High grade B-cell lymphoma (HGBL) with gene rearrangements

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Diagnostic recommendation

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Definition and characteristics

Diffuse large B-cell lymphomas (DLBCL) show a MYC rearrangement in about 11%, of which 39% show an additional BCL2, 15% a BCL6 rearrangement and 12% both rearrangements (Rosenwald et al. 2019) and are classified as high grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements (HGBL). In about 20% of the cases, they are caused by transformation from follicular lymphoma.

Compared to DLBCL, HGBL more often present with high stage, extranodal and/or CNS involvement, B-symptoms, raised white cell count or increased LDH at initial diagnosis (Davis 2019).

Classification

The term HGBL was newly introduced in the WHO classification 2017 (Swerdlow et al. 2017). A distinction is made between two categories:

1. High Grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. With the exception of a few follicular or B-lymphoblastic lymphomas with these aberrations, these are lymphomas with an 8q24/MYC rearrangement in combination with a 18q21/BCL2 and/or a 3q27/BCL6 rearrangement.
2. High Grade B-cell lymphoma not otherwise specified (HGBL, NOS) encompasses cases with no MYC and BCL2 and/or BCL6 rearrangements. They have features intermediate between DLBCL and Burkitt lymphoma (BL) or appear blastoid, but histologically they cannot be clearly assigned to a diffuse large cell lymphoma.

In the past these lymphomas were called "double-hit lymphomas" or "triple-hit lymphomas". These cases show a variable morphology of DLBCL, Burkitt lymphoma and rarely follicular lymphomas.

The term BCLU lymphoma (B-cell lymphoma, unclassifiable), which was introduced in the WHO classification 2008 and which included the majority of cases that now belong to the category of HGBLs, is no longer recommended according to the WHO classification in 2017 (Swerdlow et al. 2008, Swerdlow et al. 2017). Rarely have "quadruple-hit lymphomas" (multiple hit lymphomas) been described in which a CCND1 rearrangement is also found in addition to MYC/BCL2/BCL6 (Haberl et al. 2016). However, these are not included in the WHO classification 2017.

Diagnose

Cytomorphology

The cytomorphology is a guiding principle for the control of the downstream diagnostics. For example, the assessment of the bone marrow smear provides an initial groundbreaking statement as to whether lymphoma infiltration exists or is possible. Cytomorphology and histology are also useful for assessing the degree of lymphoma maturity.

"Double hit" HGBL show a very variable morphology. The majority (69% for MYC/BCL2 and 85% for MYC/BCL6) have a DLBCL morphology (Li et al. 2016). In contrast, the morphology of HGBL-NOS is more similar to Burkitt's lymphoma with a partly very monomorphic population, but less strongly basophilic cytoplasm and mostly lacking vacuoles.

Immunophenotyping

HGBL are mature B-cell lymphomas with expression of CD19, CD20, CD79a and Pax5 and lack of TdT. Some double-hit HGBL cases lack surface immunoglobulin expression as detected by flow cytometry, possibly due to multiple translocations in the Ig locus. The absence of Ig expression should not be interpreted as proof of a precursor B-cell phenotype. CD10 and BCL6 expression is found in most of these lymphomas (75-90%), and IRF4/MUM1 is expressed in approximately 20% of the cases.

Chromosomal analysis

Cytogenetically the HGBL - besides the defining MYC, BCL2 or BCL6 rearrangements - usually show a complex karyotype with numerous numerical and structural aberrations. Frequent cytogenetic alterations include gains of chromosomal segments 1q, 3q, 7q, 8q, 12q, 18q and losses of 17p and 6q.

FISH

In HGBL, FISH is well suited to address the gene loci known to be affected in interphase cell nuclei. In addition, FISH can clarify and back up the results in complicated chromosomal alterations in addition to the classical metaphase analysis by means of painting or 24+ colour FISH.

Molecular genetics

Molecular genetic mutations were observed in the genes TP53 (21%) and MYC (24%) (Haberl et al. 2016). TP53 mutations were more frequent in MYC/BCL2 rearranged HBL than in those with MYC/BCL6 rearrangement (Gebauer et al. 2015). MYD88 mutation was rarely found. TOF3 mutations or the D3 deletion are more common in Burkitt lymphoma.

HGBL-NOS by definition do not have a combined MYC and BCL2/BCL6 rearrangement, about 20-35% show a single MYC rearrangement.
Prognosis

HGBL is mostly an aggressive lymphoma with an adverse prognosis, because the BCL2 and/or BCL6 additional rearrangements are an independent, negative prognostic factor for survival in the first two years. There is no prognostic difference between "double hit" (MYC/BCL2 or MYC/BCL6) and "triple hit" (MYC/BCL2/BCL6) HGBL. In contrast, the MYC rearrangement partner plays a role, since the negative effect could only be shown in a MYC-IG rearrangement and in a non-IG MYC rearrangement the survival corresponds to that of classical DLBCL and/or DLBCL with sole MYC rearrangement (Rosenwald et al. 2019). In addition, patients with a morphology similar to DLBCL seem to have a better prognosis than patients with a Burkitt-like morphology.

More intensive therapies (e.g., with EPOCH-R) lead to a longer progression-free survival (Petrich et al. 2014, Dunleavy et al. 2014). Due to the high proportion of CNS involvement of up to 45%, CNS prophylaxis should also be considered (Friedberg 2017). A further improvement of the prognosis could be achieved by using specific therapies such as BCL2 inhibitors or inhibitors of the bromodomain and extra-terminal protein family (BET inhibitors). The use of anti-CD19 CAR-T cells at an early stage such as the first relapse could also further improve the prognosis (Wang et al. 2020).

Recommendation

Important notes on the test material

If enlarged lymph accounts are clinically in the foreground, one of them should be removed and processed histologically and immunohistologically. Since an infestation of the bone marrow occurs frequently (59-94%), the diagnosis can often be made in the bone marrow. In addition, a CSF examination by immunophenotyping is recommended. It should be noted that the cerebrospinal fluid should be examined within four hours on the same day if possible, in order to obtain valid results. If such a quick shipment is not possible, TransFix® tubes containing an agent that stabilizes the surface antigens for about 72 hours can be shipped.

References