastic tissues were collected from the archives. Sections with 4μ thickness were prepared. Based on H&E stainings the samples were primarily subdivided into two categories, namely 1) typical CHLs, and 2) borderline cases. Secondarily, immunostaining was performed for all cases using CD30 (N1558, DAKO, Denmark, RTU), CD15 (N1615, DAKO, Denmark, RTU), CD45 (N1514, DAKO, Denmark, RTU), ALK (N1614, DAKO, Denmark, RTU), LMP1 (M0897, DAKO, Denmark, 1/50), EMA (N1504, DAKO, Denmark, RTU), PAX-5 (NCL-LPAX-5, Novocastra, Austria, 1/50), and CD20 (N1502, DAKO, Denmark, RTU). For some selected cases CD3 (N1580, DAKO, Denmark, RTU), CD4 (M0716, DAKO, Denmark, 1/50), CD8 (N1592, DAKO, Denmark, RTU) and CD79a (M7050, DAKO, Denmark, 1/20) were also used.
Sialinizied slides were used for IHC process. Tissue sections were inserted in the incubator with 37 degree Celsius overnight. They were cooked at 60°C for 60 min and deparraffinized in xylene for 20 min. In order to Ag retrieval, the slides were inserted in Tris-EDTA (pH=9) and then they were heated by microwave for 10 min and then they were cooled gradually. The slides were put in Tris buffer (pH=7.4-7.6) and for endogenous peroxides activity inhibition, hydrogen peroxides 3%/methanol was used for 5 min (except for PAX-5). The sections were incubated with selected monoclonal antibodies for 45 min by room temperature. Some of the antibodies were diluted with antibody diluents (50809, DAKO, Denmark). In order to detecting bound primary antibody, Envision solution (DAKO, K5007) was used for 30 min and

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then (DAB) diaminobenzidine chromogen (DAKO, K3486) was used as a substrate for 5 min. The sections were stained with hematoxylin for one min. In the next step, they were washed with distilled water and then were dehydrated with grading alcohol. During the work up steps, Tris buffer solution (pH=7.4 - 7.6) was used for washing (twice and each time for 3 min) (12, 13).

The final diagnosis was based on the morphology and immunophenotype. In some selected cases, some phenotypic profiling was repetitively performed in the States Hospital of St. Gallen, Switzerland.

Stata 10 was used for data analysis, $\chi 2$ and fisher tests were used for comparing the percents of the marker's expressions in each diagnostic group.

Results

Characteristics of samples:

Clinical data from sixty-one cases were analyzed. Patients were 5 to 79 years old (mean=35.97±16.8 yr). Thirty-nine were male and 22 were female (m: f-ratio: 1.77) (Table 1).

Table 1- Characteristics of the study subjects, the main diagnosis and morphology categories

Variable	Statistics
Study Subjects (n)	61
Age (M ± SD)	35.97 ± 16.8
Sex	
Male (%)	39 (63.90)
Female (%)	22 (36.10)
Morphology (%)	
Hodgkin	39 (63.93)
Borderline	22 (36.07)
Diagnosis (%)	
CHL	50 (81.97)
ALCL ALK+	4 (6.56)
DLBCL	4 (6.56)
Unclassifiable	3 (4.92)

CHL: Classic Hodgkin Lymphoma ; ALCL ALK+: Anaplastic Large Cell Lymphoma ALK+
DLBCL: Diffuse Large B Cell Lymphoma

In a first step, all cases were stratified only based on H&E morphology alone into a first group with characteristic features of CHL (n=39) and a second group presenting borderline appearance (n=22).

In the second step, all sixty-one cases underwent additional immunophenotyping which resulted into a modified sub grouping: 50 cases of CHL (81.97%), 4 cases of ALCL (6.56%), and 4 cases of DLBCL (6.56%) while 3 cases remained unclassifiable (4.92%).

Morphology typical for CHL (group 1):

Thirty none cases had diagnostic morphologic features of CHL. Their immunophenotypic profiles: in summary CD30 was expressed in 38/39 cases (97.44%) (P=1.00), PAX-5 in 37/39 cases (94.87%) (*P*=0.001), CD15 in 34/39 cases (87.18%) (*P*<0.001), LMP-1 in 21/39 cases (53.87%) (*P*=0.03), EMA in 2/39 cases (5.12%) (*P*=0.001), CD45 in 2/39 cases (5.12%) (*P*=0.001), and ALK in null.

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Finally, the diagnosis CHL was confirmed by additional immunophenotypic profiling in all 39 cases. A single case in this group, which showed negative reaction with CD30, was morphologically sub typed as CHL, mixed cellularity exhibiting co-expression of PAX-5, CD15, and LMP-1. Seven of 39 cases (17.94%) showed CD20 immunoreactivity in the giant tumor cells, positive for CD15 and negative for CD45.

Borderline morphology (group 2):

Twenty-two cases with borderline morphology could be sub-typed according to their phenotypes into four groups as follows: (a) Eleven cases were PAX-5^{+}, $CD30^{+}$, LMP-$1^{\pm}$ and $CD15^{\pm}$. (b) Four cases were $CD30^{+}$, ALK^{+}, PAX-5^{-}, LMP-1^{-}, $CD15^{-}$, EMA^{+}, and $CD45^{+}$. (c) Four cases were $CD30^{\pm}$, ALK^{-}, PAX-5^{+}, $CD15^{-}$, LMP-$1^{\pm}$, $CD20^{+}$, $CD45^{+}$, and $EMA^{\pm}$. (d) Three cases expressed only CD30 and were negative for all other markers.

Based on immunophenotypic characteristics the diagnoses for these 22 cases were stratified as follows: All cases with CD30 positivity associated with PAX-5 and/or LMP-1 qualified for Hodgkin, if they did not express CD79a. All cases that were $CD45^{+}$, EMA^{+}, PAX-5^{-}, $CD15^{-}$, $CD30^{+}$, ALK^{+}, were classified as ALCL ALK+. All cases that were $CD30^{\pm}$, PAX-5^{+}, $CD15^{-}$, $CD20^{+}$, ALK^{-}, $CD45^{+}$ were classified as DLBCL. Three cases that did not express any markers except CD30 were defined as unclassifiable. Table 2 summarizes the individual phenotypes of 22 cases with borderline features.

Table 2-The pattern of antibodies' expression in borderline cases

Cases	CD30	CD15	PAX-5	LMP-1	EMA	ALK	CD45	CD20	CD79	CD3	CD4	CD8	Diagnosis
1	+	-	-	-	+	+	+	-	-	+	+	-	ALCL ALK+
2	+	-	-	-	+	+	+	-	-	-	+	-	ALCL ALK+
3	+	-	-	-	+	+	+	-	-	-	-	-	ALCL ALK+
4	+	-	-	-	+	+	+	-	-	-	+	-	ALCL ALK+
5	+	-	+	+	-	-	-	-	-	-	-	-	CHL
6	+	+	+	-	-	-	-	+	-	-	-	-	CHL
7	+	+	+	-	+	-	+	-	-	-	-	-	CHL
8	+	+	+	-	-	-	-	-	-	-	-	-	CHL
9	+	+	+	-	-	-	-	+	-	-	-	-	CHL
10	+	+	-	+	-	-	-	-	-	-	-	-	CHL
11	+	-	+	-	-	-	-	-	-	-	-	-	CHL
12	+	+	+	-	+	-	-	-	-	-	-	-	CHL
13	+	-	+	+	-	-	-	-	-	-	-	-	CHL
14	+	+	+	+	-	-	-	-	-	-	-	-	CHL
15	+	+	+	+	-	-	-	-	-	-	-	-	CHL
16	-	-	+	-	+	-	+	+	+	-	-	-	DLBCL
17	+	-	+	-	-	-	+	+	+	-	-	-	DLBCL
18	+	-	+	+	-	-	+	+	+	-	-	-	DLBCL
19	+	-	+	-	+	-	+	+	+	-	-	-	DLBCL
20	+	-	-	-	-	-	-	-	-	-	-	-	Unclassifiable
21	+	-	-	-	-	-	-	-	-	-	-	-	Unclassifiable
22	+	-	-	-	-	-	-	-	-	-	-	-	Unclassifiable

CHL: Classic Hodgkin Lymphoma ; DL-BCL: Diffuse Large B Cell Lymphoma
ALCL ALK+: Anaplastic Large Cell Lymphoma ALK+;

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Expression profiles of various antibodies: Frequencies of expression of various antibodies are shown in Table 3. CD30 reactivity was found in 49/50 cases (98%) of CHL, in 4/4 cases (100%) of ALK+ ALCL, in 3/4 (75%) of DLBCL, and in all three cases (100%) of unclassifiable tumors. CD15 was positive in 42/50 cases (84%) of CHL and not expressed in any other group. PAX-5 was expressed in 47/50 cases (94%) of CHL cases, in 4/4 cases (100%) of DLBCL but not in ALCL. LMP-1 was expressed in 26/50 cases (52%) of CHL and in 1/4 case (25%) of DLBCL. EMA was expressed in all 4 cases (100%) of ALK$^+$ ALCL. It was expressed in 4/50 cases (8%) of CHL and in 2/4 cases (50%) of DLBCL (focally in some cells). CD45 was expressed in all cases of ALCL and DLBCL and in 3/50 cases (6%) of CHL. CD20 was positive in 9/50 cases (18%) of CHL, and in 4/4 cases (100%) of DLBCL, but negative in ALCL. CD79a was only expressed in all cases of DLBCL.

Table 3- The percentage of different antibodies expression by diagnosis categories

Diagnosis	CD30	CD15	PAX-5	LMP-1	EMA	CD20	CD45	ALK
CHL	98.0	84.0	94.0	52.0	8.0	14.0	6.0	0.0
DLBCL	75.0	0.0	100	25.0	50.0	100	100	0.0
ALCL ALK+	100	0.0	0.0	0.0	100	0.0	100	100
Unclassifiable	100	0.0	0.0	0.0	0.0	0.0	0.0	0.0

CHL: Classic Hodgkin Lymphoma; DLBCL: Diffuse Large B cell Lymphoma
ALCL ALK+: Anaplastic Large Cell Lymphoma ALK+

Discussion

CHL, ALCL and some cases of DLBCL may show overlapping morphologic features, although they run different clinical courses. In this work, we studied the immunophenotypic profiles in a series of 61 cases of malignant lymphoma, which were morphology-based primarily diagnosed as CHL. For secondary IHC evaluation a comprehensive panel of monoclonal antibodies, including CD30, CD15, PAX-5, LMP-1, ALK-1, CD45, and EMA was used.

As summarized in Table 1, 39/61 cases corresponded to CHL both morphologically and immunophenotypically (63%). The remaining 22/61 cases presenting with borderline morphologies could be stratified immunophenotypically into CHLs (n=11), DLBCLs (n=4), and ALCLs (n=4) excluding three cases that remained unclassifiable.

According to our findings in this study, all 39 cases with typical morphologic features of CHL also revealed the prototypic phenotypic profiles. This finding is important and highly emphasizes the reliability and reproducibility of H&E morphology in daily routine diagnostics.

This issue may raise the question, whether immunophenotyping is also mandatory in cases of CHL with typical morphology. We would say that it is not necessary invariably. Secondly, one may question which antibodies should be comprised in a minimal first round set or a more comprehensive second round diagnostic panel in morphologically clear cases. To our opinion, CD15 and PAX-5 may be a reasonably economical and time saving first choice. Thus, this combination will cover at least 94% of cases according to our statistics. For cases, which are negative for CD15 and/or PAX-5, more far going

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immunophenotyping may be needed. In accordance to the German Hodgkin Study Group we recommend a broader panel of antibodies containing CD20, CD3, PAX-5, CD15, CD30, and LMP-EBV which could be completed for some special cases by ALK-1, CD4, CD8, EMA, and J-chain.

Borderline cases with excess of mononuclear blast cells or excess of RS cells or RS like cells as found in 36% of our series definitely need IHC profiling for a final diagnosis. The most crucial differential diagnoses in this group are CHL, ALCL and anaplastic variant of DLBCL. Which panel can be used for such cases to reveal reliable and reproducible routine diagnostics? We suggest CD30, CD15, PAX-5, LMP-1, ALK and CD20 as a minimal panel. We do not recommend CD45 and EMA (Fig. 1). This panel can cover almost all cases, although three cases in this study remained unclassifiable. However, in general, CD45 positivity/negativity has an enormous differential diagnostic impact in this context!

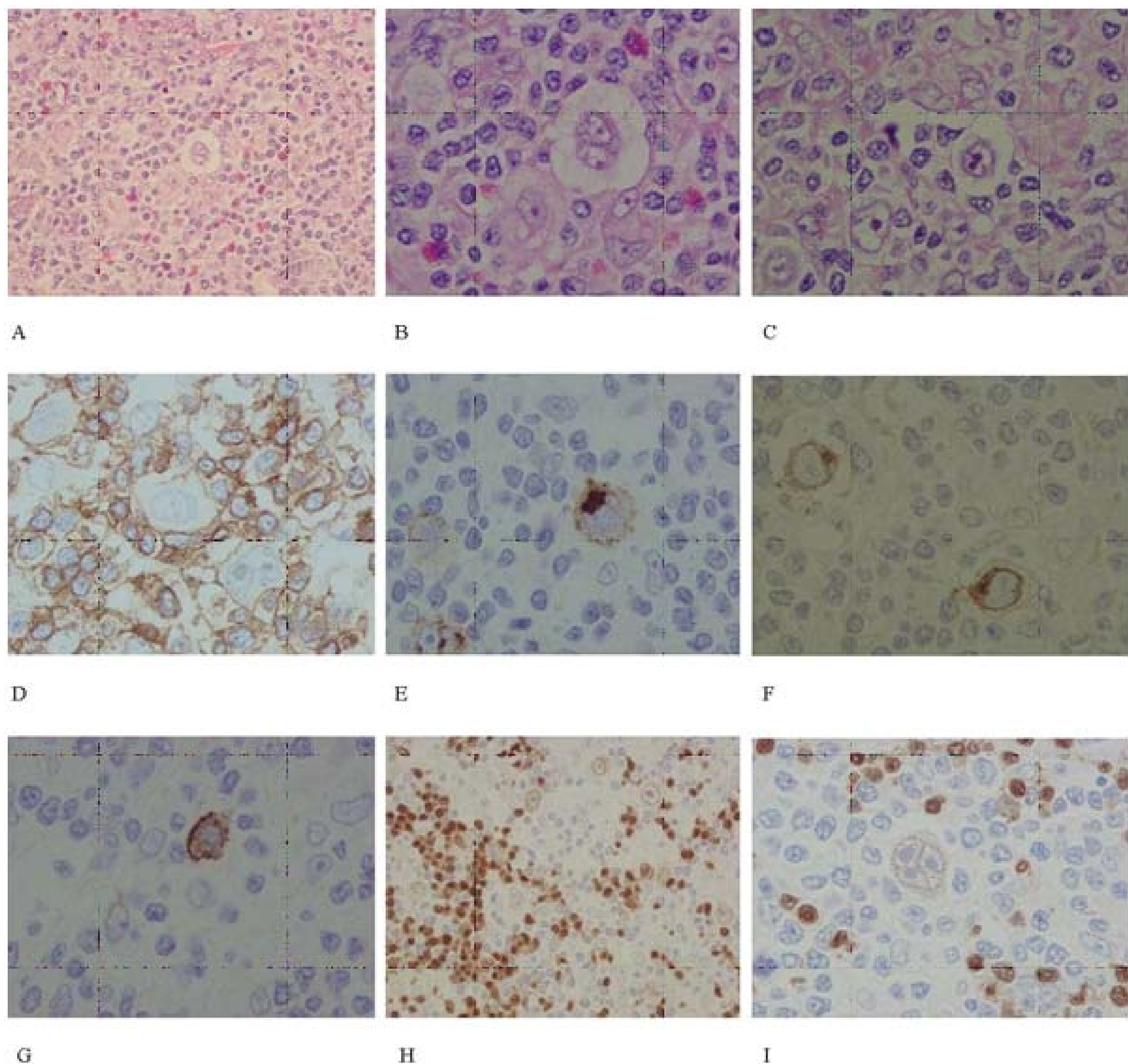

Fig. 1- Hodgkin Lymphoma
A: H&E of typical Hodgkin lymphoma(×40)
B,C: H&E of typical Hodgkin lymphoma(×400)
D: RS cells are CD3 negative but they are surrounded by T -lymphocytes in rosette like shape(×400)

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E: CD15+,RS cells show dot like paranuclear and cytoplasmic staining (400X)
F: CD30+,RS cells show dot like paranuclear and cytoplasmic staining (400X)
G: LMP-1+,cytoplasmic reaction (400X)
H,I: PAX-5+. Small mature lymphocyte are stained intensely with PAX-5 but HRS cells show weakly positive nuclear reaction(40X,400X)

With these panel cases of ALCL can be distinguished (Fig. 2). ALK positive cases will be easily diagnosed (14-16). The diagnosis of ALK negative cases is crucial. Such cases express CD30, CD4 and MUM-1(not included in our study) and should be negative for LMP-1 and PAX-5 (8;17-19). In our study, 4 of 50 CHL cases (8%) expressed EMA despite of PAX-5 positivity. Three cases of CHL cases (6%) carried both CD45 and PAX-5. It means that the stratification based on EMA and CD45 is equivocal. PAX-5 is a transcription factor that is expressed in primary precursors (pro, pre B cell) of B cell and matures B-lymphocytes but it is negative in plasma cell. This marker differentiates B cell lymphomas from T cell lymphomas (8;17;20-22). In some studies, PAX-5 is recommended as a gold standard marker for distinction of CHL from ALCL (9). In this study, 94% of CHL cases were PAX-5 positive, so we cannot rely on this single marker alone. Some other studies showed the same result (5,8,19,23,24). LMP-1 is positive in CHL and DLBCL while cases of ALCL were invariably LMP-1 negative (5, 18). Expression of LMP-1 in PAX-5 negative cases favors the diagnosis of CHL and speaks against ALCL (DLBCL is also ruled out because all cases of DLBCL are PAX-5 positive) (5,8,17,21). The incidence of LMP-1 expression depends considerably on the provenience of the patients, since the prevalence of EBV shows a high geographic variability (5,6). In a previous study, 30% of Iranian CHL patients were EBV positive (2). In our study, the rate was 52%. Eight four percent of CHL cases in our study expressed CD15. CD15 positivity favors the diagnosis of HL but CD15 can be positive in rare cases of ALCL, too. In some studies up to 10% of ALCL cases express CD15; therefore, CD15 as a single marker is not too discriminative (5,6,8).

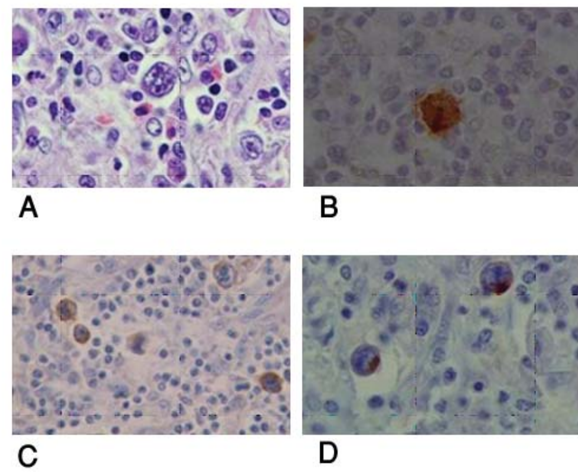

Fig. 2- Anaplastic Large Cell Lymphoma
A: Morphologic features, ×400 (H&E)
B: ALK+,blast cells show nuclear,cytoplasmic reaction (×400)
C: CD30+,blast cells show dot like paranuclear and cytoplasmic staining (×100)
D: EMA+,blast cells show dot like paranuclear and cytoplasmic staining (×400)

Today we know that CHL are in most cases follicle centre cell derived B-cell lymphomas. While PAX-5 is expressed in 90-100% of CHL cases (5,9,15), CD20 may be positive in only 25-40 % of CHL cases (5, 8). In our study, 94% of CHL cases expressed PAX-5 and 14% of them were CD20 positive. Thus, neither PAX-5 nor CD20 are helpful discriminative markers between CHL and DLBCL (8). CD15 can be a helpful marker to differentiate CHL from DLBCL (Fig. 3). Positive reaction with CD15 speaks in favor

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of CHL (5, 7). However, there are some cases of CHL, which are negative for CD15. In such cases, other antibodies such as CD79a, BOB1, and OCT-2 can be used (8, 24). In this study, we used CD79a. CD79a is positive in all cases of DLBCL, and it may be expressed in only rare cases of CHL. BOB-1 and OCT-2 can be used.

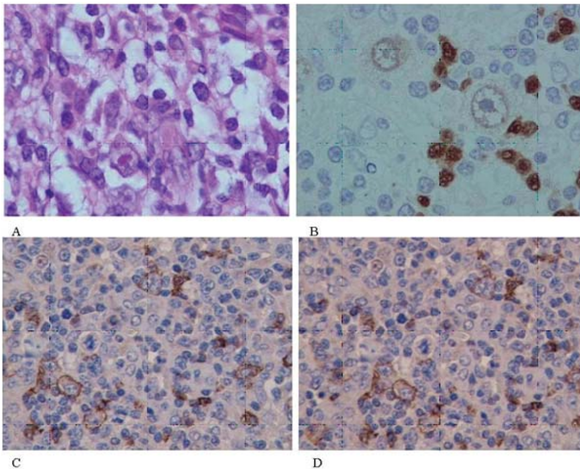

Fig. 3- Diffuse Large B cell Lymphoma
A. Morphologic feature, ×400 (H&E)
B.PAX-5+, there are weak positive nuclear reaction with blast cells and strong staining with reactive B cells (×400)
C.CD20+, blast cells show membranous reaction (×400)
D.CD79a+, blast cells show membranous reaction (×400)

PAX-5 and CD20 are useful and enough for the differentiation of DLBCL and ALCL. (8, 15, 23). In our study, this discriminative impact was confirmed.

Conclusion

There were 3 cases in our study, where the differentiation between CHL and ALK negative ALCL could not be achieved based on morphology and immunophenotyping alone. Additional PCR amplification revealed clonal T-cell receptor rearrangements in all three cases, and FISH analyses an additional *t* (2, 5) chromosomal translocation in one case and thus it was possible to make the diagnoses of ALCL in all three cases.

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