Morphology: diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), or Burkitt lymphoma

↓

BLYMF / B-Cell Lymphoma, FISH, Tissue *MYC* break-apart FISH probe (BAP) and *IGH/MYC* dual fusion FISH (D-FISH) probe

Branch 1: Positive for *MYC* rearrangement but negative for *IGH/MYC* fusion

↓

FISH: *BCL2* and *BCL6* BAP. Add *IGK/MYC* and *IGL/MYC* D-FISH only if pediatric patient and/or high suspicion for Burkitt lymphoma

↓

Negative for *BCL2* and *BCL6* rearrangements

↓

Morphology: DLBCL vs HGBCL vs Burkitt lymphoma

- HGBCL vs Burkitt lymphoma
  ↓
  IHC: CD10, CD43, BCL2, BCL6, MUM1, MYC
  ↓
  - CD10+, CD43+, BCL6+, MUM1−, MYC+, BCL2−
    ↓
    Probably Burkitt lymphoma, particularly if *IG/MYC* identified. Confirm with morphology and clinical.
  - Any other phenotype
    ↓
    HGBCL, not otherwise specified
- DLBCL
  ↓
  COO IHC (CD10, BCL6, MUM1) and double expresser IHC (BCL2 and MYC)

Branch 2: Positive for *MYC* rearrangement and/or positive for *IGH/MYC* fusion

↓

FISH: *BCL2* and *BCL6* BAP

↓

Positive for *BCL2* and/or *BCL6* rearrangements

↓

High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements

Branch 3: Negative for *MYC* rearrangement and negative for *IGH/MYC* fusion

↓

Morphology: DLBCL vs HGBCL

- DLBCL
  ↓
  Cell of origin (COO) immunohistochemistry (IHC) (CD10, BCL6, MUM1) and double expresser IHC (BCL2 and MYC)
- HGBCL, not otherwise specified

Burkitt lymphoma likely excluded, however,
- Consider CMAPT / Chromosomal Microarray, Tumor, Formalin-Fixed Paraffin-Embedded for 11q23 aberrancy and 11q24-ter deletion
- Consider D-FISH for *IGK/MYC* and *IGL/MYC* to exclude a *MYC* rearrangement completely, especially in a pediatric patient

COO IHC: CD10

- POSITIVE → Germinal center B-cell phenotype
- NEGATIVE → BCL6
  - POSITIVE → MUM1
    - POSITIVE → Non-germinal center B-cell phenotype
    - NEGATIVE → Germinal center B-cell phenotype
  - NEGATIVE → Non-germinal center B-cell phenotype

Double expresser IHC: BCL2 and MYC

- BCL2+ and MYC+ → Double expresser
- All others → Not a double expresser

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