Algorithms for WHO-5th Edition

(Selected algorithms with significant changes), Ver 3/23/2024

Myeloid: Leukemia (2022) 36:1703–1719; https://doi.org/10.1038/s41375-022-01613-1

Lymphoid: Leukemia (2022) 36:1720–1748; https://doi.org/10.1038/s41375-022-01620-2

Myeloblasts in BM (>5%)

A-Myeloblasts >20%->AML-> Order: std flow, cytogenetics, Rapid AML Therapeutic Panel,
PCR for bcr::abl1, NGS myeloid profile, for known APL->quant PCR PML::RARA,
for known t(8;21)->quant PCR RUNX1::RUNX1T1

(a) AML with defining genetic abnormalities:
PML::RARA, RUNX1::RUNX1T1, CBFB::MYH11, DEK::NUP214, RBM15::MRTFA, BCR::ABL1,
KMT2A rearrangement, MECOM rearrangement, NUP98 rearrangement, NPM1 mutation,
CEBPA mutation

(b) AML, myelodysplasia-related:
b1.Defining cytogenetic abnormalities:
Complex karyotype (≥3), 5q(-), Monosomy 7, 7q(-), 11q(-), 12p(-), Monosomy 13, 13q(-),
17p(-), Iso 17q, idic(X)(q13)

b2.Defining somatic mutations:
ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2

B-Myeloblast 5-19% -> Order: std flow, cytogenetics, Rapid AML Therapeutic Panel
(a) AML with defining genetic abnormalities (exceptions: bcr::abl1, CEBPA):
PML::RARA, RUNX1::RUNX1T1, CBFB::MYH11, DEK::NUP214, RBM15::MRTFA,
KMT2A rearrangement, MECOM rearrangement, NUP98 rearrangement, NPM1 mutation
(b) MDS with defining genetic abnormalities ->MDS (biTP53)
(c) MDS w/o defining genetic abnormalities ->MDS, morphologically-defined
(MDS-increased blasts, MDS-fibrosis)

Cytopenia with BM myeloblasts <5%

-Order: cytogenetics, MDS FISH, NGS myeloid profile
(a) MDS defining genetic abnormalities ->MDS (5q, SF3B1)
(b) MDS w/o defining genetic abnormalities ->MDS, morphologically-defined
(MDS-low blast, MDS-hypoplastic)
(c) No MDS defining genetic abnormalities, no dysplasia:
NGS Myeloid Profile detects presence of a somatic mutation at a variant allele frequency of
at least 2% (DNMT3A, TET2, JAK2, SF3B1, ASXL1, TP53, CBL, GNB1, BCOR, UZAF1,
CREBBP, CUX1, SRSF2, WILL2, SETD2, SETDB1, GNAS, PPM1D, BCORL1)
->Clonal cytopenia of undetermined significance (CCUS),
odds of progression to overt neoplasia are approximately 0.5-1% per year, similar to MGUS

Pancytopenia in pediatrics

-Order: Constitutional Cytogenetics, Bone Marrow Failure NGS Panel (vs other etiologies)
(peripheral blood, 2 x 4ml EDTA tubes, requires consent form)

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (MLN-TK)

-Order: Cytogenetics, Eosinophilia FISH Panel (PDGFRa, CHIC2, FIP1L1 (4q12); PDGFRb (5q33); FGFR1 (8p11); CBFB inv(16), t(16;16))

[Note that no tests available for: JAK2 rearrangement, FLT3 rearrangement, ETV6::ABL1 fusion, other defined tyrosine kinase fusions: ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; FGFR1OP::RET]

Differential Diagnosis of previous B-PLL includes:

(1) a variant of mantle cell lymphoma, positive for IGH:: CCND1;
(2) prolymphocytic progression of CLL/SLL, defined by CD5-positive non-mantle B-cell neoplasm with >15% prolymphocytes in the peripheral blood and/or bone marrow,
(3) other cases, classified as "splenic B-cell lymphoma/leukaemia with prominent nucleoli" [was also "hairy cell variant"]

Follicular Lymphoma:

1.Classic Follicular Lymphoma: grading (1,2,3A) is optional
2.Follicular Large B Cell Lymphoma: was FL Grade 3B
3.Follicular Lymphoma with uncommon features:
-Blastoid or large centrocyte variant: needs to be differentiated from LBCL with IRF4 rearrangement
-Diffuse growth variant: (+)CD23, (-)IgH::BCL2

Aggressive B-cell lymphomas (ABCL)

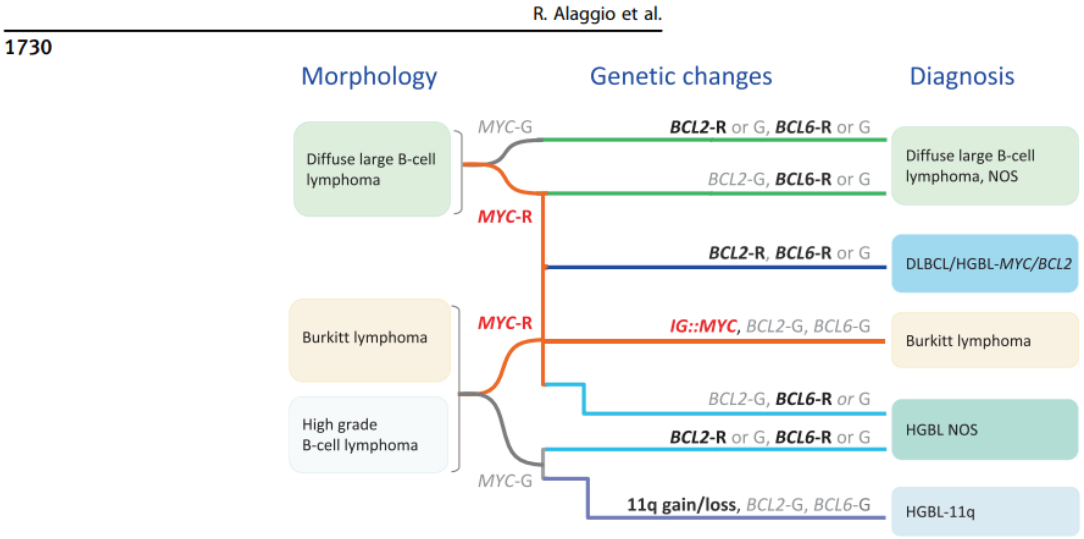

Fig. 4 Algorithm for classification of aggressive B-cell lymphomas in WHO-HAEM5 in the light of *MYC*, *BCL2* and *BCL6* rearrangement and complex 11q gain/loss patterns. HGBL high grade B-cell lymphoma, R rearrangement, G germline configuration.

Practical approach to signing out reports:

-Perform IHCs that include CD79a, CD5, CD10, bcl6, MUM1, bcl2, Myc, Ki67, bcl1
-Send for 3 FISH tests:
(a) High grade B cell lymphoma for myc, bcl2, bcl6 rearrangement
(b) 11q (gain/loss)
(c) bcl1 rearrangement

Assess morphology and IHC findings to sign out prelim reports:

1-If morphology is s/o BL, IHC s/o BL-> sign out as ABCL, most likely BL, pending FISH to r/o DLBCL/HGBL-myc/bcl2,

HGBL-NOS (myc/bcl6 or bcl2/bcl6),
HGBL-11q
(BL)

2-If morphology is s/o BL, IHC not s/o BL-> sign out as ABCL, pending FISH to r/o
DLBCL/HGBL-myc/bcl2,
HGBL-11q
BL
(HGBL, NOS: myc/bcl6 or bcl2/bcl6)

3-If morphology is s/o DLBCL with large size, IHC not s/o BL -> sign out as DLBCL, subtype GC/ABC, pending FISH to r/o
DLBCL/HGBL-myc/bcl2
(DLBCL)

4-If morphology is with intermediate size, IHC not s/o BL -> sign out as ABCL, pending FISH to r/o
DLBCL/HGBL-myc/bcl2
DLBCL
(HGBL, NOS: myc/bcl6 or bcl2/bcl6)

5-if morphology is s/o ABCL, IHC c/w MCL (pos bcl1)-> sign out as MCL (pleomorphic var)

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IHC:

BL is typically
(+) CD10, bcl6, ki67 (≥ 90%)
(-) CD5, (-/weak) bcl2

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FISH:

-BL: only pos for myc
-DLBCL/HGBL-myc/bcl2: myc+/bcl2+/bcl6(+/-)
-HGBL-NOS: (myc/bcl6) or (bcl2/bcl6)
-HGBL: 11q only

Legends:
s/o: suggestive of
ABCL: aggressive B cell lymphoma
DLBCL: diffuse large B cell lymphoma
BL: Burkitt lymphoma
HGBL: high grade B cell lymphoma
myc/bcl2: myc/bcl2 rearrangement
11q: 11q (gain/loss)
GC/ABC: germinal center/activated B cell
MCL: mantle cell lymphoma

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Three-part nomenclature for lymphoid proliferations and lymphomas arising in the setting of immune deficiency/dysregulation

Immune deficiency/dysregulation setting:
◦ Inborn error of immunity (IEI)
◦ HIV infection
◦ Posttransplant (solid organ/bone marrow)
◦ Autoimmune disease
◦ Iatrogenic/therapy-related
◦ Immune senescence

Viral association:
◦ EBV +/−
◦ KSHV/HHV8 +/−

Histological diagnosis:
◦ Hyperplasia (specify type)
◦ Polymorphic lymphoproliferative disorder
◦ Mucocutaneous ulcer
◦ Lymphoma (classify as for immunocompetent patients)

New conditions in plasma cell diseases

-Monoclonal gammopathy of renal significance (MGRS)
-Cold agglutinin disease (CAD)
-TEMPI syndrome (telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting)
-AESOP syndrome (adenopathy and extensive skin patch overlying a plasmacytoma)

LISTING OF MOLECULAR PANELS

NGS Myeloid Profile
Gene list: ABL1, ASXL1, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CBLC, CDKN2A, CEBPA, CSF3R, CUX1, DNMT3A, DDX41, ETNK1, ETV6, EZH2, FBXW7, FLT3, GATA1, GATA2, GNAS, GNB1, HRAS, IDH1, IDH2, IKZF1, JAK2 including V617F and Exons 12+14, JAK3, KDM6A, KIT, KRAS, MLL, MPL, MYD88, NF1, NOTCH1, NPM1, NRAS, PDGFRA, PHF6, PML, PPM1D, PTEN, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, STAT3, STAT5B, TET2, TP53, U2AF1, WT1, ZRSR2

BMF NGS panel
This panel evaluates genes associated with various forms of BMFS including Fanconi anemia, dyskeratosis congenita, and Diamond-Blackfan anemia
Gene list: AP3B1, BRCA2, BRIP1, CSF3R, CXCR4, DKC1, ELANE, ERCC4, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, G6PC3, GATA1, GATA2, GFI1, HAX1, LAMTOR2, LYST, MPL, NHP2, NOP10, PALB2, RAB27A, RAC2, RAD51C, RBM8A, RMRP, RPL11, RPL15, RPL26, RPL35A, RPL5, RPS10, RPS17, RPS19, RPS24, RPS26, RPS7, RTEL1, RUNX1, SBDS, SLC37A4, SLX4, SRP72, TAZ, TERC, TERT, TINF2, USB1, VPS13B, VPS45, WAS, WRAP53 (60 genes).