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Rare hematologic tumors

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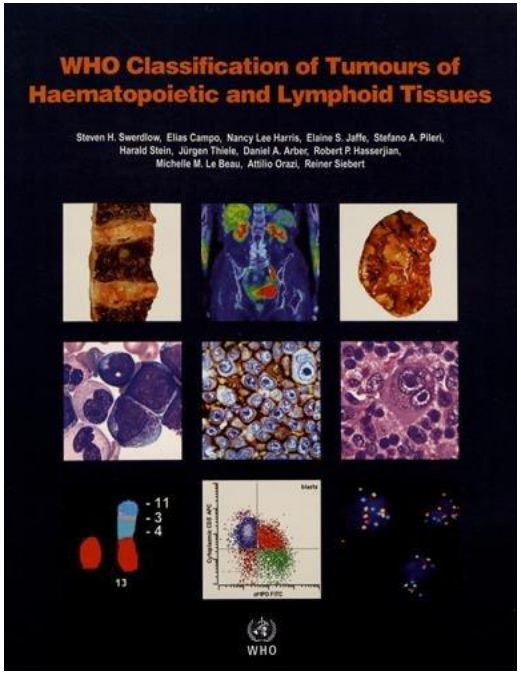
Disclosures

- Advisory boards: Abbvie, Celgene, Gilead, Janssen, Roche, Takeda, Servier
- Speaker: BMS, Celgene, Gilead, Janssen, Roche, Servier

WHO 2016 Classification of Tumours of Haematopoietic and Lymphoid Tissues

- The World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues was first introduced in 1999 and updated in 2008 and 2016.
- It defines each entity according to:
  - morphologic features
  - immunophenotype
  - genetic features
  - postulated normal counterpart
  - clinical features



Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition. IARC. Lyon, 2016

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The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Updates in WHO 2016 classification of lymphomas

- 37 changes in the new update in lymphoid malignancies
- Better characterization of previously known entities
- Recognition of new entities

Entity/category	Change
CLL/SLL	• Cytopenias or disease-related symptoms are now insufficient to make a diagnosis of CLL with $<5 \times 10^9$/L PB CLL cells. • Large/confluent and/or highly proliferative proliferation centers are adverse prognostic indicators. • Mutations of potential clinical relevance, such as *TP53*, *NOTCH1*, *SF3B1*, *ATM*, and *BIRC3*, have been recognized.
Monoclonal B-cell lymphocytosis	• Must distinguish low-count from high-count MBL. • A lymph node equivalent of MBL exists.
Hairy cell leukemia	• *BRAF* V600E mutations in vast majority of cases with *MAP2K1* mutations in most cases that use IGHV4-34 and lack *BRAF* mutation.
Lymphoplasmacytic lymphoma (LPL)	• *MYD88* L265P mutation in vast majority of cases impacting diagnostic criteria even though finding is not specific for LPL. • IgM MGUS is more closely related to LPL and other B-cell lymphomas than to myeloma.
Follicular lymphoma (FL)	• Mutational landscape better understood but clinical impact remains to be determined.
In situ follicular neoplasia	• New name for in situ follicular lymphoma reflects low risk of progression to lymphoma.
Pediatric-type FL	• A localized clonal proliferation with excellent prognosis; conservative therapeutic approach may be sufficient. • Occurs in children and young adults, rarely in older individuals.
Large B-cell lymphoma with *IRF4* rearrangement	• New provisional entity to distinguish from pediatric-type FL and other DLBCL. • Localized disease, often involves cervical lymph nodes or Waldeyer ring.
Duodenal-type FL	• Localized process with low risk for dissemination.
Predominantly diffuse FL with 1p36 deletion	• Accounts for some cases of diffuse FL, lacks *BCL2* rearrangement; presents as localized mass, often inguinal.

Swerdlow SH, et al. Blood 2016;127(20):2375-2390

Updates in WHO 2016 classification of lymphomas

Mantle cell lymphoma (MCL)	• Two MCL subtypes recognized with different clinicopathological manifestations and molecular pathogenetic pathways: one largely with unmutated/minimally mutated IGHV and mostly SOX11^{+} and the other largely with mutated IGHV and mostly SOX11^{-} (indolent leukemic nonnodal MCL with PB, bone marrow (BM), ±splenic involvement, may become more aggressive). • Mutations of potential clinical importance, such as *TP53*, *NOTCH 1/2*, recognized in small proportion of cases. • *CCND2* rearrangements in approximately half of cyclin D1^{-} MCL.
In situ mantle cell neoplasia	• New name for in situ MCL, reflecting low clinical risk.
Diffuse large B-cell lymphoma, NOS	• Distinction of GCB vs ABC/non-GC type required with use of immunohistochemical algorithm acceptable, may affect therapy. • Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma). • Mutational landscape better understood but clinical impact remains to be determined.
EBV^{+} DLBCL, NOS	• This term replaces EBV^{+} DLBCL of the elderly because it may occur in younger patients. • Does not include EBV^{+} B-cell lymphomas that can be given a more specific diagnosis.
EBV^{+} mucocutaneous ulcer	• Newly recognized entity associated with iatrogenic immunosuppression or age-related immunosenescence.
Burkitt lymphoma	• *TCF3* or *ID3* mutations in up to ~70% of cases.
Burkitt-like lymphoma with 11q aberration	• New provisional entity that closely resembles Burkitt lymphoma but lacks *MYC* rearrangement and has some other distinctive features.
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* translocations	• New category for all "double-/triple-hit" lymphomas other than FL or lymphoblastic lymphomas.
High-grade B-cell lymphoma, NOS	• Together with the new category for the "double-/triple-hit" lymphomas, replaces the 2008 category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU). • Includes blastoid-appearing large B-cell lymphomas and cases lacking *MYC* and *BCL2* or *BCL6* translocations that would formerly have been called BCLU.

Swerdlow SH, et al. Blood 2016;127(20):2375-2390

Updates in WHO 2016 classification of lymphomas

T-cell large granular lymphocyte leukemia	• New subtypes recognized with clinicopathologic associations. • *STAT3* and *STAT5B* mutations in a subset, latter associated with more clinically aggressive disease.
Systemic EBV$^+$ T-cell lymphoma of childhood	• Name changed from lymphoproliferative disorder to lymphoma due to its fulminant clinical course and desire to clearly distinguish it from chronic active EBV infection.
Hydroa vacciniforme–like lymphoproliferative disorder	• Name changed from lymphoma to lymphoproliferative disorder due to its relationship with chronic active EBV infection and a spectrum in terms of its clinical course.
Enteropathy-associated T-cell lymphoma (EATL)	• Diagnosis only to be used for cases formerly known as type I EATL, typically associated with celiac disease.
Monomorphic epitheliotropic intestinal T-cell lymphoma	• Formerly type II EATL; segregated from type I EATL and given a new name due to its distinctive nature and lack of association with celiac disease.
Indolent T-cell lymphoproliferative disorder of the GI tract	• New indolent provisional entity with superficial monoclonal intestinal T-cell infiltrate, some cases show progression.
Lymphomatoid papulosis	• New subtypes described with similar clinical behavior but atypical histologic/immunophenotypic features.
Primary cutaneous γ δ T-cell lymphoma	• Important to exclude other cutaneous T-cell lymphomas/lymphoproliferative disorders that may also be derived from γ δ T cells such as mycosis fungoides or lymphomatoid papulosis.
Primary cutaneous acral CD8$^+$ T-cell lymphoma	• New indolent provisional entity, originally described as originating in the ear.

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Updates in WHO 2016 classification of lymphomas

Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder	• No longer to be diagnosed as an overt lymphoma due to limited clinical risk, localized disease, and similarity to clonal drug reactions. • Remains a provisional entity.
Peripheral T-cell lymphoma (PTCL), NOS	• Subsets based on phenotype and molecular abnormalities being recognized that may have clinical implications but are mostly not a part of routine practice at this time.
Nodal T-cell lymphomas with T-follicular helper (TFH) phenotype	• An umbrella category created to highlight the spectrum of nodal lymphomas with a TFH phenotype including angioimmunoblastic T-cell lymphoma, follicular T-cell lymphoma, and other nodal PTCL with a TFH phenotype (specific diagnoses to be used due to clinicopathologic differences). • Overlapping recurrent molecular/cytogenetic abnormalities recognized that potentially could impact therapy.
ALK^- anaplastic large-cell lymphoma	• Now a definite entity that includes cytogenetic subsets that appear to have prognostic implications (eg, 6p25 rearrangments at *IRF4/DUSP22* locus).
Breast implant–associated anaplastic large cell lymphoma	• New provisional entity distinguished from other ALK^- ALCL; noninvasive disease associated with excellent outcome.
Nodular lymphocyte–predominant Hodgkin lymphoma	• Variant growth patterns, if present, should be noted in diagnostic report, due to their clinicopathologic associations. • Cases associated with synchronous or subsequent sites that are indistinguishable from T-cell histiocyte-rich large B-cell lymphoma (THRLBCL) without a nodular component should be designated THRLBCL-like transformation.
Lymphocyte-rich classical Hodgkin lymphoma	• Features recognized that are intermediate between NLPHL and other types of classical Hodgkin lymphoma.
Erdheim-Chester disease	• Should be distinguished from other members of the juvenile xanthogranuloma family; often associated with *BRAF* mutations.
Other histiocytic/dendritic neoplasms	• Clonal relationship to lymphoid neoplasms recognized in some cases.

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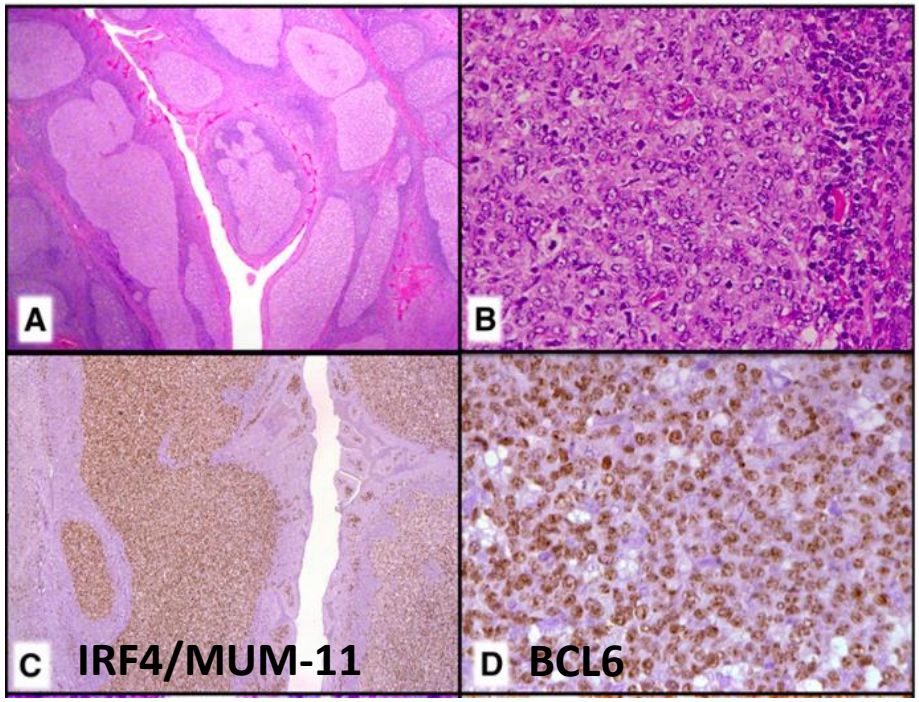
Large B-cell lymphoma (LBCL) with IRF4 rearrangement

- Occurs most commonly in children and young adults
- Most typically occur in Waldeyer ring and/or cervical lymph nodes and are low stage.
- May have a follicular, follicular and diffuse, or pure diffuse growth pattern
- Strong IRF4/MUM1 expression is seen usually with BCL6 and a high proliferative fraction.
- Most cases have IG/IRF4 rearrangements
- Lack BCL2 rearrangements.



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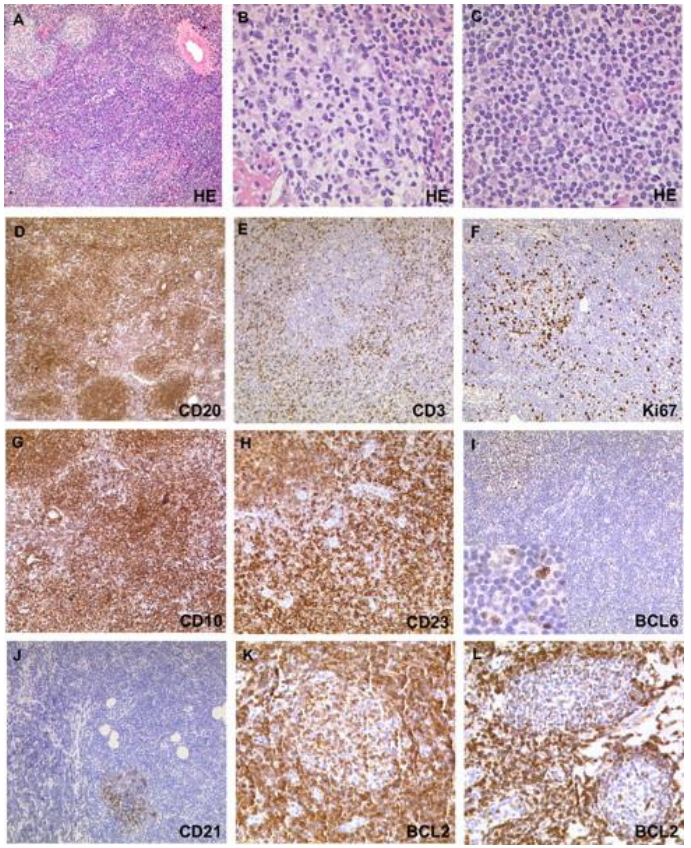
Predominantly diffuse Follicular Lymphoma with del1p36 or TNFRSF14 mutations

- Follicular lymphoma but with diffuse pattern rather than nodular.
- Lack of BCL-2 rearrengement
- CD23+
- STAT6 mutations and nuclear P-STAT6 expression was detectable in the mutated cases by IHC
- Localized mass
- Often inguinal



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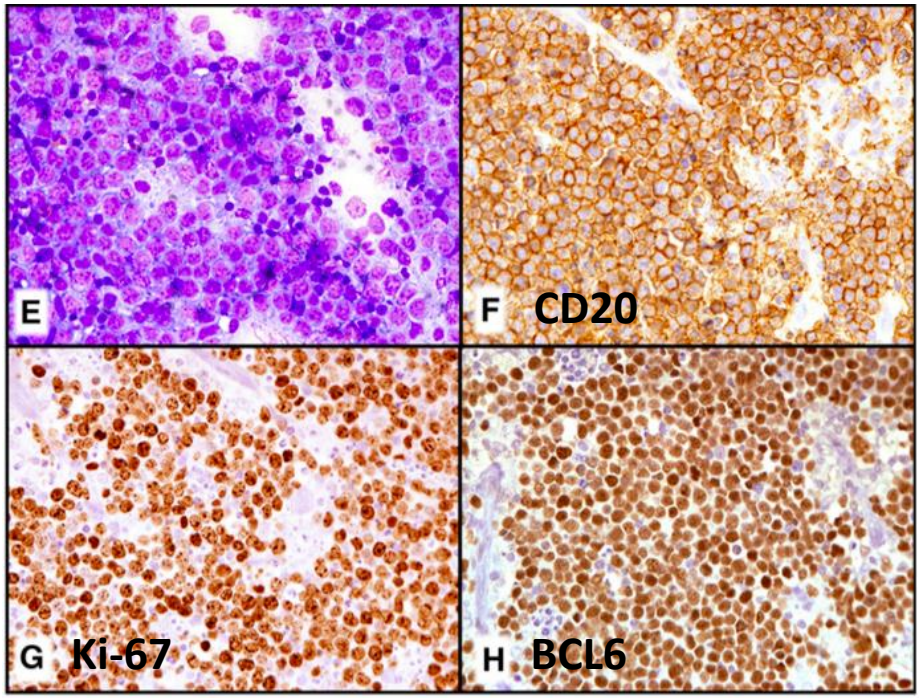
Burkitt-like lymphoma with 11q aberration

- BL morphologically
- Lack MYC rearrangements.
- Chromosome 11q alteration characterized by proximal gains and telomeric losses.
- More complex karyotypes
- Lower levels of MYC expression
- Cytological pleomorphism



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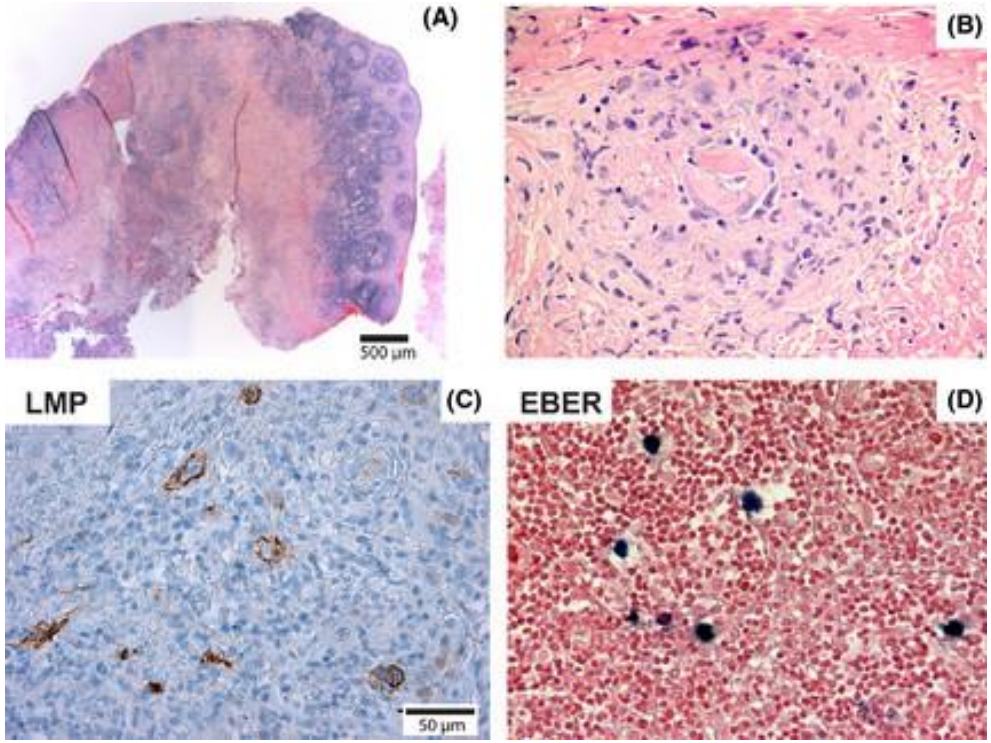
EBV+ mucocutaneous ulcer

- It has been segregated from EBV+ DLBCL
- Self-limited growth potential
- Response to conservative management.
- These lesions may present in advanced age or with iatrogenic immunosuppression



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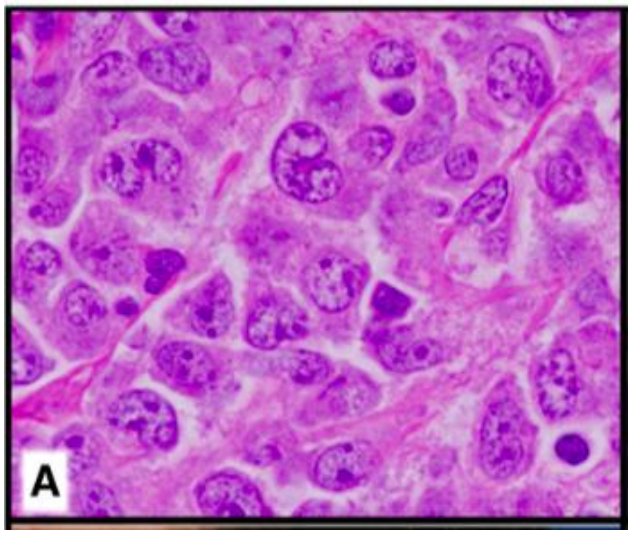
ALK- ALCL with DUSP22 rearrangement

- Monotonous proliferation of large transformed cells and classic “Hallmark” cells.
- Rearrangements at the locus containing DUSP22 and IRF4 in chromosome 6p25 tends to be relatively monomorphic
- Lack cytotoxic granules
- Better prognosis
- Small subset with TP63 rearrangements are very aggressive



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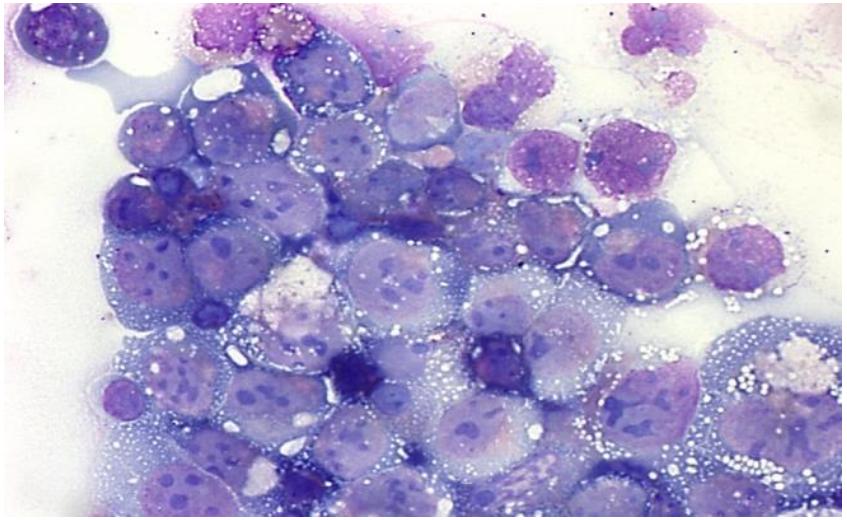
Breast implant-associated anaplastic large cell lymphoma

- The underlying mechanism is thought to be due to chronic inflammation from indolent infections, leading to malignant transformation of T cells that are anaplastic lymphoma kinase (ALK) negative and CD30 positive.
- Ultrasonography with fluid aspiration can be used for diagnosis.



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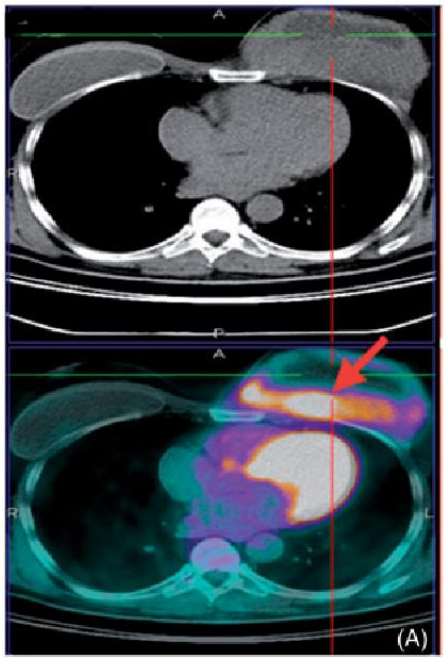
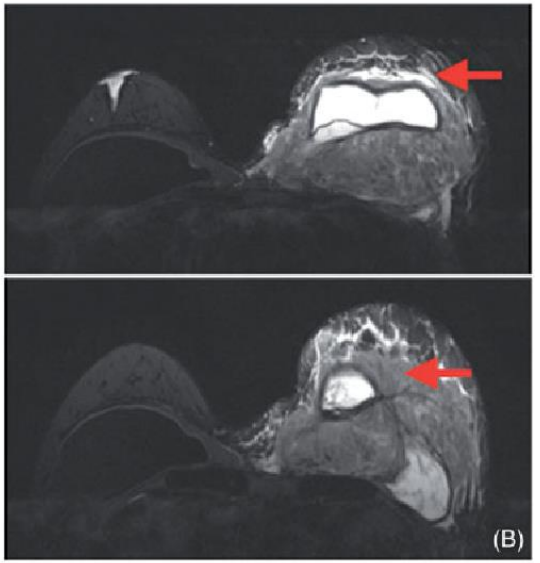
Breast implant-associated anaplastic large cell lymphoma

- The mean time to presentation is approximately 10 years after implant placement
- 2/3 of patients are initially seen with an isolated late-onset seroma and less than 10% with an isolated new breast mass
- Treatment must include removal of the implant and surrounding capsule.
- More advanced disease may require radiotherapy in extracapsular involvement and chemotherapy if lymph node are infiltrated





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The 2016 revision of the World Health Organization classification of myeloid neoplasms

AML with recurrent genetic abnormalities

- 11 acute myeloid leukemias and related neoplasms with recurrent genetic abnormalities
- 2 new provisional entities

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1

Arber DA et al. Blood 2016;127(20):2391-2405

AML with recurrent genetic abnormalities

- 9 acute lymphoblastic leukemias with recurrent genetic abnormalities
- 2 new provisional entities

Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21

Arber DA et al. Blood 2016;127(20):2391-2405

Myeloid neoplasms with germ line predisposition

Myeloid neoplasm classification
Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation*
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation*
Myeloid neoplasms with germ line *ANKRD26* mutation*
Myeloid neoplasms with germ line *ETV6* mutation*
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with BM failure syndromes
Myeloid neoplasms associated with telomere biology disorders
JMML associated with neurofibromatosis, Noonan syndrome or
Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome*

*Lymphoid neoplasms also reported.

- Most cases of MDS or acute leukemia are sporadic diseases
- A subgroup of cases is associated with germ line mutations and is familial
- Germ line mutations in:
  - CEBPA
  - DDX41
  - RUNX1
  - ANKRD26
  - ETV6
  - GATA2

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Juvenile myelomococytic leukemia

JMML diagnostic criteria
I. Clinical and hematologic features (all 4 features mandatory)
• PB monocyte count ≥1 × 10^9/L
• Blast percentage in PB and BM <20%
• Splenomegaly
• Absence of Philadelphia chromosome (*BCR/ABL1* rearrangement)
II. Genetic studies (1 finding sufficient)
• Somatic mutation in *PTPN11** or *KRAS** or *NRAS**
• Clinical diagnosis of NF1 or *NF1* mutation
• Germ line *CBL* mutation and loss of heterozygosity of CBL†
III. For patients without genetic features, besides the clinical and hematologic features listed under I, the following criteria must be fulfilled:
• Monosomy 7 or any other chromosomal abnormality or at least 2 of the following criteria:
• Hemoglobin F increased for age
• Myeloid or erythroid precursors on PB smear
• GM-CSF hypersensitivity in colony assay
• Hyperphosphorylation of STAT5

Modified from Locatelli and Niemeyer[25] with permission.
*Germ line mutations (indicating Noonan syndrome) need to be excluded.
†Occasional cases with heterozygous splice site mutations.

- Infancy and early childhood
- Excessive proliferation of cells of monocytic and granulocytic lineages that is included as a MDS/MPN subtype
- Approximately 90% of patients carry either somatic or germ line mutations of PTPN, KRAS, NRAS, CBL, or NF1.
- These genetic aberrations are largely mutually exclusive and activate the RAS/MAPK pathway.

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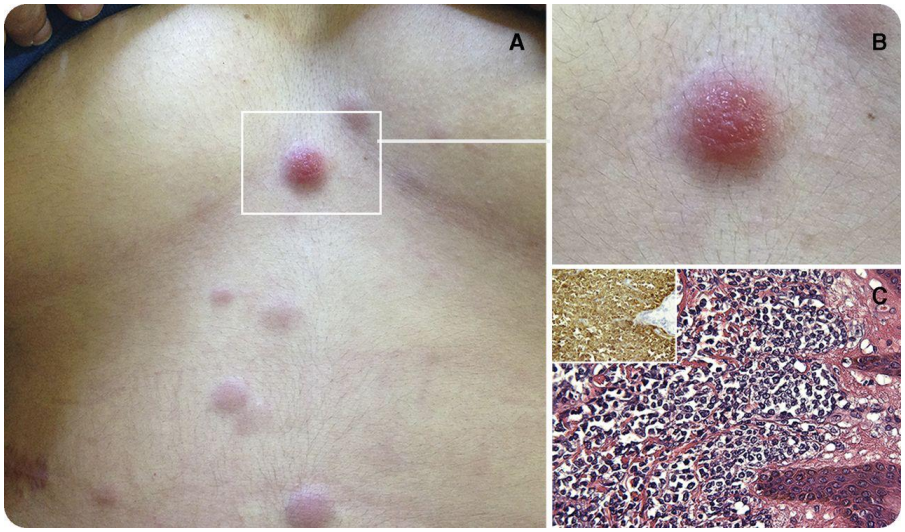
Myeloid sarcoma

- Myeloid sarcoma remains in the classification as a unique clinical presentation of any subtype of AML.
- Myeloid sarcoma may present de novo, may accompany PB and marrow involvement, may present as relapse of AML, or may present as progression of a prior MDS, MPN, or MDS/MPN



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Take-home messages

- The incorporation of new diagnostic techniques such as NGS has led to the identification of very rare entities with specific features that worth the recognition by the WHO classification as a new entity
- The knowledge of genetic background could lead to tailor therapy in the future with targeted therapies
- Rare hematologic tumours need of reference centres for accurate diagnosis
- Since the frequency is quite low, we must implement networks among all healthcare professionals involved not only in diagnosis but in patient’s care

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