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ORIGINAL ARTICLE

Pathomorphological and clinical features of diffuse large B-cell lymphoma in Southeastern Serbia – seven-year experience at a tertiary center

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Summary

Purpose: *This study aimed to comprehensively analyze pathological features of diffuse large B-cell lymphoma (DLBCL), an aggressive non-Hodgkin lymphoma, in patients from Southearstern Serbia, as well as to determine the frequency of extranodal disease and certain morphologic variants and immunophenotypic subtypes of DLBCL.*

Methods: *A total of 229 DLBCL cases that were diagnosed at the Center for Pathology, University Clinical Center, Nis, between January 2014 and December 2020 were analyzed.*

Results: *DLBCL constituted 32.2% of all lymphoid neoplasms diagnosed during the designated period. The majority of DLBCL had extranodal presentation (58.5%). Gastrointestinal system was the most common extranodal location, and stomach was the single leading site. The most frequent DLBCL immunophenotypic subtype was germinal center (GCB) in 47.2%, followed by non-GCB DLBCL in 39.7%, while in 5.2% DLBCL was classified as CD5-positive. DLBCL with nodal and extranodal initial location did not differ significantly in respect of immunophenotypic subtype. The vast majority of DLBCL showed centroblastic morphology (81.6%), 6.6% was immunoblastic, while anaplastic and rare variants constituted 3.1% and 8.2%, respectively. Anaplastic morphologic variant was the more frequently found in nodal DLBCL than in cases with extranodal presentation ($p \leq 0.05$).*

Conclusions: *The task of the pathologist is to provide the clinician with the most precise diagnosis required for therapeutic and prognostic stratification of patients, selection of adequate additional diagnostic procedures and application of modern personalized and targeted therapy. Accurate and precise diagnosis of DLBCL is crucial for the timely application of contemporary immunochemotherapy, which transformed DLBCL into a curable disease in over 60% of patients.*

Key words: *diffuse large B-cell lymphoma, diagnosis, pathology, extranodal, immunophenotype, morphology*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma with frequent extranodal presentation. It is the globally most common neoplastic lymphoproliferative disease that accounts for almost a third of all newly diagnosed lymphomas. DLBCL is a biologically and clinically heterogeneous disease with multiple subtypes in regard to micromorphology and immunophenotype, localization and clinical behavior, genetic and epigenetic alterations, therapeutic response and prognosis. Accurate and precise diagnosis of DLBCL is crucial for the timely application of therapy [1-3].

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Patients with DLBCL clinically present with progressive lymphadenopathy or extranodal disease. The most common extranodal sites affected by DLBCL include gastrointestinal tract, stomach at the first place, Waldeyer ring, bone, testes, spleen, salivary glands, liver, kidney, but virtually any organ can be affected. The median patient age is in the sixth and seventh decade, but it can occur in any age group, including children and young adults [1,4]. The clinical picture depends on the site of involvement, and extranodal presentation can mimic numerous other malignant or benign, mostly inflammatory conditions. This plethora and diversity of symptomatology (pain, bowel obstruction, intraabdominal or pelvic infiltrative mass) occasionally results in unnecessary radical surgical interventions and excision of organs or blocks of organs. Apparently justified surgical treatment in such cases does not cure the patient and can even cause long term disability and decrease in quality of life. The standard approach in the treatment of both nodal and extranodal DLBCL is rituximab-containing immunochemotherapy [5,6]. Therefore, thorough preoperative preparation and preliminary endoscopic or small tissue biopsy must be considered in case of any clinical suspicion of lymphoma.

The diagnosis of DLBCL requires an experienced hematopathologist. A representative, sufficiently large excision biopsy of the affected lymph node or extranodal tissue is required to make the diagnosis. Needle biopsies and incision tissue samples may suffice, however, occasionally do not provide enough tissue for proper assessment of histological architectural details. Routine diagnostic protocol includes careful micromorphological analysis and determination of tumor immunophenotype, which is essential for the differentiation of DLBCL subtypes. Routine immunohistochemical (IHC) analyses (possibly flow cytometry) are most often used for this purpose. Tumor cells in DLBCL express pan B-cell antigens (CD19, CD20, CD79α, PAX5), whose IHC verification excludes differential diagnostic options, including other large cell lymphomas, anaplastic carcinomas, melanoma and other neoplasms. For more precise subtyping it is necessary to use CD3, CD5, CD10, Bcl-2, Bcl-6, Ki67, IRF4/MUM1, CD30 and MYC. Most cases are classified as DLBCL NOS (not otherwise specified) and, in relation to morphology, are divided into centroblastic, immunoblastic and anaplastic subtypes, with several additional rare morphological variants [7,8].

The introduction of anti-CD20 monoclonal antibody (rituximab) into DLBCL therapy has led to dramatic advances in the treatment of this aggressive disease. The combined R-CHOP regimen, which includes five drugs (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) had transformed DLBCL into a curable disease in over 60% of the patients. However, a significant number of the patients is resistant to treatment with this protocol, and develop relapsing or progressive disease that is often fatal [2,6,9].

The aim of this study was to comprehensively analyze the pathological features of DLBCL in patients from Southearstern Serbia and to determine the frequency of extranodal disease, and certain morphologic variants and immunophenotypic subtypes of this condition.

Methods

A total of 229 DLBCL cases that were diagnosed in the Center for Pathology, University Clinical Center, Nis, between January 2014 and December 2020 were analyzed. The patient data were retrospectively collected from archived medical records. Baseline clinical characteristics were evaluated, including patient age, gender, and localization of lymphoma presentation.

Formalin-fixed and paraffin-embedded tissue sections stained with hematoxylin and eosin were used for the diagnosis and assessment of pathologic parameters. Pathologic diagnosis and classification of DLBCL were based on the current 2017 World Health Organization classification [1].

Immunohistochemical analysis comprised the following IHC panel in all of the cases: CD20, CD79α, PAX5, CD3, CD5, CD10, Bcl-2, Bcl-6, MUM1, Ki67. Only cases from latter years were stained to EBV (LMP1) and C-MYC due to unavailability of these IHC markers before 2019. Many DLBCLs were immunohistochemically assessed for expression of other antibodies, especially cases with extranodal presentation, anaplastic growth, sheeth-like or pseudoalveolar growth that were associated with broad differential diagnosis possibilities.

Hans immunohistochemical algorithm, based on the expression of CD10, BCL6, and MUM1, was used for classification of DLBCL in germinal center (GCB) and non-germinal center (non-GCB) immunophenotypic subtype [10].

Statistics

All data analyses were processed using the SPSS package, version 24.0 statistical software (SPSS, Chicago, IL). The associations of assessed features were tested by the x^2 test. A p value of ≤0.05 was considered indicative of statistically significant difference.

Results

During the seven-year period, a total of 710 lymphoma cases were diagnosed in the Center for Pathology, University Clinical Center, Nis. The diagnosis of DLBCL was established in 229 cases, which constitute 32.2% of all newly diagnosed lymphoid neoplasms.

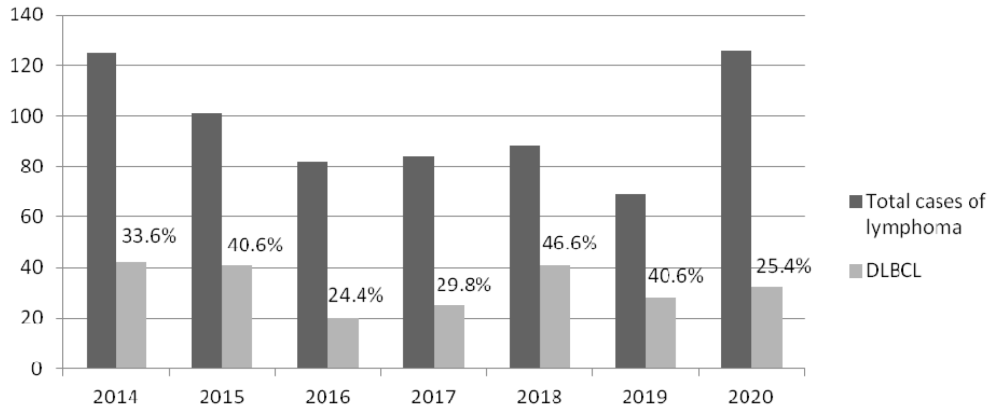

Figure 1. The chart represents the yearly distribution of a total number of lymphoma cases diagnosed in the University Center Nis during a seven year period (n=710), and a number of diffuse large B-cell lymphoma (n=229). The percentage of DLBCL cases of all diagnosed lymphomas is shown.

The percentage of annually diagnosed DLBCL in total lymphoma cases varied from 25 to 47%, with an average 34.4% (Figure 1). The majority of DLBCL in our center had extranodal presentation (134 cases; 58.5%). (Figure 2). Gastrointestinal system was the most common extranodal site, with stomach as the single leading location (23 cases; 10%), followed by urogenital tract, tonsils, CNS, spleen, and skin. Rare localizations for DLBCL diagnosis included ovary, gallbladder, and lungs (Tables 1 and 2). Nodal presentation was observed in 41.5%. Although many patients presented with progressive generalized lymphadenopathy, and less frequently as single nodal enlargement, the majority of the cases were diagnosed in cervical lymph node biopsies. Mediastinal or intraabdominal node acquisition requires more demanding surgical interventions, thus these were provided as diagnostic material in a modest number of cases, generally in patients with no enlarged palpable nodes.

The majority of the patients (88%) were diagnosed with DLBCL, NOS (not otherwise specified). There was 5 (2.1%) cases of primary mediastinal B-cell lymphoma, 13 patients (5.7%) had T-cell/histiocyte rich large B-cell lymphoma (THRLBCL), 2 cases (0.9%) were EBV-positive DLBCL, previously referred to as DLBCL of the elderly, while 6 (2.6%) cases were primary cutaneous DLBCL, leg type. Five patients (2.1%) had primary DLBCL of the CNS, while other patients initially diagnosed from brain biopsy had disseminated disease of DLBCL, NOS.

In regard of immunophenotypic subtype, most frequent DLBCL phenotype was germinal center (GCB) in 47.2%, followed by non-GCB DLBCL in 39.7%. In 5.2% DLBCL was classified as CD5-positive subtype (Table 3, Figure 3). Eighteen cases could not be classified based on immunohistochemical markers expression. DLBCL with nodal and extranodal initial location did not differ significantly in respect of immunophenotypic subtype.

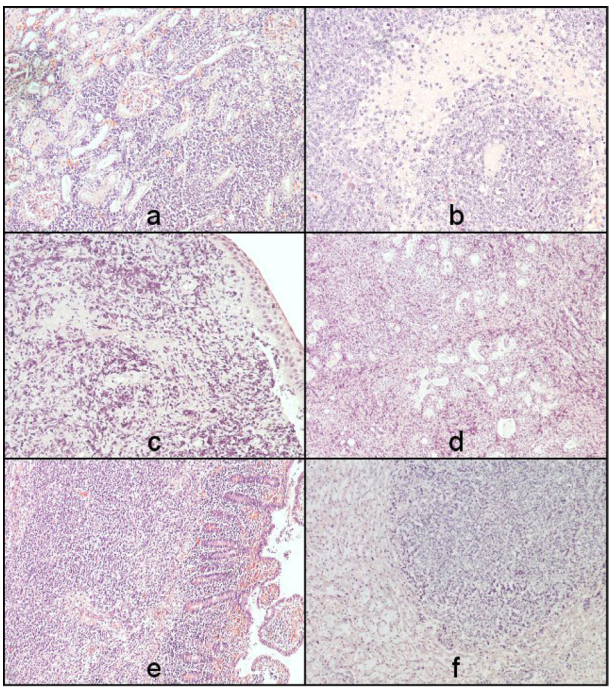

Figure 2. Extranodal DLBCL (HE stain): **(a)** DLBCL of the kidney: neoplastic blasts infiltrate kidney parenchyma; **(b)** Primary DCBCL of the CNS: atypical basophilic lymphoid infiltrate in white matter with characteristic perivascular cuffing; **(c)** DLBCL in nasopharynx, with preserved squamous epithelium on the surface; **(d)** lymphoid infiltrate encroaches minor salivary glands in DLBCL of the oral cavity; **(e)** intestinal wall effacement by DLBCL blasts; **(f)** nodular DLBCL infiltrate in the liver. Original magnification **(a,d)** ×100 and (b-d, f) ×200.

The vast majority of DLBCL showed centroblastic morphology (81.6%), 6.6% predominantly consisted of immunoblastic population, while an-

Table 1. Clinicopathological characteristics of newly diagnosed cases of diffuse large B-cell lymphoma

Year	*N (DLBCL)*	*Average patient age (yrs)*	*Female patients*	*%*	*Nodal localization*	*%*	*Extranodal sites*	*%*
2014	42	63.3	22	53.4	23	54.8	19	45.2
2015	41	58.4	22	53.7	18	43.9	23	56.1
2016	20	67.2	12	60.0	4	20.0	16	80.0
2017	25	64.1	10	40.0	10	40.0	15	60.0
2018	41	64.2	16	39.0	18	43.9	23	56.1
2019	28	62.4	11	39.3	9	32.1	19	67.9
2020	32	61.8	14	43.8	13	40.6	19	59.4
Total	229	62.7	107	46.7	95	41.5	134	58.5

aplastic and rare variants (signet ring cell variant, spindle cell type, variant with myxoid stroma and rosettes) constituted 3.1% and 8.2%, respectively. Anaplastic morphologic variant was significantly more frequently found in nodal DLBCL than in cases with extranodal presentation ($p \leq 0.05$).

Discussion

Non-Hodgkin lymphoma is a disease with the highest incidence in affluent countries, and was responsible for more than 544.000 new cases and 260.000 deaths in 2020 [11]. According to the global incidence, DLBCL is the most common lymphoid neoplasm, accounting for 30-40% of all lymphomas, and in our geographical region the situation is similar [12]. Our results show that DLBCL accounts for 32.2% of all newly diagnosed lymphomas in a 7-year period. The proportion of DLBCL slightly varied during the analyzed years, although the overall incidence of DLBCL in our region is in a slow and steady increase. A possible explanation for the relative decline of the proportion of DLBCL in the total number of diagnosed lymphoproliferative diseases may lie in significant changes in the classification of lymphomas and improved diagnostics. Better availability and enhanced applications of auxiliary methods for the diagnosis of hematopathological disorders immensely contribute to their classification accuracy, precise diagnosis and prognostic stratification.

Over half of DLBCL in our Center were diagnosed as extranodal disease. A recently published study investigated extranodal DLBCL in terms of clinical characteristics and outcomes for stage I disease in the rituximab era [9]. According to this study, DLBCL had extranodal presentation in two thirds of the patients, similarly to the frequency of extranodal DLBCL in our study group. Namely, we detected DLBCL in almost 60% of the cases in tissues other than lymph nodes, although it is traditionally considered that DLBCL is initially extranodal in 40% [1]. After a median follow-up period of 5.5 years, it was found that patients with stage I extranodal DLBCL had worse disease-free survival and shorter progression-free survival than patients with nodal disease at presentation [9]. Extranodal disease was linked to worse outcome compared with nodal disease [3,13,14].

Table 2. Structure of diagnosedcases of diffuse large B-cell lymphoma by initial primary nodal and extranodal locations

DLBCL diagnostic site	*n (%)*
Nodal localization	95 (100)
Cervical lymph nodes	55 (57.9)
Axillary lymph nodes	15 (15.8)
Inguinal lymph nodes	13 (13.7)
Abdominal lymph nodes	7 (7.3)
Mediastinal lymph nodes	5 (5.3)
Extranodal site	134 (100)
Waldeyer's ring	16 (11.9)
Maxillofacial region/oral cavity	17 (12.7)
Bone marrow	11 (10.4)
CNS/brain	13 (7.5)
Stomach	23 (17.1)
Colon/Intestine	8 (6.0)
Spleen	10 (7.5)
Liver, Gallbladder	7 (5.2)
Urogenital system	9 (6.7)
Skin	8 (6.0)
Retroperitoneum	5 (3.7)
Bone	3 (2.2)
Thyroid gland	3 (2.2)
Lung/bronchus	1 (0.7)

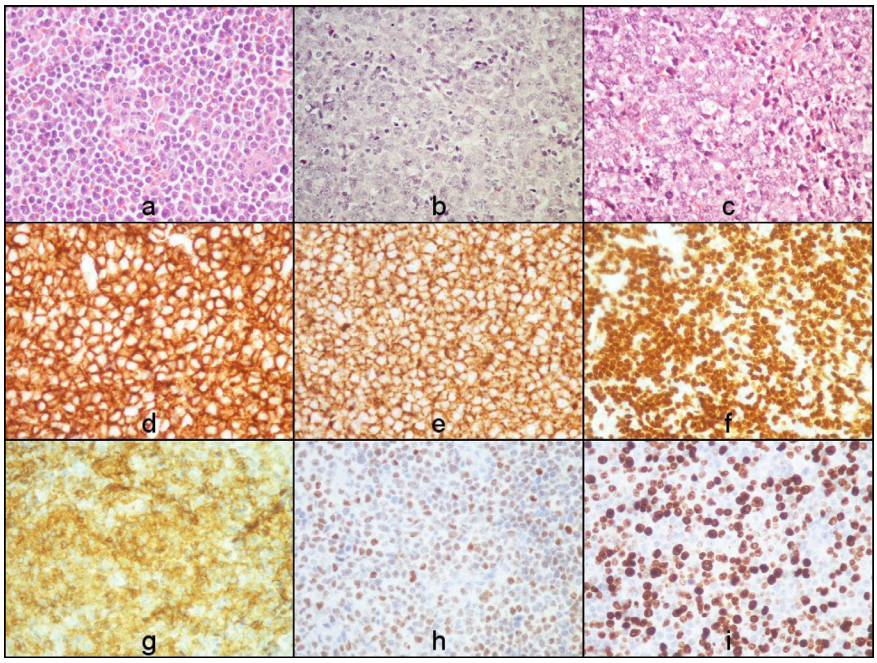

Figure 3. Morphology and immunohistochemical profile of DLBCL: **(a-c)** HE stain depicting variable histology of centroblastic DLBCL; **(d-f)** strong and diffuse, robust expression of B-cell markers CD20, CD79α and BSAP/PAX5 in DLBCL; **(g-i)** positive expression of CD10, Bcl-6 and MUM1, basic immunohistochemical markers used in widely accepted algorithms for classification of DLBCL in germinal center (GCB) and non-germinal center (non-GCB) immunophenotypic subtype. Original magnification ×400.

Table 3. Immunophenotypic classification and morphological subtypes in respect of initial location of DLBCL presentation

DLBCL	*Σ (n)*	*(%)*	*Nodal site (n=95)*	*Extranodal site (n=134)*	*p value*
Immunophenotypic subtype					
Germinal center (GCB)	108	47.2	42	66	>0.05
Non- germinal center (Non-GCB)	91	39.7	38	50	
CD5-positive subtype	12	5.2	8	7	
Unclassifiable	18	7.9	7	11	
Morphologic variants					
Centroblastic	187	81.6	76	119	0.03*
Immunoblastic	15	6.6	6	8	
Anaplastic	7	3.1	8	1	
Other/rare	20	8.7	5	6	

*x^2 test was performed; p≤0.05 was considered statistically significant.

Gastrointestinal tract is the most common site of DLBCL extranodal involvement [5]. DLBCL is most frequently diagnosed in stomach, followed by small intestine and colon. Moreover, DLBCL is the most common non-Hodgkin lymphoma of the digestive system. In our study, stomach was the number one individual extranodal organ of DLBCL diagnosis. Every fourth extranodal DLBCL arose in the digestive system. DLBCL in gastrointestinal tract arises *de novo* or from transformation of indolent lymphoma, usually MALT. *De novo* DLBC is usually BCL2 and CD10 positive, while cases arising from MALT are more often BCL2 and CD10 negative [5,15]. Contrary to other initially extranodal DLBCL, gastrointestinal DLBCL has better outcome after treatment with immunochemotherapy compared to other extranodal locations [13,14]. In addition to gastrointestinal, DLBCL with craniofacial, thyroid and localized bone presentation lack *MYD88* mutations and

have excellent prognosis with R-CHOP-based treatment protocol [16]. We made the initial diagnosis of DLBC from bone marrow samples in 10% of the cases. Involvement of bone marrow, as well as lung, kidney, or ovary, usually signifies disseminated disease and is associated with unfavorable prognosis. DLBCL diagnosed at these sites is often associated with concurrent *MYC* and *BCL2* or *BCL6* rearrangements [16].

The median time for occurrence of relapses in extranodal DLBCL was 37 months, and the most frequent sites were lymph nodes and CNS [9]. Extranodal DLBCL of certain locations share biologic and molecular characteristics with primary CNS DLBCL and show high propensity to involve CNS in any stage of the disease. These include DLBCL of testis, breast, uterus and skin, which frequently have high MUM1 expression, non-GCB phenotype and often carry *MYD88/CD79B* mutation. Therapeutic management of these lymphomas should include CNS prophylaxis to prevent recurrent disease [16].

A standard approach for all DLBCLs is rituximab-based immunochemotherapy. Surgical treatment is not required for any primary site. For some extranodal DLBCLs consolidation radiation therapy is recommended. Radiation therapy is linked to prolonged progression-free survival in primary bone and testis DLBCL [3,6,16].

Molecular subtypes of DLBCL, defined on the basis of cell of origin (COO), were found to be characterized by different genetic expression profile (GEP) and different response to therapy and overall survival [17]. The molecular classification DLBCL based on COO, which is mandatory according to the current WHO 2017 classification, identifies the type of germinal center B-cell (GCB) and activated B-cell (ABC) DLBCL, that involve different oncogenic mechanisms in pathogenesis. Molecular subtypes are important prognostic indicators in patients treated with the R-CHOP protocol, where the GCB molecular subtype significantly correlates with better response to therapy and longer overall survival. Since molecular profiling (GEP) of DLBCL is not available in routine pathological practice, the use of IHC algorithms is considered an acceptable substitute for a more accurate diagnosis of DLBCL. Namely, by using several IHC markers in pathological practice DLBCL can be classified into three immunophenotypic subtypes that correlate well with molecular subtypes, and whose determination requires more sophisticated molecular techniques. The IHC subtypes of DLBCL are: germinal-center (GCB) which shows great overlap with the GCB molecular subtype, postgerminal-center (non-GCB), DLBCL which correlates with the ABC molecular subtype and has a more aggressive clinical course and poorer therapeutic response, and CD5-positive [10,18]. In our study the most frequent DLBCL phenotype was GCB immunophenotypic subtype (47.2%), while non-GCB DLBCL was diagnosed in 39.7%. In 5.2% DLBCL was classified as CD5-positive subtype. This subtype is associated with poor prognosis and increased relapses in the central nervous system. Rituximab therapy significantly improves overall survival of patients with CD5+ DLBCL [18].

Non-GCB DLBCL is more often positive to CD30. Immunohistochemical expression of CD30, which is often associated with anaplastic morphology and is found in 10-20% of DLBCL, is an independent predictor of better prognosis in R-CHOP protocol therapy regardless of the COO subtype [19,20]. In addition, determination of IHC expression of MYC, BCL2, and BCL6 can identify a DLBCL fraction whose accurate diagnosis requires additional cytogenetic (FISH) or molecular (PCR) assays because these lymphomas may be associated with genetic alterations and rearrangement of MYC and BCL2 and/or BCL6 genes (double hit or triple hit high grade B-cell lymphomas) [21,22].

Increasing number of research indicates the great importance of the tumor microenvironment and the role of the complex milieu of stromal and immune cells that surround and are in constant interaction with tumor cells. In DLBCL, differential stromal gene signatures have been identified by GEP that correlate with good or poor outcome in patients treated with the R-CHOP protocol and are prognostic predictors independent of the COO profile. Future guidelines in the diagnosis of DLBCL are likely to consider and include this important aspect of the tumor [23,24].

Conclusion

DLBCL is the most common lymphoma in Southeastern Serbia and constitutes one third of all diagnosed lymphoproliferative diseases. More than half of 229 DLBCL cases diagnosed during a 7-year period in our Center had extranodal presentation. The most frequent DLBCL immunophenotypic subtype was GCB, followed by non-GCB, while CD5-positive DLBCL represented only 5.2%. The vast majority of DLBCL demonstrated centroblastic morphology. Anaplastic DLBCL showed preponderance of nodal growth.

The task of the pathologist is to provide the clinician with the most precise and accurate diagnosis required for therapeutic and prognostic

stratification of patients, selection of adequate additional diagnostic procedures and application of modern personalized and targeted therapy, which significantly improves the disease outcomes. Pathologists and clinicians are on a common task to precisely define the profile of high-risk disease and recognize DLBCL with a poor response to standard therapy in order to improve future personalized therapeutic approaches.

Conflict of interests

The authors declare no conflict of interests.

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