Changes in the Lymphoid Neoplasms : WHO 5th Edition

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INTRODUCTION

- The WHO-HAEM5 applies a hierarchical system for classification.
- It organises diseases in increasing order of specification.
- Category;(mature B cell)
- Family/class(large B cell lymphoma)
- Entity /type(diffuse large B cell lymphoma ,not otherwise specified)
- Subtype(Diffuse Large B cell Lymphoma, not other wise specified , germinal centre B cell like)

- WHO defines ESSENTIAL criteria and DESIRABLE criteria
- Essential criteria are minimal criteria to allow the diagnosis of thr entity as universally as possible
- Desirable criteria are those that aid in confirmation and refinement of the diagnosis and usually require the application of advanced techniques.

B CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS

- NEW ADDITIONS-Tumour like lesions with B cell predominance(covers non neoplastic B cell predominant lymphoid neoplasms involving lymph node or extranodal sites).
- CASTLEMAN's DISEASE- Unicentric Castleman's disease,
  Idiopathic multicentric Castleman's disease,
  HHV8 associated multicentric Castlemans disease.

- IgG4 related disease.
- Infectious mononucleosis
- Florid reactive lymphoid hyperplasia
- SLE

Table 1. WHO Classification of Haematolymphoid Tumours, 5th edition: B-cell lymphoid proliferations and lymphomas.

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Tumour-like lesions with B-cell predominance	
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma	*Not previously included*
IgG4-related disease	*Not previously included*
Unicentric Castleman disease	*Not previously included*
Idiopathic multicentric Castleman disease	*Not previously included*
KSHV/HHV8-associated multicentric Castleman disease	Multicentric Castleman disease

B LYMPHOBLASTIC LEUKEMIA /LYMPHOMA(B-ALL);NEW GENETICALLY DEFINED ENTITIES AND SUBTYPES

- The rare B-ALL with TCFB3::HLF fusion has been added.(aggressive disease course)

- B- ALL with BCR::ABL-1 like features is now an entity(previously a provisional entity)

- B- ALL with other defined genetic abnormalities- includes

B ALL with DUX4, MEF2D, ZNF384 or NUTM1 rearrangements, with IG::MYC fusion and with PAXalt or PAX5 p.P80R abnormalities.

Precursor B-cell neoplasms	
B-cell lymphoblastic leukaemias/lymphomas	
B-lymphoblastic leukaemia/lymphoma, NOS	(Same)
B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy	B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy	(Same)
B-lymphoblastic leukaemia/lymphoma with iAMP21	(Same)
B-lymphoblastic leukaemia/lymphoma with *BCR::ABL1* fusion	B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*
B-lymphoblastic leukaemia/lymphoma with *BCR::ABL1*-like features	B-lymphoblastic leukaemia/lymphoma, *BCR-ABL1*-like
B-lymphoblastic leukaemia/lymphoma with *KMT2A* rearrangement	B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); *KMT2A*-rearranged
B-lymphoblastic leukaemia/lymphoma with *ETV6::RUNX1* fusion	B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukaemia/lymphoma with *ETV6::RUNX1*-like features	*Not previously included*
B-lymphoblastic leukaemia/lymphoma with *TCF3::PBX1* fusion	B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-lymphoblastic leukaemia/lymphoma with *IGH::IL3 fusion*	B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3*
B-lymphoblastic leukaemia/lymphoma with *TCF3::HLF* fusion	*Not previously included*
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities	(Same)

MATURE B CELL NEOPLASMS

- Pre neoplastic and neoplastic small lymphocytic proliferations:

MBL and CLL/SLL remain, B-PLL is no longer recognized as an entity.

- WHO- HAEM5 recognizes three subtypes of monoclonal B cell lymphocytosis(MBL):
- Low count MBL or clonal B cell expansion- below $0.5X10^9$ /L
- CLL/ SLL type MBL-monoclonal CLL/SLL phenotype ,B-cell count> or = $0.5X10^9$/ L with no features diagnostic of CLL/SLL and total B cell countless than $5X10^9$/L.
- Non CLL/SLL type MBL-Any monoclonal non CLL/SLL phenotype Bcell expansion with no symptoms or features diagnostic of another mature Bcell neoplasm.

- The International Prognostic score for early stage CLL/SLL includes- IGHV mutation status, absolute lymphocyte count >15X10^9/ L , and presence of palpable lymph node.

- In the setting of transformation, RICHTER transformation is prefered over RICHTER SYNDROME.

- B-PLL no longer recognized.-reclassified into

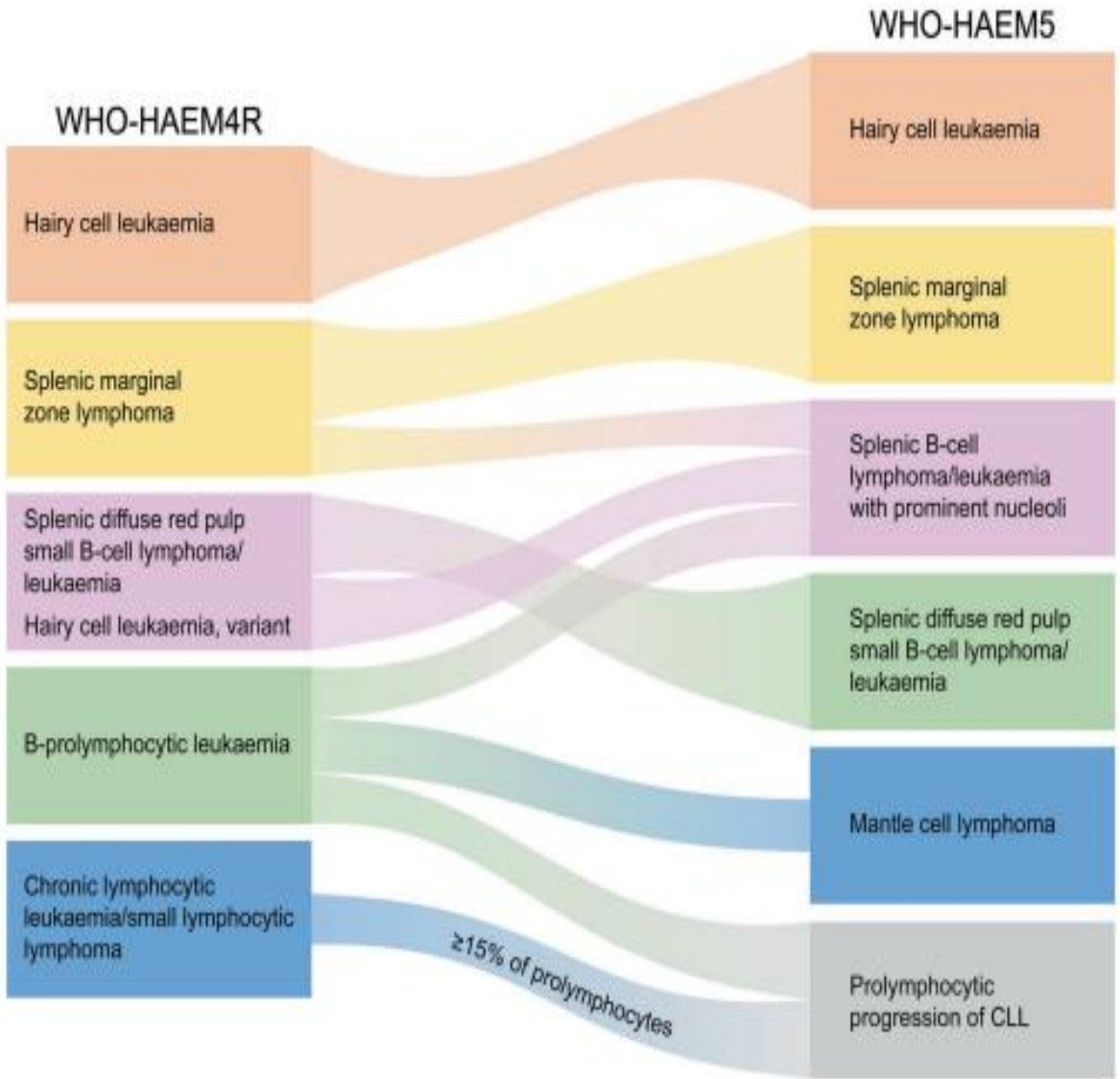
→A variant of mantle zone lymphoma with IGH:: CCND1

→Prolymphocytic progression of CLL/SLL(CD5 positive non mantle neoplasm with > 15% prolymphocytes in peripheral blood or bone marrow.

→splenic B cell lymphoma/ leukemia with prominent nucleoli.

- The term “Splenic B cell lymphoma/ leukemia with prominent nucleoli” now replaces “hairy cell leukemia variant” and “ CD5 negative B cell prolymphocytic leukemia.”

- negative for HCL markers- CD25, AnnexinA1, TRAP and CD123.


WHO-HAEM4R
Hairy cell leukaemia
Splenic marginal zone lymphoma
Splenic diffuse red pulp small B-cell lymphoma/ leukaemia
Hairy cell leukaemia, variant
B-prolymphocytic leukaemia
Chronic lymphocytic leukaemia/small lymphocytic lymphoma
≥15% of prolymphocytes
WHO-HAEM5
Hairy cell leukaemia
Splenic marginal zone lymphoma
Splenic B-cell lymphoma/leukaemia with prominent nucleoli
Splenic diffuse red pulp small B-cell lymphoma/ leukaemia
Mantle cell lymphoma
Prolymphocytic progression of CLL

MARGINAL ZONE LYMPHOMAS

- Paediatric nodal marginal zone lymphoma gets upgraded to a separate entity.

- Primary cutaneous marginal zone lymphoma – a separate entity.

- More emphasis on cytogenetic and mutational profiles and on anatomic sites.

FOLLICULAR LYMPHOMA

- CLASSIC FOLLICULAR LYMPHOMA- composed of centrocytes and centroblasts and harbour t (14:18) associated with IGH::BCL2 fusion.
- FOLLICULAR LARGE B CELL LYMPHOMA
- FOLLICULAR LYMPHOMA WITH UNCOMMON FEATURES.

Grading of follicular lymphoma , which is only pertinent to classic follicular lymphoma is no longer mandatory.

- The newly introduced subtype – uFL includes two subsets.
- 1) blastoid or large centrocyte variant→ inferior survival
- 2)FL with a predominant diffuse growth pattern→large inguinal tumour;

  IGH::BCL2- ABSENT

  CD23+

  STAT6 mutation+

MANTLE CELL LYMPHOMA-improved risk stratification.

- IN SITU MANTLE CELL NEOPLASM- rare , represents colonization of mantle zones of lymphoid follicles by B cells carrying an IG::CCND1 fusion.
- Occasional cases→cryptic reaarangements of IGK or IGL enhancers with CCND1
- Non nodal MCL- Lack of SOX11 expression,

  low Ki67

  higher somatic hypermutation

  lack of CD5 expression.

LARGE B CELL LYMPHOMAS

- DIFFUSE LARGE B CELL LYMPHOMA, NOS- Two main subtypes

1)Germinal centre B cell like(GCB) subtype: enriched for IGH::BCL2

2) Activated B cell Like(ABC) subtype:IRF4/MUM1,MYD88

- WHO HAEM5 recognises 17 specific entities as large B cell lymphomas.

Large B-cell lymphomas	
Diffuse large B-cell lymphoma, NOS	(Same)
T-cell/histiocyte-rich large B-cell lymphoma	(Same)
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements	High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
ALK-positive large B-cell lymphoma	(Same)
Large B-cell lymphoma with *IRF4* rearrangement	(Same)
High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration
Lymphomatoid granulomatosis	(Same)
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
Fibrin-associated large B-cell lymphoma	*Not previously included* (Previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
Fluid overload-associated large B-cell lymphoma	*Not previously included*
Plasmablastic lymphoma	(Same)
Primary large B-cell lymphoma of immune-privileged sites	*Not previously included*, encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4th edition (*plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis)*
Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
Intravascular large B-cell lymphoma	(Same)
Primary mediastinal large B-cell lymphoma	(Same)
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
High-grade B-cell lymphoma, NOS	(Same)

LARGE B CELL LYMPHOMAS OF IMMUNOPRIVELEGED SITES.

- A new umbrella term introduced for aggressive B cell lymphomas that arise as primary tumors in the CNS, the vitreoretinal compartment and the testes of the immunocompetent patients.

- They arise in immune sanctuaries created by their respective anatomical structures(the blood brain, blood retinal and blood testicular barriers), and immune regulation system within their respective primary sites.

FLUID ASSOCIATED LARGE B CELL LYMPHOMAS

- Distinct from Primary Effusion lymphomas.

- Adults, predominantly elderly without underlying immunodeficiency, who present with exclusive involvement of body cavities, most commonly the pleural cavity.

- Frequently have an underlying condition- Chronic heart failure, renal failure ,protein losing enteropathy or liver failure.

- KSHV/HHV – negative: EBV – positive in 13-30% cases.

MEDIASTINAL GREY ZONE LYMPHOMA

- B cell lymphoma with overlapping features between primary mediastinal B cell lymphoma and classic Hodgkin's lymphoma.

BURKITT LYMPHOMA-

From endemic, sporadic and immunodeficiency associated to

EBV positive and EBV negative Burkitt lymphoma.

LYMPHOID PROLIFERATION AND LYMPHOMAS ASSOCIATED WITH IMMUNE DEFICIENCY AND DYSREGULATION

- The new standardised nomenclature builds on an integrated approach to diagnosis that combines all relevant data into a reporting system as follows-

1) Histological diagnosis according to accepted criteria and terminology.
2) The clinical setting/ immunodeficiency background.
3) Presence or absence of one or more oncogenic virus(es).

Primary immunodeficiencies , associated with germline mutations have been renamed as " INBORN ERRORS OF IMMUNITY"

HODGKINS LYMPHOMA

- WHO HAEM5 continues to list nodular lymphocyte predominant Hodgkin's lymphoma under the family of Hodgkin's lymphoma.

- Caution to be excercised in immunodeficiency setting- mimickers to be considered-nodal T follicular helper cell lymphomas and lymphoproliferative disorders arising in immunodeficiency/dysregulation settings that may contain EBV positive HRS like cells.

- However NLPHL is more accurately called "NODULAR LYMPHOCYTE PREDOMINANT B CELL LYMPHOMA", since the neoplastic cells have a functional B cell program.

PLASMA CELL NEOPLASMS AND OTHER DISEASES WITH PARAPROTEINS

NEW ENTITIES

- MGRS: Monoclonal gammopathy of renal significance
- CAD: cold agglutinin disease
- TEMPI SYNDROME:characterised by telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection and intrapulmonary shunting.
- AESOP SYNDROME- (Adenopathy and extensive skin patch overlying a plasmacytoma)

The skin biopsies show diffuse hyperplasia of dermal vessels with surrounding mucin.

COLD AGGLUTININ DISEASE

- Autoimmune haemolytic anaemia mediated by monoclonal cold agglutinins and driven by an underlying clonlal B cell lymphoid proliferation not fulfilling criteria for a B cell lymphoma.

- The risk stratification model for IgM MGUS and non- IgM MGUS has been updated.

1) An abnormal free light chain ratio
2) IgA or IgM type MGUS
3) Serum M protein value>1.5g/dL.

T- CELL and NK cell LYMPHOID PROLIFERATIONS AND LYMPHOMAS

- TUMOUR LIKE LESIONS WITH T CELL PREDOMINANCE : A new class of tumour like lesions; includes-
- 1) indolent T lymphoblastic proliferation(ITLP)
- 2)Kikuchi Fujimoto disease
- 3) Autoimmune lymphoproliferative syndrome.

- NK- LYMPHOBLASTIC LEUKEMIA/LYMPHOMA is considered a provisional entity in WHO-HAEM4R , is not separately listed in WHO-HAEM5, due to lack of clear cut and reliable diagnostic criteria, and lack of published information on NK cell associated antigens.

PRIMARY CUTANEOUS T CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS

~~CUTANEOUS PERIPHERAL T CELL LYMPHOMA~~

- NEW ENTITIES-
- Primary cutaneous gamma/delta T cell lymphoma
- CD8 positive T cell lymphoproliferative disorder
- Acral CD8 positive T cell lymphoproliferative disorder
- CD4 positive small to medium Tcell lymphoproliferative disorder.

INTESTINAL T CELL AND NK CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS

- ~~INDOLENT T CELL LYMPHOPROLIFERATIVE DISORDER OF GI TRACT~~

- INDOLENT T CELL LYMPHOMA OF GI TRACT

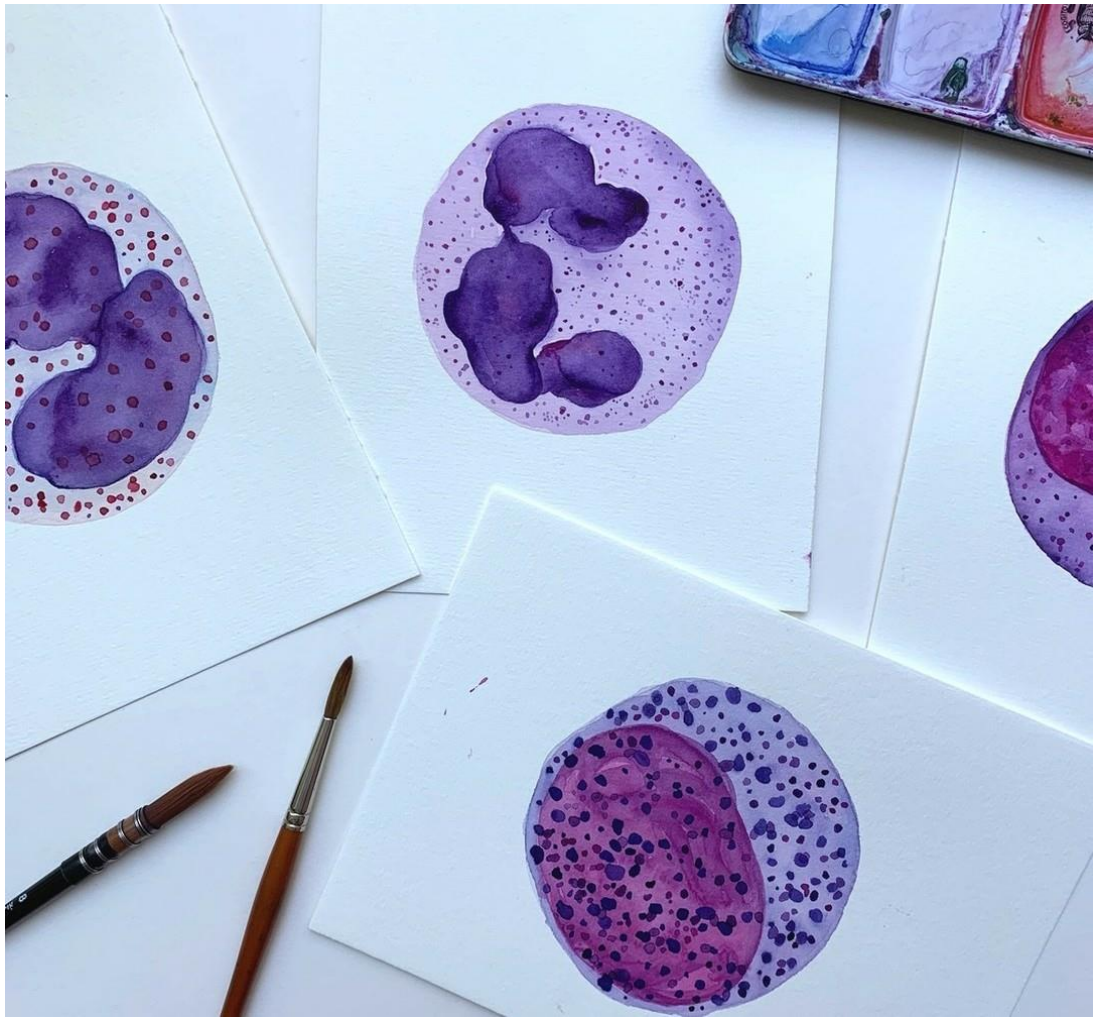
~~LYMPHOMATOID GASYROPATHY OF GI TRACT~~

INDOLENT NK CELL LYMPHOPROLIFERATIVE DISORDER OF GI TRACT.

STROMA DERIVED NEOPLASMS OF LYMPHOID TISSUES

Table 3. WHO Classification of Haematolymphoid Tumours, 5th edition: Stroma-derived neoplasms of lymphoid tissues.

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Mesenchymal dendritic cell neoplasms	
Follicular dendritic cell sarcoma	(Same)
EBV-positive inflammatory follicular dendritic cell sarcoma	Inflammatory pseudotumour-like follicular/fibroblastic dendritic cell sarcoma
Fibroblastic reticular cell tumour	(Same)
Myofibroblastic tumour	
Intranodal palisaded myofibroblastoma	*Not previously included*
Spleen-specific vascular-stromal tumours	
Splenic vascular-stromal tumours	
Littoral cell angioma	*Not previously included*
Splenic hamartoma	*Not previously included*
Sclerosing angiomatoid nodular transformation of spleen	*Not previously included*



"Reality is infinitely diverse(...and) reality resists classification"

Thank You!