Primary testicular diffuse large B-cell lymphoma belongs to the nongerminal center B-cell-like subgroup: a study of 18 cases

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The most common type of primary testicular lymphoma is diffuse large B-cell type, which has the potential for aggressive clinical behavior. Diffuse large B-cell lymphoma can be further subclassified into two major prognostic categories: germinal center B-cell-like and nongerminal center B-cell-like. Such distinction is made possible using the immunohistochemical expression of CD10, Bcl-6 and MUM1. The aim of this study was to stratify primary testicular lymphoma of the diffuse large B-cell type according to this scheme. Immunohistochemical stains for CD10, Bcl-6 and MUM1 were performed on 18 cases of primary testicular lymphoma of diffuse large B-cell type. Subclassification was carried out as previously described where CD10 and/or Bcl-6 positivity and negativity for MUM1 were considered indicative of germinal center B-cell-like type and the opposite expression as nongerminal center B-cell-like type. The proliferative activity was determined using immunostaining with the Ki-67 antibody. Of 18 cases, 16 (89%) were found to belong to the nongerminal center B-cell-like type. Two cases (11%) were classified as germinal center B-cell-like type; one had a CD10-positive, Bcl-6-positive and MUM1-negative profile, and the other was CD10 negative, Bcl-6 positive and MUM1 negative. The former occurred in a 38-year-old patient who was human immunodeficiency virus positive. All the cases expressed high proliferative activity ($\geq 50\%$ Ki-67 labeling). We conclude that most (89%) primary testicular lymphomas of the diffuse large B-cell type belong to the nongerminal center B-cell-like subgroup and have high proliferative activity.

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Before the era of human immunodeficiency virus (HIV) infections, primary testicular lymphomas were estimated to comprise 3–5% of all testicular tumors, with tendency to occur in the elderly.^{1–4} However, more recent reports indicate a higher incidence and a broader age spectrum.^{5–7} In HIV-positive patients, the incidence of primary testicular lymphoma is increased, and it usually occurs at a younger age and sometimes is the initial manifesta-

tion of the disease, facts that may partially account for the changing demographics.^{8,9} It is believed that the overall incidence and mortality from primary testicular lymphomas is on the increase, a trend that has been found not only in North America but also in the United Kingdom, Italy and the Netherlands.^{5–11} Although they encompass a heterogeneous group of lymphomas, the most common primary testicular lymphoma is diffuse large B-cell lymphoma, which comprises more than 70% of the cases in most reported series.^{1–4} The other subtypes that are frequently reported include follicular lymphoma, plasmacytoma and lymphoblastic and Burkitt's-like lymphoma.^{1,12–19} The typical presentation is a testicular mass of variable size that is usually unilateral. However, bilateral involvement can occur at presentation and has been reported in up to 18% of the cases.^{3,10,20–22}

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Historically, the clinical behavior of testicular diffuse large B-cell lymphoma has been aggressive with frequent involvement of extranodal sites at presentation and at relapse.^{3,4,12} Seymour *et al*³ analyzed the survival status of 25 cases of primary testicular lymphoma of diffuse large B-cell type. They found that despite the fact that 86% of their patients had initial remission, recurrence and relapse increased year after year, and only 23% were in remission after 10 years. At relapse, involvement of the central nervous system and Waldeyer's ring is common and carries a poor prognosis.^{4,12,23}

Recently, diffuse large B-cell lymphoma of lymph node origin has been subdivided into three prognostically important categories by gene expression profiling using cDNA microarrays.^{24,25} These include: germinal center B-cell-like diffuse large B-cell lymphoma, activated B-cell-like diffuse large B-cell lymphoma and type 3. The latter two are together considered of non-germinal center origin. It is now accepted that the clinical outcome of germinal center-diffuse large B-cell lymphoma is better than nongerminal center-diffuse large B-cell lymphoma.^{24,26} These two prognostic categories showing germinal center and nongerminal center differentiation may also be identified by the immunohistochemical expression pattern for CD10, Bcl-6 and MUM1.²⁶ Germinal center-diffuse large B-cell lymphoma is assigned to those that express CD10 and Bcl-6 and nongerminal center-diffuse large B-cell lymphoma to those negative for CD10 and positive for MUM1. In this multicenter study, we investigated the immunoprofile of 18 primary testicular diffuse large B-cell lymphomas using the same approach. Expression of Bcl-2 was also performed and analyzed. In addition, semiquantitative measurements of the proliferative index were carried out using expression for Ki-67 (Mib 1 antibody). Correlation with available follow-up data was performed.

Materials and methods

Pathology reports and available material on primary testicular lymphomas seen at Wayne State University affiliated hospitals in Detroit, Michigan, Indiana

University affiliated hospitals in Indianapolis, Indiana, University of Jordan in Amman, Jordan and the Saudi Aramco Dhahran Medical Center in Dhahran, Saudi Arabia were retrieved and reviewed. Primary testicular lymphoma was defined as the presence of a testicular mass in the absence of lymph node or bone marrow involvement. The search yielded 34 cases, some of which dated back to 1977. However, only 18 cases were classified as diffuse large B-cell lymphoma and had enough material to perform the intended immunohistochemical stains. Standard well-controlled immunohistochemical stains for a panel of antibodies were performed using the modified avidin-biotin method as shown in Table 1. The cut sections were 4–6 μ m from formalin-fixed, paraffin-embedded tissue blocks. The sections were deparaffinized, rehydrated, blocked with 3% hydrogen peroxide, appropriately retrieved, incubated with the primary antibody, and followed with secondary detection system as recommended by the manufacturer. Tonsillar tissue was used as a control. Similar to the method of Hans *et al*,²⁶ the immunostains for CD10, Bcl-6 and MUM1 were evaluated semiquantitatively where positivity was determined if more than 30% of the tumor cells were immunoreactive. For each stain, 10 high-power fields were evaluated where an estimate of percent positive cells was recorded for each field and then the average was recorded. Bcl-2 protein expression was considered positive if there was either cytoplasmic or nuclear envelope staining. For Ki-67, immunoreactivity was evaluated semiquantitatively using estimated percent positive cells in 10 high-power fields and the average for each case was recorded. Only nuclear staining was considered positive for MUM1, Bcl-6 and Ki-67. Available clinical and follow-up data were retrieved and tabulated (Table 2).

Results

All the patients had stage I disease where only the testicular region was involved and there was no evidence of lymph node or bone marrow involvement. The age of the patients ranged from 19 to 87 years, with a mean age at presentation of 58 years

Table 1 A detailed list of the antibodies utilized in this study

Antibody	Clone	Company	Primary incubation method	Concentration
CD20	L 265	Ventana Medical Systems, Inc., Tuscon, AZ, USA	Benchmark for 16 min	RTU
KI-67 (Mib 1 equivalent)	K-2	Ventana Medical Systems, Inc., Tuscon, AZ, USA	Benchmark for 16 min	RTU
MUM1	MuM1p	Dako Inc., Carpinteria, CA, USA	Manual overnight at 4°C	1:20
CD 45	IF6	Ventana Medical Systems, Inc., Tuscon, AZ, USA	Benchmark for 16 min	RTU
CD 10	56 C6	Novocastra Laboratories Ltd, Norwell, MA, USA	Manual for 2 h at RT	1:20
Bcl-6	GI191E/A8	Ventana Medical Systems, Inc., Tuscon, AZ, USA	Benchmark for 32 min	RTU
Bcl-2	Bcl-2/100/D5	Ventana Medical Systems, Inc., Tuscon, AZ, USA	Benchmark for 32 min	RTU

RT, room temperature; RTU, ready to use.

Table 2 Summary of the clinical and immunohistochemical findings of 18 primary testicular lymphomas

Case #	Age	Site	Size (cm)	LCA	CD 20	CD 10	Bcl-6	Bcl-2	Mum-1	% Ki-67	Follow up (months)
1	64	R	3.2	+	+	—	—	+	+	75	AFOD (28)
2	60	L	6.0	+	+	—	—	+	+	75	DOD (96)
3	47	L	3.3	+	+	—	—	+	+	75	AFOD (58)
4	56	L	5.4	+	+	—	+	+	+	90	NA
5	36	L	3.5	+	+	—	—	—	+	70	DOD (7)
6	56	R	7.0	+	+	—	—	+	+	60	NA
7	87	L	NA	+	+	—	—	+	+	70	NA
8	67	L	3.0	+	+	—	—	—	+	70	NA
9	43	R	6.5	+	+	—	—	+	+	90	AFOD (70)
10	79	R	8.0	+	+	—	—	+	+	70	AFOD (60)
11	68	L	3.8	+	+	—	—	+	+	50	AFOD (39)
12	62	R	4.0	+	+	—	—	—	+	90	AFOD (23)
13	60	L	6.0	+	+	—	—	+	+	70	DOD (96)
14	78	B	4.0 each	+	+	—	—	+	+	70	AFOD (22)
15	77	R	7.0	+	+	—	—	+	+	70	DOD (24)
16	48	R	7.5	+	+	—	+	+	+	70	AFOD (24)
17	19	NA	NA	+	+	—	+	+	—	90	AFOD (20)
18	38	R	9.0	+	+	+	+	—	—	70	DOD (6)

AFOD, alive free of disease; NA, not available; DOD, died of disease; B, bilateral.

and a median of 60 years. In all the cases, a testicular mass was the presenting sign; seven involved the right testis, nine the left, one was bilateral and in one the laterality was not known. In 16 cases, the size was recorded, averaging 5.5 cm (range 3–9 cm). All cases were classified as diffuse large B-cell lymphoma as they infiltrated the interstitium in a diffuse pattern (Figure 1a and b) and the tumor cells expressed CD20 and leukocyte common antigen. The histological features of these cases were similar and no recognizable differences were appreciated among the cases from the four geographically distinct institutions. As shown in Table 2, of the 18 cases examined, 16 (89%) were found to belong to the nongerminal center B-cell-like type (Figure 2a–c). Two cases (11%) were classified as germinal center B-cell-like type. Case 17 had a CD10-negative, Bcl-6-positive and MUM1-negative profile, and case 18 had a CD10-positive, Bcl-6-positive and MUM1-negative immunophenotype (Figure 2e–g). The latter (case 18) occurred in a 38-year-old African-American patient who was HIV positive and the testicular mass was the initial presentation of his HIV status. Of these two cases, one was Bcl-2 positive (case 17) and the other was negative. Of the 16 cases that belonged to the nongerminal center B-cell-like type, 14 cases (88%) revealed Bcl-2 expression. The proliferative index, as assessed by evaluating the percentage of tumor cells expressing Ki-67 antibody, revealed strong nuclear immunoreactivity in all cases with a range of 50–90% (Figure 2d and h).

Follow-up survival status was available for 14 patients with a mean survival of 76 months (s.e. = 11, 95% CI = 54–98) and a median of 96 months. The Kaplan–Meier overall survival curve is shown in Figure 3. Because of the multi-institutional nature

Figure 1 (a) Diffuse intertubular infiltration by tumor cells of case 16 (H&E, $\times 100$). (b) High-power view from case 18 showing occasional infiltration of seminiferous tubules by lymphoma cells (H&E, $\times 200$).

Figure 2 The immunohistochemical panel for case 3 (upper row) with CD10 negative (a), Bcl-6 negative (b), MUM1 positive (c) and high proliferative activity as labeled by Ki-67 (d). This case belongs to the nongermlinal center B-cell-like subtype and similar findings were seen in the other 15 cases. The immunohistochemical panel for case 18 (lower row) with CD10 positive (e), Bcl-6 positive (f), MUM1 negative (g) and high proliferative activity as labeled by Ki-67 (h). This case belongs to the germinal center B-cell-like subtype.

Figure 3 The Kaplan–Meier overall survival curve for 14 patients with a mean survival of 76 months (s.e. = 11, 95% CI = 54–98) and median of 96.

of the study and the long period over which it occurred, treatment information was not retrieved.

Discussion

Similar to other series, we found that primary testicular diffuse large B-cell lymphomas usually present with a unilateral testicular mass with essentially equal distribution between right and left. The mean age of patients with primary testicular lymphomas has shifted in recent years to a younger age group, a recent observation that is noted in multiple countries.^{8,9} In our study, the median age was 60 years. In three previous studies, the median ages were reported as 67, 69 and 66 years, respectively.^{1–3} Although the number of patients in our study is smaller compared to these previous studies, the age differences using the Mann–Whitney *U*-test are statistically significant (*P*-value <0.01). However, due to our small sample,

interpretation of these differences should be done with caution.

As shown by gene expression studies and subsequently reproduced and confirmed by immunohistochemical stains, diffuse large B-cell lymphoma in general is a heterogeneous group that differs in clinical behavior.^{24–26} Many markers have been used to segregate the different groups in regard to their cell of origin and the impact on prognosis and clinical behavior.^{27–45} However, it is now accepted that the expression of CD10, Bcl-6 and MUM1 can be used to subclassify diffuse large B-cell lymphoma into germinal center B-cell-like and nongermlinal center B-cell-like groups. Thus, it has been shown that the combined expression, or lack thereof, of CD10, Bcl-6 and MUM1 is the best immunohistochemical approach to subclassify diffuse large B-cell lymphoma into two major prognostically different categories using the method of Hans *et al.*²⁶ Those with CD10 and/or Bcl-6 expression and lack of MUM1 have a germinal center B-cell-like phenotype and better overall survival; the other group, with a CD10-negative/Bcl-6-negative/MUM1-positive immunophenotype, has nongermlinal center B-cell-like differentiation and worse overall survival.^{24,26}

Yoshida *et al.*⁴⁶ used the method of Hans *et al* to subclassify 15 cases of primary diffuse large B-cell lymphomas of the breast and found that all cases had a nongermlinal center B-cell immunophenotype with a high proliferative rate and an anticipated poor prognosis. In our study, and similar to the observation of Yoshida *et al*, 16/18 (89%) of primary testicular diffuse large B-cell lymphomas belonged to the nongermlinal center group and all (18/18) expressed high proliferative activity. To our knowledge, this is the first study to investigate the immunophenotype of a series of primary testicular lymphomas with respect to their germinal center or nongermlinal center differentiation and the first to

demonstrate an overwhelming predominance of the latter.

One case in our group, case 18, revealed a germinal center B-cell-like phenotype and occurred in a patient who was positive for HIV. This patient presented with a testicular mass at the age of 38 years and clinically was thought to have seminoma. After the diagnosis of diffuse large B-cell lymphoma, an HIV test was performed and found to be positive. The patient died of septic shock 6 months later. Although this patient's lymphoma was classified as a germinal center B-cell-like phenotype, he was the one from the group with the shortest survival. This patient was noncompliant and HIV positive, factors that may explain his quick demise. The relationship between HIV and the germinal center B-cell-like phenotype of diffuse large B-cell lymphoma is not entirely clear at the present time. Carbone *et al*⁴⁷ investigated the different immunophenotypic features of HIV-associated lymphomas. Their non-Hodgkin lymphoma group included primary central nervous system lymphoma, primary effusion lymphoma, plasmablastic lymphoma of the oral cavity, diffuse large B-cell lymphoma, Burkitt lymphoma and immunoblastic lymphoma. They grouped the latter three together (total of 47 cases) and, using the Hans scheme, 55% (26/47) were germinal center B-cell-like type and 45% (21/47) nongerminal center B-cell-like type. However, the bulk of the germinal center B-cell-like type cases were Burkitt lymphomas. Therefore, the rate of nongerminal center B-cell-like lymphoma among the remainder is 88% (23/26), similar to our rate. Recently, Madan *et al*⁴⁸ performed hierarchical cluster analysis using scores of immunohistochemical stains for germinal center differentiation and activated B-cell markers on diffuse large B-cell lymphoma from two groups of patients, one with positive and the other with negative HIV status. They concluded, despite the overlap in their clusters, that diffuse large B-cell lymphomas have different immunophenotypes in patients with the acquired immunodeficiency syndrome (AIDS) compared to those without. They also concluded that definitive understanding of the pathogenesis of AIDS-related diffuse large B-cell lymphoma is still lacking. The other patient with germinal center B-cell-like type primary testicular lymphoma was the youngest patient in our series (19 years) and he is alive after 20-month follow up.

As an antiapoptotic factor, overexpression of Bcl-2 protein in lymphomas was shown to be associated with an aggressive behavior and shortened overall survival.^{49–53} Furthermore, recent investigation revealed that Bcl-2 overexpression in diffuse large B-cell lymphoma of the nongerminal center B-cell-like type in particular was associated with a shorter overall survival.⁵² In our study, Bcl-2 expression was seen in 89% of cases and 88% of nongerminal center B-cell-like-diffuse large B-cell lymphomas. It appears that Bcl-2 expression correlates with increased proliferative activity.

The median overall survival in our series was 96 months, which is longer than what is published in previous studies.^{3,4} As all our cases were stage I at the time of diagnosis in contrast to the aforementioned studies, it is likely that this discrepant finding in overall survival is a function of clinical stage.

In conclusion, most (89%) primary testicular lymphomas of the diffuse large B-cell type belong to the nongerminal center B-cell-like subgroup and all exhibit high proliferative activity. The vast majority (89%) express Bcl-2. The uncommon primary testicular lymphoma of germinal center B-cell-like type may correlate with a positive HIV status as seen in one of our cases.

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