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Primary testicular lymphoma: A strictly homogeneous hematological disease?

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Abstract. Primary testicular lymphomas display mostly aggressive diffuse large cell B-cell lymphomas, which could be further subclassified into germinal center B-cell-like and an activated B-cell phenotype via immunohistochemistry. A retrospective analysis of primary testicular lymphomas diagnosed at the Institute of Pathology, Salzburger Landeskliniken (SALK) between January 1997 and December 2008 was done. Immunohistochemical staining and complete clinical data evaluation was carried out and linked to overall survival time. We found 18 cases of primary testicular lymphoma diagnosed in elderly patients showing no side predilection and having an aggressive clinical behavior with short overall survival independent of treatment. The lymphomas could for the most be classified into diffuse large cell B-cell lymphomas [15/18 (83.3%)] showing a non-significant prevalence of activated B cell phenotype [9/15 (60%)] compared to the germinal centre phenotype [6/15 (40%)]. Two of the cases were mantle cell lymphomas consisting of the infrequent pleomorphic subtype. The survival analysis revealed no significant difference for any of the investigated antigens. Primary testicular lymphomas are for the most DLBCL, but subtype classification reveal molecular heterogeneity inside this lymphoma entity. A distinction between those subtypes is necessary because of different clinical behavior and treatment.

Introduction

Primary testicular lymphoma is a rare disease occurring for the most in elderly men. As only 1% of testicular neoplasms and about 5% of all lymphoma presentations are due to primary testicular lymphomas, most of the publications dealing with testicular lymphomas are case reports (1). Newer publications tried to characterize this rare testicular entity on larger series systematically in retrospective analyses (2-4). Patients usually present with enlargement of testis caused by a homogeneous tumor mass. Radiologically or clinically the suspicious mass cannot be differentiated between testicular cancer and a hematological lesion. Further histological analyses of these neoplasms mainly reveal diffuse large B-cell lymphomas (DLBCL). In a minority follicular lymphoma or mantle cell lymphomas are diagnosed (5). The prognosis of primary testicular lymphomas, especially of DLBCL is poor (6), as this entity has the tendency to spread to extranodular sites (7). Common sites for metastases are the contralateral testis and the central nervous system. More infrequent locations for metastases are the skin, lung, pleura and the Waldeyer's ring (6,7). Using gene and protein expression profiling, those nodular DLBCL can be further subdivided into an activated B cell (ABC) phenotype and a germinal centre (GC) pheno-type (8,9) which have different clinical outcomes (10,11).

Differently to previous studies dealing with primary testicular lymphoma (2,12) this retrospective analyses investigated the clinical outcome (overall survival) (OS) based on the expression pattern of hematological differentiation markers.

Materials and methods

Patient characteristics. A complete retrospective data query of the digital patient files of the SALK institutions were carried out to explore patients diagnosed with primary testicular lymphoma in the period covering 1997-2008. All the patients were admitted to hospital for surgery due to a newly diagnosed mass of the testis. According to Vitolo *et al* (1), lymphomas were stated as primary testicular lymphomas if the testicular lesion was the primary manifestation of the disease or the predominant site of involvement. Further clinical and radiological investigations were done to stage the lymphoma in accordance to the Ann-Arbor-Classification (13) and to evaluate the IPI (international prognostic index)

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Table I. Clinical characteristics of patients presenting with primary testicular lymphoma (n=18).

Case-ID	Age at presentation (years)	Site	Size (cm)	Diagnosis	Clinical stage	IPIS	Chemotherapy	Treatment	Survival time (months)
1	86.6	Left	6.5	DLBCL	I	2	None	Surgery	2.4
2	50.8	Left	5	DLBCL	I	1	CHOP	Surgery, chemotherapy, radiotherapy	Until now alive
3	39.7	Left	[c]	LNOS	n.a.	n.a.	Data not available	Data not available	Data not available
4	87.5	Left	4.4	ML	IV	2	chlorambucil, prednisolone	Surgery, chemotherapy	1.9
5	94.5	Left	6	DLBCL	IV	3	None	Surgery	2.5
6	87.8[a1]	Right	5.4	DLBCL	IV	2	R-CHOP	Surgery, Chemotherapy	11.6
7	88.3[a1]	Left	5.3	DLBCL	IV	2	R-CHOP	Surgery, chemotherapy	
8	63.3	Right	4.5	DLBCL	I	3	R-CHOP	Surgery, chemotherapy	26.5
9	60.5	Left	4.5	DLBCL	IV	5	R-CHOP	Surgery, chemotherapy	16.2
10	75.2[b2]	Right	6.5	DLBCL	IV	3	R-CHOP	Surgery, chemotherapy	48.5
11	75.2[b2]	Left	3	DLBCL	IV	3	R-CHOP	Surgery, chemotherapy	
12	63.2[a3]	Left	8	DLBCL	III	3	R-CHOP	Surgery, chemotherapy	15.6
13	71.3	Right	4.5	DLBCL	I	1	R-CHOP	Surgery, chemotherapy	Until now alive
14	80.3	Right	6.5	DLBCL	IV	4	R-CHOP	Surgery, chemotherapy	1.5
15	63.3[a3]	Right	5.5	DLBCL	III	3	R-CHOP	Surgery, chemotherapy, radiotherapy	See case-id 12
16	79.1	Right	5.2	ML	IV	2	R-COMP in with combination with methotrexate (intrathecal)	Surgery, chemotherapy	Until now alive
17	56.2[b4]	Right	5	DLBCL	IV	3	R-CHOP in combination with methotrexate, IMVP-Dexa, cytarabin (intrathecal)	Surgery, chemotherapy	Until now alive
18	56.2[b4]	Left	3.5	DLBCL	IV	3	R-CHOP in with combination methotrexate, IMVP-Dexa, cytarabin (intrathecal)	Surgery, chemotherapy	

DLBCL, diffuse large B-cell lymphoma; ML, mantle cell lymphoma; LNOS, lymphoma not otherwise specified; n.a., not applicable; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-COMP, rituximab, cyclophosphamide, liposomal doxorubicin, vincristine and prednisolone; IMVP-Dexa, ifosfamide, etoposide (VP-16), methotrexate, and dexamethasone. IPIS, international prognostic index. [a]Same patient with bilateral lymphoma on a second admission; [b]same patient with bilateral lymphoma at the same admission; [c]only biopsy.

Immunohistochemistry observations of cases with diffuse large B-cell lymphomas (n=15 of 18).

Case-ID	BCL-2	BCL-6	CD10	Mum1	FOXP1	AID	p53	Ki-67 (%)
1	**+**	**+**	**+**	**+**	**+**	**+**	**-**	**90**
2	+	-	-	+	+	-	+	85
5	**+**	**+**	**+**	**+**	**+**	**-**	**-**	**80**
6	**-**	**+**	**+**	**+**	**+**	**-**	**-**	**75**
7	**+**	**-**	**+**	**+**	**+**	**+**	**-**	**65**
8	+	-	-	+	+	-	-	80
9	+	-	-	-	+	-	+	70
10	**+**	**+**	**+**	**+**	**+**	**+**	**-**	**70**
11	**+**	**+**	**+**	**+**	**+**	**+**	**-**	**75**
12	+	-	-	-	-	-	-	65
13	+	-	-	+	+	+	-	70
14	+	-	-	+	+	+	+	65
15	+	-	-	-	+	-	+	70
17	-	+	-	+	+	+	-	85
18	-	+	-	+	-	-	-	80

Cases shown in bold are germinal centre phenotype.

or rather the age-adjusted IPI (14). Due to federal regulations of Austria all patients diagnosed at our Institute are reported to the Institute of Pathology at the University Hospital Salzburg of the Paracelsus Private Medical University after death. The study was performed in accordance with the guidelines of the local research ethics committee and with preoperative patients' informed consent.

Immunohistochemistry. Immunohistochemistry was done using routine diagnostic methods as published recently (15). In short, specimens were fixed in 5% buffered formalin before paraffin-embedded. To evaluate morphology, haematoxylin-eosin (HE) staining was used. For additional classification, immunohistochemical stainings were carried out using an autostainer system (Dako) according the manufacturer's recommendations. Antigen retrieval was performed by heat-induced epitope retrieval in pH 9.0 antigen retrieval buffer (Dako) at 95˚C for 60 min. The following monoclonal antibodies were applied to further characterize lymphoid infiltrates: CD3 [polyclonal rabbit (pr), dilution 1:200, Dako], CD5 [mouse monoclonal (mm), 1:25, NovoCastra], CD10 (mm, 1:20, NovoCastra), CD20 (mm, 1:200, Dako), CD30 (mm, 1:50, NovoCastra), CD79a (mm, 1:200, Dako), BCL-2 (mm, 1:100, Dako), BCL-6 (mm, 1:10, Dako), MUM1 (mm, 1:50, Dako), Forkhead Box P1 (FOXP1) (mm, 1:500, ACRIS Antibodies), Activation-induced Cytidine Deaminase (AID) (pr, 1:100, ACRIS Antibodies) as well as Ki-67 (mm, 1:500, Dako) and p53 (mm, 1:200, Dako). Tonsils and lymph node served as positive controls; control experiments were negative using phosphate-buffered saline replacement of primary or secondary antibodies and same processing as described above (not shown).

To exclude solid tumors of the testis (seminoma or non-seminoma testicular cancer) immunohistochemical staining with the antibodies PLAP (mm, 1:100, NovaCastra), ß-HCG (pr, 1:1000, Dako), AE1/AE3 (mm, 1:400, Dako) and AFP (pr, 1:1500, Dako) were done.

Interpretation of immunohistochemistry. Immunohistological staining of BCL-2, CD10, BCL-6, MUM1, FOXP1 and AID as well as of p53 was interpreted as positive if more than 30% of all cells displayed a positive signal (2). The expression of BCL-2 and AID (16) was positive if cytoplasm or nuclear envelope was stained positive. For expression of MUM1, FOXP1, BCL-6 and Ki-67 only a nuclear staining was considered as positive. Finally, for Ki-67 the percentage of the proliferating fraction was estimated. To further classify the diffuse large cell lymphoma (DLBCL) into GC or ABC phenotype the criteria of Hans *et al* (9) were used. In short, DLBCLs were regarded as GC phenotype if they were $CD10^+$ or $CD10^-$, $BCL\text{-}6^+$ and $MUM1^-$. All other cases were classified as ABC phenotype (in detail: cases with $CD10^-$ and either $BCL\text{-}6^-$, or $BCL\text{-}6^+$ and $MUM1^+$ expression pattern).

Statistical analysis. χ^2-test or Student's t-test was used to compare data of nominal or interval level. Survival data were analyzed using the Kaplan-Meier method and compared using a log-rank test. Crude survival curves and adjusted survival curves, taking into account the age of the patients at presentation, were done. In addition, multivariate analysis was carried out using Cox regression technique. Differences were regarded significant if the p-value was <0.05.

Results

Between 1997 and 2008 eighteen primary testicular lymphomas were diagnosed (Table I) at our institution. The median/mean age at time of surgery was 73.3/71.7 years

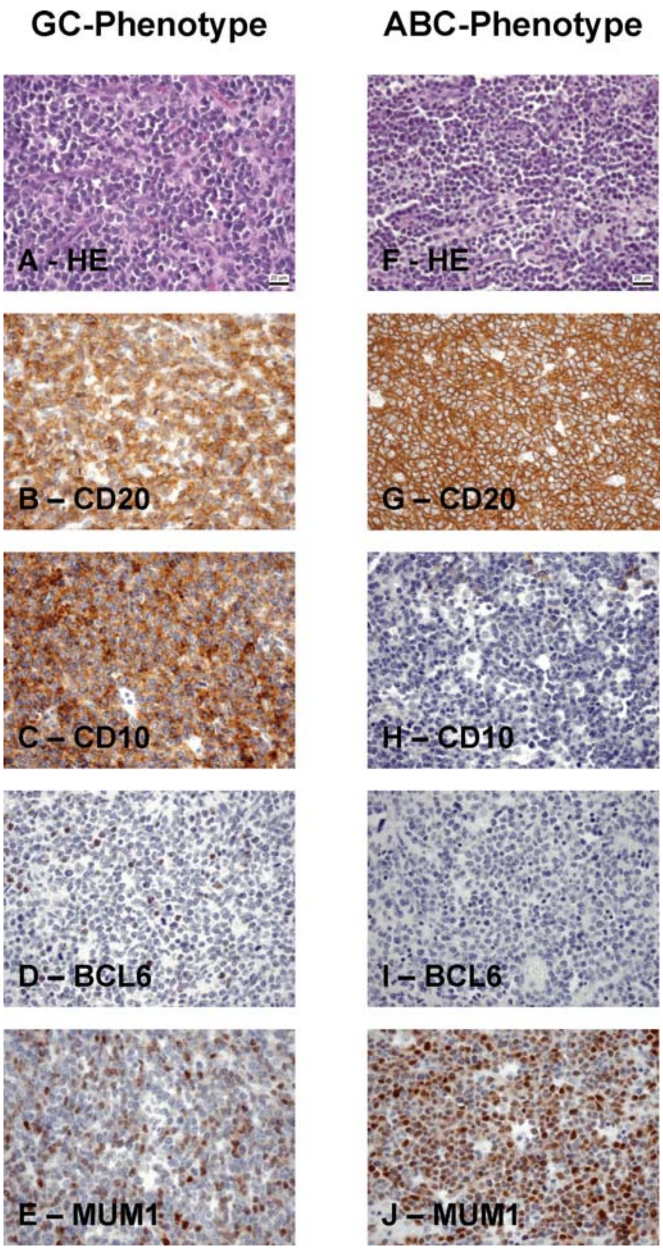

Figure 1. Representatively, a diffuse large B-cell lymphoma of the testis showing a germinal centre phenotype (A-E, case-Id #5) or an activated B cell phenotype (F-J, case-Id #13) (magnification, x400).

(range 39.7-94.5 years). Four patients [4/14 (28%)] displayed lymphomas of both testes, of which two patients presented with bilateral lymphoma at the first time of admission. Two patients developed another testicular lymphoma 6.4 months (case 6) and 9.3 (case 12) months later to primary diagnosis. No significant difference could be found in side distribution (right/left) or size of testicular lymphoma neither looking to all cases nor in subgroups ($p>0.05$, χ^2-test/t-test).

With immunohistochemistry using lymphatic panel markers (listed above) a diffuse large B-cell lymphoma (DLBCL) was diagnosed in 15 cases [15/18 (83.3%)]. The remaining three cases were classified as mantle cell lymphomas [2/18 (11.1%)] and one case [1/18 (5.6%)] as a lymphoma, which could not be classified further due to sparse biopsy material. Both mantle cell lymphomas consisted of heterogeneous atypical lymphocytes with large cleaved to oval nuclei representing a blastoid variant of mantle cell lymphomas. Additional immunohistochemical analysis excluded other co-existing testicular tumors like seminoma or non-seminoma as well as precursor lesions of intratubular germ cell neoplasia.

The primary treatment consisted of orchiectomy and adjuvant chemotherapy in [11/14 (78.5%)] cases applying mainly the R-CHOP (rituximab, cyclophosphamide hydroxydaunorubicin, vincristine, prednisone) chemoregimen (Table I). The clinical stage of disease and IPI-score ranged from I to IV (median: IV) and 1 to 5 (median: 3), respectively (Table I).

Further subclassification of the DLCBL-cases by expression pattern of CD10, BCL-2, BCL-6 and MUM1 confirmed six germ-cell (GC) phenotypes [6/15 (40%)] and nine activated-B-cell (ABC) phenotypes [9/15 (60%)] (Table II; Fig. 1). All cases of DLBCL with a GC phenotype stained positive for CD10, but none displayed solitary expression of BCL-6 and coexistent negativity of CD10 and MUM-1 (Table II). FOXP1 and AID was expressed in 6/6 (100%) and 4/6 (66.7%) cases of DLBCL with GC phenotype as well as in 7/9 (77.8%) and 3/9 (33.3%) cases of DLBCL with ABC phenotype ($p>0.05$, (χ^2-test) (expression pattern of AID see Fig. 2). The immunohistochemical expression of BCL-2 [12/15 (80%)] and Ki-67 (mean: 75.0 ± 8.0) was high, whereas p53-positivity was a rare event [4/15 (26.6%)] in the DLBCL-cases showing no statistical difference between the GC and the ABC phenotypes of DLBCL ($p>0.05$, χ^2-test, t-test). At clinical presentation cases with GC phenotype were significantly older than cases with ABC phenotypes ($p<0.01$, t-test), whereas the clinical staging and the IPI scoring revealed no statistical difference between GC and APC phenotypes ($p>0.05$, t-test).

The median/mean [95%-confidence interval (CI)] OS of all cases was 11.6 (95%-CI: 0-38.2)/14.1 (95%-CI: 3.9-24.2) months. Among the DLBCL subgroups, OS of GC phenotype patients was 2.5 (95%-CI: 0-11.6)/16.3 (95%-CI: 0-37.8) months and 15.6 (95%-CI: 1.2-30.0)/15.0 (95%-CI: 4.9-25.0) months ($p<0.05$, crude Cox rank test) of ABC phenotype, respectively. Noteworthy, patients with GC phenotype of DLBCL showed a trend for longer overall survival using age adjusted survival data analysis (Fig. 3). Further survival analysis was done for all molecular markers to differ between the GC and the ABC phenotypes. No difference in survival was found for expression of any of these individual markers for either crude or age adjusted survival data (Table III).

Discussion

In this study we present the complete clinical and immunohistochemical analysis of 14 cases presenting with primarily testicular lymphoma at the Institute of Pathology, SALK. These cases exist of elderly patients had for the most DLBCL being associated with a short overall survival time. These findings are somewhat in line, but also inconsistent to earlier observations. The primary testicular lymphomas showed no side predilection, are generally DLBCLs, and have a poor outcome (6). The overall survival is influenced by the intensity of the chemotherapeutical treatment which is for the

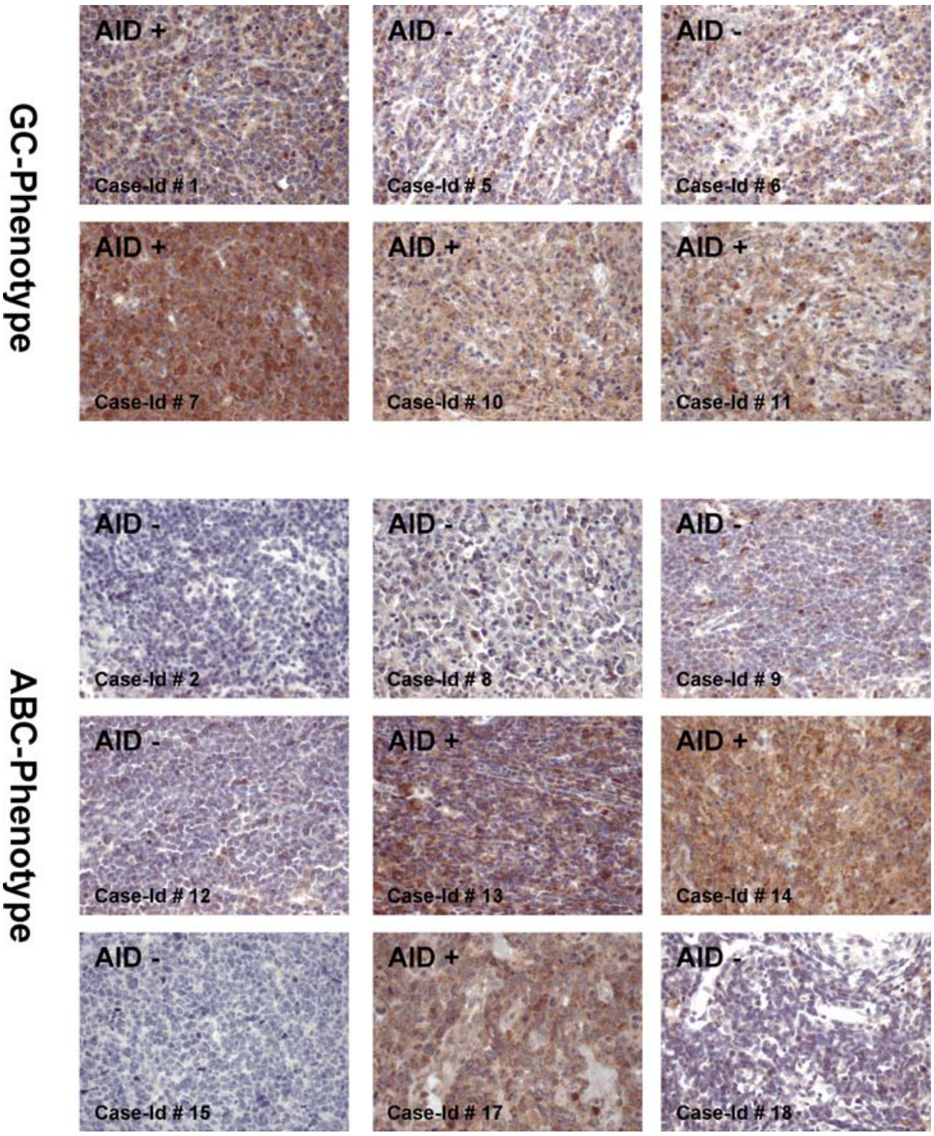

Figure 2. The protein AID was heterogeneously expressed inside diffuse large B-cell lymphoma of the testis with more association to the GC than to ABC phenotype (GC phenotype: case-id #1, #5, #6, #7, #10, #11; ABC phentoype: case-id #2, #8, #9, #12, #13, #14, #15, #17, #18; magnification, x400).

Table III. Tabular presentation of age-adjusted COX proportional hazards model showing the effect of the clinical and molecular markers of the primary testicular DLBC lymphoma.

Immunophenotype	Risk ratio	95%-CI	P-value
GC/ABC phenotype	1.017	0.982-1.054	0.348
Stage	1.001	0.994-1.008	0.739
IPSS	1.004	0.989-1.020	0.597
BCL-2	1.002	0.967-1.039	0.907
BCL-6	1.002	0.983-1.021	0.850
CD10	1.002	0.983-1.021	0.850
MUM-1	0.998	0.977-1.019	0.839
FOXP1	1.008	0.974-1.044	0.641
AID	1.001	0.979-1.022	0.960
p53	1.133	0.288-4.459	0.859
Ki-67[a]	1.008	0.988-1.029	0.433

[a]Ki-67, the expression of Ki-67 was classified as low for cases <80% and high for ≥80%.

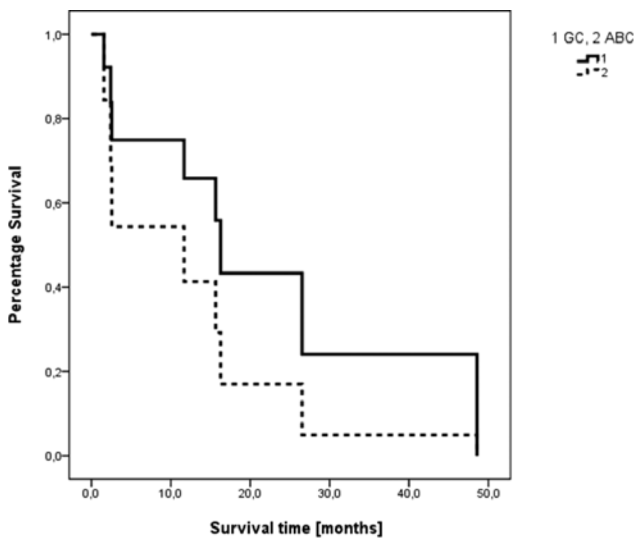

Figure 3. Age adjusted survival analysis comparing GC and ABC-types of primary testicular DLBC lymphomas.

most limited by co-morbidities of the elderly patients and by the toxicities of the drugs. In contrast to earlier reports this investigation discovered that the median age of patients at admission is changing to younger men (2). Additionally, previous published patient cohorts consist of patients with acquired immune defect (17,18). In our cases no HIV-infection could be detected. However, the statistical power of our study is reduced by the small sample size.

DLBCLs can be distributed into two different phenotypes by analyses of BCL-2, BCL-6 and Mum-1 protein expression: i) the germ-cell like (GC) phenotype ($CD10^+$ or $CD10^-$, BCL-6^+ and $MUM1^-$) with a better prognosis (overall survival); and into a ii) non-germinal, activated B-cell (ABC) phenotype ($CD10^-$ and either BCL-6^-, or BCL-6^+ and $MUM1^+$) with a worse overall survival. In contrast to the study of Abbadi *et al* (2) with 18 cases of mainly younger patients (median/mean age of 60/58 years) we could detect that 40% (6/15 of cases) showed a GC phenotype and 60% (9/15 of cases) an ABC phenotype. In the study of Abbadi *et al* (2) only cases with testicular lymphoma were excluded if any involvement of lymph nodes or bone marrow was present. Looking at other reports, the definition of primary testicular lymphoma was different and therefore showing other phenotype rates of DLBCLs (7). In our investigation, a heterogeneous differentiation of DLBCLs of primary testicular lymphomas was detected using immunohistochemistry and being in line with the observations of Booman *et al* (4). Interestingly, all cases with a GC-phenotype were positive for CD10 with parallel co-expression of MUM-1 being in line the with the used algorithm (9). In contrast Chang *et al* classified all DLBCLs with simultaneous expression of GC and ABC markers as an 'activated' GC-phenotype of DLBCLs (19) showing a likewise worse overall survival compared to the ABC-phenotype. This is supported by our observation that all of our DLBCL cases of the 'classical' GC phenotype express FOXP1, a typical marker of ABC phenotype. On the other hand, the expression of AID in DLBCLs was to a greater extent associated with the GC-phenotype than with the ABC-phenotype. This is an argument for a closer association to a GC differentiation (20). Nevertheless, heterogeneous results are published, if AID is directly linked to somatic hypermutation (16,21). Since we are not able to carry out somatic hypermutation analysis and cDNA microarray hybridization due to missing frozen tissue samples, we cannot exclude that all of our DLBCL with 'classical' GC phenotype are indeed of an ambiguous immunophenotype as concluded by Booman *et al* (4).

Additionally, our cases with testicular lymphoma had comparable expression pattern of markers like other extra nodal DLBCLs such as gastric and intestinal (12). In this context it is of interest that a study of gastric and intestine DLBCLs discovered that gastric DLBCLs displayed for the most the activated B-cell phenotype, whereas intestinal DLBCLs showed germinal-cell phenotype differentiation. This indicates a possible association with low grade gastric lymphomas of marginal zone type (12). Until now an association of pre-existing chronic inflammation and precursor lesions of primary testicular lymphomas could not be stated (1). Primary testicular mantle cell lymphoma is a rare event in our study. This lymphoma entity showed a characteristic expression of CD5 with nuclear co-expression of cyclin-D1. It is noteworthy, that cyclin-D1 expression could also be found in cases of B-CLL transformed into DLBCLs gaining highly specific chromosomal translocation t(11;14)(q13;q32) of mantle cell lymphoma during lymphoma progression (22). In our cases displaying Mantle cell lymphoma a pre-existing B-CLL could not be determined.

The median/mean (95%-CI) overall survival in our cases was 11.6 (95%-CI: 0-38.2)/14.1 (95%-CI: 3.9-24.2) months. This in line with prior findings where the clinical stage was evaluted (1) but it is shorter than in the series of Abadi *et al* (2) being a multi-institutional study. It is remarkable that primary testicular lymphoma has a bad prognosis being possibly linked to the immune-privileged site (23). Survival analysis using age adjusted Kaplan-Meier method showed no significant difference between GC and ABC phenotype of DLBCLs, but GC phenotype patients had a trend towards longer OS. Classical prognostic factors for DLBCLs such as BCL-2, Ki-67 and p53 were overexpressed throughout all DLBCLs with heterogeneous expression of p53 (24-26). Additionally, the expression of any individual markers (including BCL-2, Ki-67 and p53) for either crude or adjusted survival time could not identify any single prognostic marker. This decreases the clinical impact of these accepted prognostic criterions of DLBCLs (25). The statistical power might be influenced by our small sample size, so more primary testicular lymphomas of multiple institutes need to be analyzed with adequate clinical information.

In conclusion, in our study primary testicular lymphomas display, in contrast to other publications, heterogeneous subtypes of germ-cell like and activated-B-cell like types, whereby the GC-phenotype DLBCLs showed an activated B-cell-like subtype characteristics possibly being responsible for the worse survival overall (4). At this point, a re-classification of GC-phenotype primary testicular lymphomas according to the new WHO classification should be done using further molecular analyses such as somatic hypermutation and cDNA microarray hybridization (4) as

GH array analysis (27) to assess the management nent of patients suffering from primary testicular lymphoma.

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