

Primary Diffuse Large B-Cell Lymphoma in Bladder

Subjects: **Oncology**

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Diffuse large B-cell lymphoma (DLBCL) represents the most frequent type of non-Hodgkin lymphoma. Globally, DLBCL is an aggressive disease, requiring an accurate *diagnosis* and prompt treatment. Primary urinary bladder lymphoma represents only 0.2% of extranodal non-Hodgkin lymphomas, whereas secondary involvement of the urinary bladder by a systemic lymphoma is a more common event. Despite being rare, DLBCL is considered to represent the predominant primary urinary bladder lymphoma.

Diffuse Large B-cell Lymphoma

urinary bladder

urinary tract

diagnosis

Treatment

1. Primary Diffuse Large B-cell Lymphoma (DLBCL) of the Urinary Bladder: Clinical Features

Although Kempton et al. as well as others stated that the most common type of primary urinary bladder (UB) lymphoma is mucosa-associated lymphoid tissue (MALT) lymphoma (44.4%) followed by diffuse large B-cell lymphoma (DLBCL) in 20% of cases ^{[1][2]}, in the recent study by Lontos et al., DLBCL was recognized to be the predominant histology comprising 60.3% of primary UB lymphoma, whereas MALT lymphoma was identified in 22.7% of UB lymphoma cases ^[3]. The study by Liu et al., evaluating 489 patients with urinary tract (UT)-DLBCL diagnosed between 1975 and 2016, is the first study analyzing the clinical features and survival outcomes for UT-DLBCL in a large population ^[4]. Liu et al. found that the majority of UT-DLBCL originates from the kidney (72.39% of cases), followed by the UB (24.95% of cases) ^[4].

Patients over 60 years are more likely to be affected by UT-DLBCL, with a mean age of 69 years at diagnosis. Patients with kidney DLBCL are younger (68 years) than those with UB-DLBCL (76 years). The increase in UT-DLBCL with aging is likely to be due to the decline of the immune system in older individuals, which is known as immune senescence; chronic inflammation, which increases with aging, is an additional factor predisposing to lymphoma development.

Kidney DLCL is the most frequent form in males (59.89%) and UB-DLBCL in females (59.84%)

Hematuria is the most common presenting symptom of UB-DLBCL; other symptoms are urinary frequency, dysuria, nocturia, pain in the lower abdomen, and frequent UT infections.

Most UB-DLBCL (56.56%) are diagnosed as stage 1, compared with only 25.71% of kidney DLBCL cases. Older age represents a poor prognostic factor in UT lymphomas in general [3], and in UT-DLBCL as well, the mortality of patients over 75 years is 2–3 times higher than that of younger patients [4], with a 5-year overall survival (OS) of 27.10% for patients over 75 years compared to 64.29% for patients under 60 years.

2. Diagnostic Approach for Primary Urinary Bladder Lymphoma

On the basis of nonspecific lower urinary tract symptoms (LUTS), the initial clinical impression for primary UB lymphoma may be of UT infection or urothelial carcinoma. A delay in diagnosis and treatment of UB lymphoma may be caused by the rather nonspecific symptomatology. Diagnosing a lymphoma in the UB relies on imaging techniques, cystoscopy, and a complete pathologic evaluation of UB biopsies.

Imaging techniques such as ultrasound, computed tomography (CT) scan, and magnetic resonance imaging (MRI) can provide detailed information about size and localization of any tumor in the UT, including the UB. CT and MRI features do not allow to suspect UB carcinoma rather than UB lymphoma. Cystoscopy and histological evaluation of biopsy samples play a major role in the diagnostic work-up of patients with a UB neoplasm. In particular, the diagnosis of UB lymphoma needs the histological evaluation of the tumor tissue with proper ancillary techniques such as immunohistochemical stainings and sometimes molecular testing.

When a diagnosis of DLBCL is made on UB biopsies, staging procedures are essential in order to establish if UB involvement is secondary to a systemic lymphoma, which is a more common event, or if the UB itself represents the primary site of disease occurrence.

The definition of primary versus secondary lymphoma involvement of extranodal sites such as the UB may be problematic. Following the criteria proposed by Krol et al., any lymphoma initially presenting at an extranodal site should be considered extranodal; similarly, in cases of disseminated diseases, if the extranodal component is clinically dominant, the lymphoma should be considered extranodal [5]. Due to its higher sensitivity, in the context of DLBCL, 18F-fluorodeoxyglucose positron-emission tomography with computed tomography (PET-CT) replaced CT scan for staging as well as for evaluating end of therapy response.

3. Histology, Immunophenotype, and Genetic Features of DLBCL, NOS

DLBCL represents a heterogeneous category and, in the current WHO classification, under the broad heading of DLBCL, there are several entities with distinct clinicopathological and biologic features [6][7][8].

DLBCL, NOS is the most common category of DLBCL, representing about 80–85% of cases [6]. Histologically, DLBCL, NOS consists of a diffuse proliferation of large-sized cells effacing the architecture of the involved tissue.

Neoplastic cells resemble either centroblasts (CBs) in 80% of cases or immunoblasts (IBs) in about 10% of cases. In rare cases of the so-called anaplastic variant, the cells have a bizarre, pleomorphic appearance.

Neoplastic elements are positive for pan B-cell markers (CD20, CD79 alpha, PAX5, CD22, and CD19) and CD45 and, usually, express surface immunoglobulin.

Based on gene expression profiling (GEP), DLBCL is classified into distinct prognostic subgroups as follows: the germinal center B-cell (GCB)-like subtype (40–50% of cases), the activated B-cell (ABC)-like subtype (50–60%) and unclassified subtype (10–15%) [9][10]. DLBCL of GCB subtype shows a gene signature characteristic of normal germinal center B cells with CD10 and *BCL6* expression, hypermutated immunoglobulin, and ongoing somatic hypermutation. DLBCL of ABC subtype has a gene signature of post-germinal center B cells with expression of MUM1/IRF4 and nuclear factor kappa B (NF-κB) activation. The cell of origin (COO) classification identifies distinct prognostic subgroups with the ABC subtype being associated with a worse outcome compared to the GCB subtype. The introduction of rituximab in DLBCL treatment has reduced the prognostic impact of COO classification, despite remaining the ABC subgroup less responsive to therapy [11][12][13][14].

Despite the prognostic significance of the GEP-based classification, the need for fresh or frozen (FF) samples makes GEP not easily applicable in routine daily practice; hence, several immunohistochemistry (IHC) algorithms have been proposed as a surrogate for GEP analysis [6][15][16][17]. The Hans and Tally algorithm, based on the expression of CD10, *BCL6*, and MUM1/IRF4, is the widest method applied [6][15]. However, the rate of concordance between GEP and immunohistochemical algorithms is variable (65–90%) and, in particular, subjectivity in immunohistochemical result interpretation, as well as variability in the immunohistochemical techniques performed, makes immunohistochemistry-based algorithms not completely reliable.

Subsequently, customized GEP mostly applied on the NanoString platform to formalin-fixed, paraffin-embedded (FFPE) samples has been found to represent a more reliable technique for predicting prognosis compared to the immunohistochemical algorithms [18].

In a subset of B-cell lymphomas, which, based on morphology and phenotype, would be regarded as DLBCLs-NOS, genetic rearrangements of *C-MYC*, *BCL6*, and *BCL2* have been identified by fluorescent in situ hybridization (FISH) analysis. These lymphomas are known as double-hit (DH) or triple-hit (TH) lymphomas and, in the 2017 WHO classification, they belong to the provisional category of High-grade B-cell lymphomas with *MYC* and *BCL2* or *BCL6* rearrangements, or both (HGBCL-DH/TH) [6]. This category shows a worse outcome and may require more intense chemotherapeutic strategies than standard R-CHOP regimen. In order to identify this more aggressive subset of lymphomas, FISH analysis should be applied to all DLBCL-NOS cases.

New insights into DLBCL pathogenesis have been recently provided by high-throughput techniques identifying genetic subtypes of DLBCL with distinct clinical behavior [19].

A total of four main genetic subtypes of DLBCL have been identified by Schmitz et al.; they have been designated N1 (on the basis of *NOTCH1* mutations), EZB (on the basis of *EZH2* mutations and *BCL2* translocations), MCD (because of the co-existence of *MYD88* and *CD79B* mutations), and BN2 (based on *BCL6* fusions and *NOTCH2* mutations) ^[19].

The BN2 and ENZ subtypes showed a better prognosis compared to the MCD and N1 subtypes ^[19].

4. EBV-Positive DLBCL, NOS and Primary Bladder Lymphoma

Of the DLBCL cases primarily occurring in the UB, the majority are DLBCL, NOS, with only two cases of EBV-positive DLBCL, NOS reported so far ^{[20][21]}.

EBV-positive DLBCL, NOS was initially described in patients older than 50 years and, hence, named EBV-positive DLBCL of the elderly in the 2008 WHO classification ^{[22][23]}. The terminology has been changed in the current WHO classification as the disease has been identified even in individuals younger than 50 years ^{[6][24][25]}. EBV-positive DLBCL, NOS may arise at nodal and extra-nodal sites. In younger patients the disease more often arises at nodal sites, presenting at lower stage and with a better outcome ^{[24][25]}. In older individuals the disease more often occurs at extranodal sites, following a worse prognosis ^[26].

Among the extranodal sites, skin, lung, and gastrointestinal tract (GIT) are more often involved ^{[26][27][28][29]}.

One of the two cases of EBV-positive DLBCL, NOS arising in the bladder occurred in a patient undergoing treatment for prostate cancer with enzalutamide and lymphoma spontaneously regressed after the cessation of this therapy ^[21]. This latter case would probably be reclassified as iatrogenic immunodeficiency-associated lymphoproliferative disorder (LPD), according to the current WHO classification ^[6].

A total of two morphological patterns are recognized in EBV-positive DLBCL, NOS: the monomorphic pattern and the polymorphic pattern. The former is composed of sheets of large-sized cells and is indistinguishable from the EBV-negative counterpart of DLBCL, NOS, unless in situ hybridization for EBV-encoded RNA (EBER) is performed.

The polymorphic or T-cell/histiocyte-rich large B-cell lymphoma-like pattern consists of scattered large-sized cells often resembling Hodgkin and Reed–Sternberg cells, admixed with inflammatory elements. Necrosis is often found. Of the two reported cases of EBV-positive DLBCL, NOS primarily arising in the UB, one showed a polymorphic pattern ^[20].

Overall, compared with the EBV-negative form, EBV-positive DLBCL, NOS more often shows a non-GCB phenotype. CD30 is often expressed with rare CD15 positivity. EBER expression in the majority (about 80%) of neoplastic cells is required for diagnosis ^{[6][23]}. Type II or type III latency pattern are usually observed in the disease, LMP1 expression being found in 2/3 of cases and EBNA2 in 1/3 of cases.

The genetic profile of EBV-positive DLBCL, NOS is different from its negative counterpart. In EBV-positive DLBCL, NOS, EBV itself favors the activation of the Janus kinase signal-transducer and activator of transcription (JAK-STAT) and NF-Kappa B pathways [30]. In addition, in the EBV-positive form, chromosomal gains at 9p24.1 contribute to increasing the expression of programmed cell death ligand 1 and 2 (PD-L1 and PD-L2), therefore, favoring immune tolerance and tumor evasion [26].

5. Treatment of Primary UB-DLBCL

The use of chemo-immunotherapy usually with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) scheme represents the mainstay of nodal DLBCL lymphoma treatment [31], and it is used in extranodal DLBCL as well. In the study by Liu et al., patients not undergoing chemo-immunotherapy had about twice the risk of death compared to patients receiving the treatment [4].

Unlike patients with nodal DLBCL obtaining benefit from radiation therapy, patients with UT-DLBCL had no survival benefits with radiotherapy.

Surgery resulted in being beneficial, especially for kidney DLBCL, whereas no beneficial effect was seen on patients with UB-DLBCL, possibly because of the morbidity and mortality associated with surgery in UB lymphomas.

In general, the category of DLBCLs can be cured with the R-CHOP regimen in more than 60% of cases and new therapeutic approaches have been used in cases in which R-CHOP failed [32]. Because of the rarity of UT-DLBCL, further studies are essential in order to better define the benefit of immunochemotherapy in terms of survival.

As a whole, the prognosis of patients with EBV-positive DLBCL, NOS is worse compared with patients with the EBV-negative counterpart [33]. Currently, in different types of tumors, the immune evasion by PD-L1 and PD-1 pathways represents a potential therapeutic target [34]. Compared to EBV-negative DLBCL, NOS, in the EBV-positive counterpart there is a higher rate of PD-L1 expression on neoplastic cells and cells of the microenvironment such as macrophages and dendritic cells [35][36]. Therefore, despite the R-CHOP regimen being used even in EBV-positive DLBCL, NOS, immunomodulatory therapies, targeting the axis PD-1/PD-L1 and drugs targeting the JAK-STAT and NF-κ pathways may represent attractive therapeutic options [25].

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