

BURKITT LYMPHOMA

Burkitt Lymphoma

- Definition:
 - Highly aggressive lymphoma often presenting at extranodal sites or as an acute leukemia
 - Composed of monomorphic medium-sized B-cells with basophilic cytoplasm and numerous mitotic figures
 - Translocation involving MYC is a constant genetic feature
 - EBV is found in a variable proportion of cases
 - Low socio-economic status and early EBV infection are associated with higher prevalence of EBV positive BL

Synonyms

- Rappaport: Undifferentiated lymphoma, Burkitt type
- Lukes-Collins: Small non-cleaved follicular center cell
- WF: Small non-cleaved cell, Burkitt type
- Kiel: Burkitt and Burkitt lymphoma with intracytoplasmic immunoglobulin
- REAL: Burkitt Lymphoma
- FAB: ALL-L3

Epidemiology

- Three clinical variants are recognized
- Each manifesting differences in clinical presentation, morphology and biology

Epidemiology

- Endemic BL: This variant occurs in equatorial Africa representing the most common malignancy of childhood
- Peak incidence at 4 to 7 years
- Male to female ratio of 2 to 1
- BL is also endemic in Papua, New Guinea

Epidemiology

- Sporadic BL: Seen throughout the world, mainly in children and young adults
- The incidence is low, 1-2% of all lymphomas in Western Europe and in USA
- BL accounts for approx. 30 to 50% of childhood lymphomas
- Median age in adult pts is 30 years
- Male to female ratio is about 3 to 1
- In some parts of the world, e.g. in South America and North Africa, the incidence is intermediate between sporadic and endemic variants

Epidemiology

- Immunodeficiency associated BL: Seen primarily associated with HIV infection
- EBV is identified in 25-40% of the cases
- BL is less often seen in other immunodeficiency states

Sites of Involvement

- Extranodal sites are most often involved
- In all three variants pts are at risk for CNS involvement
- In endemic BL, the jaws and other facial bones are the site of presentation in about 50% of the cases
- In sporadic BL, the majority of cases present with abdominal masses
- In immunodeficiency-associated BL, nodal and bone marrow involvement are common

Clinical Features

- Pts present with bulky disease
- The clinical presentation varies according to the epidemiologic subtype and the site of involvement
- Some pts mainly men, present as acute leukemia with PB and BM involvement
- BM involvement is a poor prognostic sign and is often found in pts with high tumor burden
- Pts with bulky tumors or leukemia, high uric acid and high LDH are usually seen

Clinical Features

- BL is staged according to the system of Murphy et al
- Localized stages (I and II) are found in approx. 30% of the cases
- Advanced stages (III and IV) are seen in about 70% of cases at presentation
- The tumor lysis syndrome is often seen with therapy and is characteristic of BL

Etiology

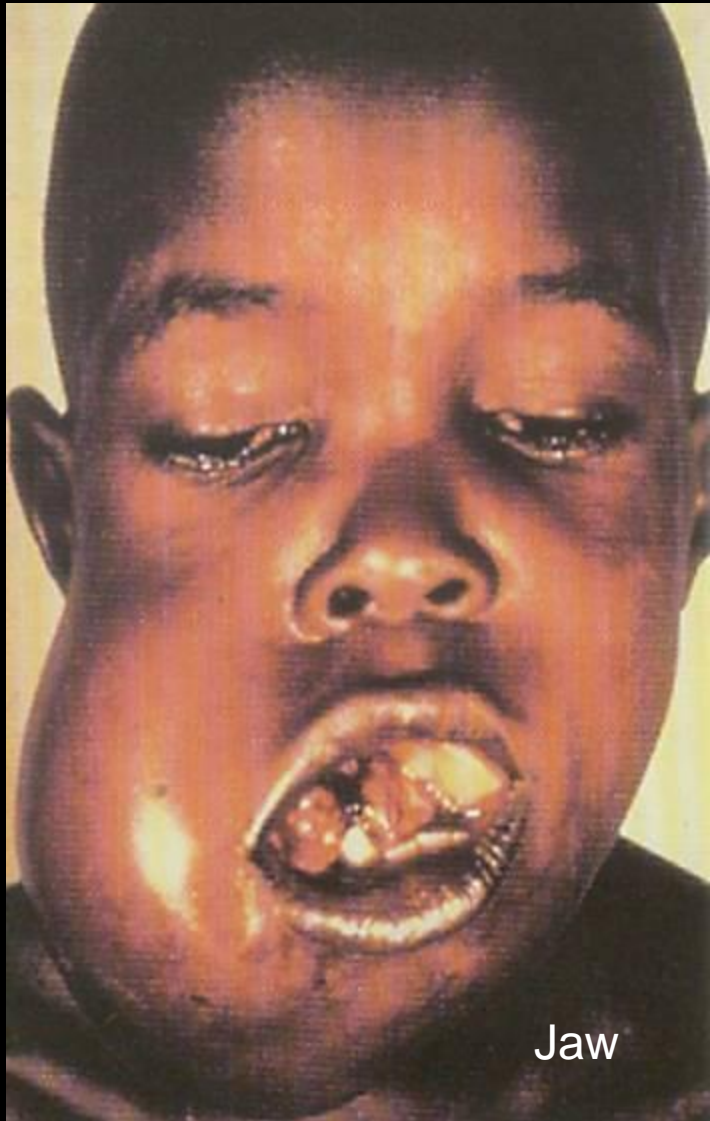
- EBV plays an important role in endemic BL
- ~~EBV was first discovered from a BL cell line~~
- In endemic BL, the EBV genome is present in the majority of neoplastic cells in all pts
- The lymphoma is preceded by a long period of polyclonal B-cell activation due to multiple bacterial, viral (EBV, HIV) and parasitic infection
- In sporadic BL, the frequency of EBV association is low, less than 30% of the cases
- Low socio-economic status and early EBV are associated with higher prevalence of EBV-BL

Etiology

- In immunodeficiency-associated cases, EBV is identified only in 25 to 40% of the cases
- In cases of EBV negative BL, it is hypothesized that the virus may not be essential in the pathogenesis, but rather represent only a co-factor
- Genetic abnormalities involving the MYC gene at chromosome 8q24 play an essential role in the pathogenesis

Macroscopy

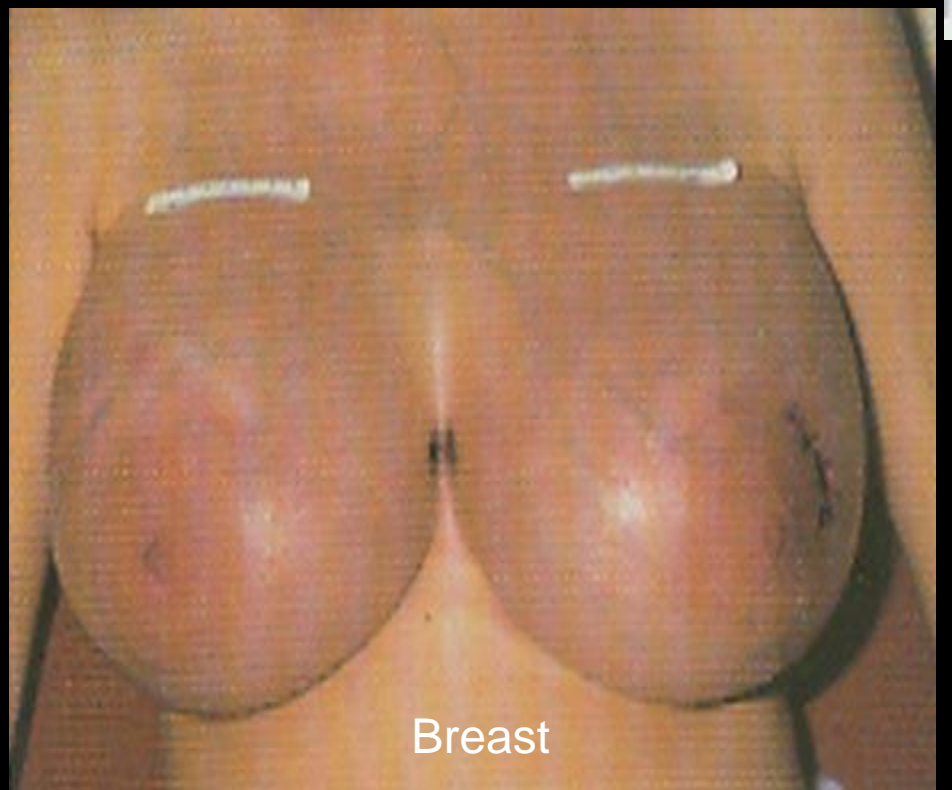
- Involvement of organs is replaced by masses of fish-appearing tissue
- Often associated with hemorrhage and necrosis
- Adjacent organs are compressed or infiltrated
- Nodal involvement is rare in endemic and sporadic BL



Jaw



Ovary



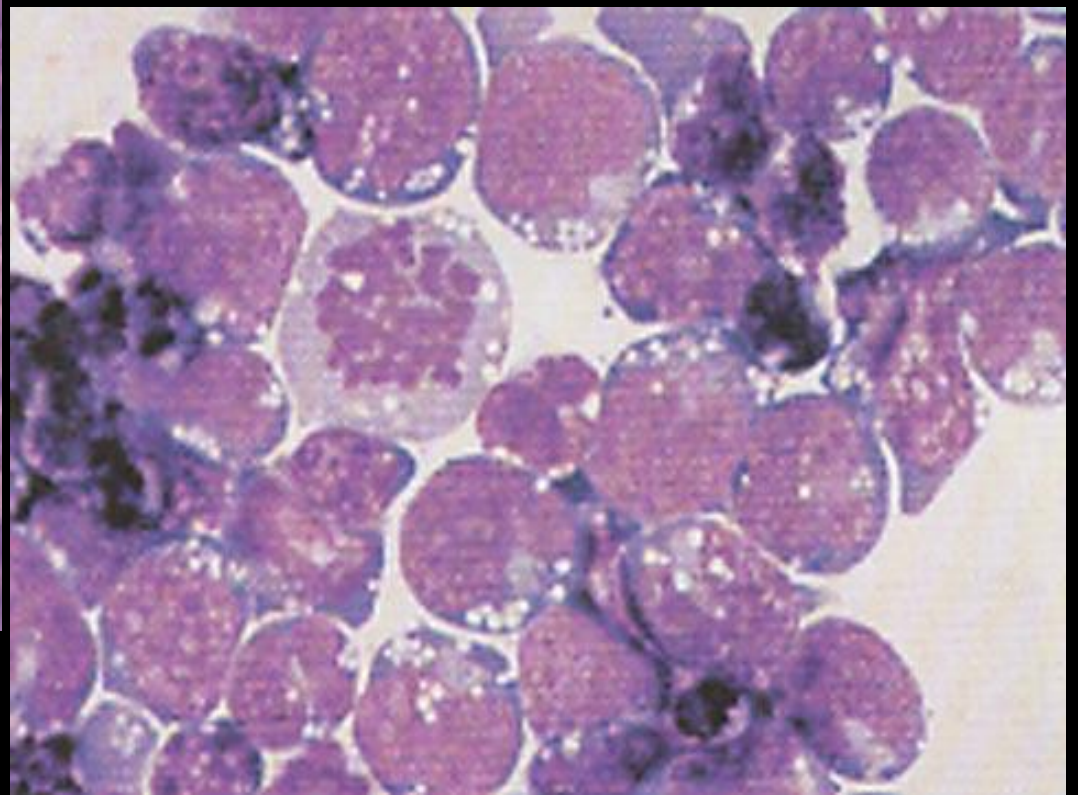
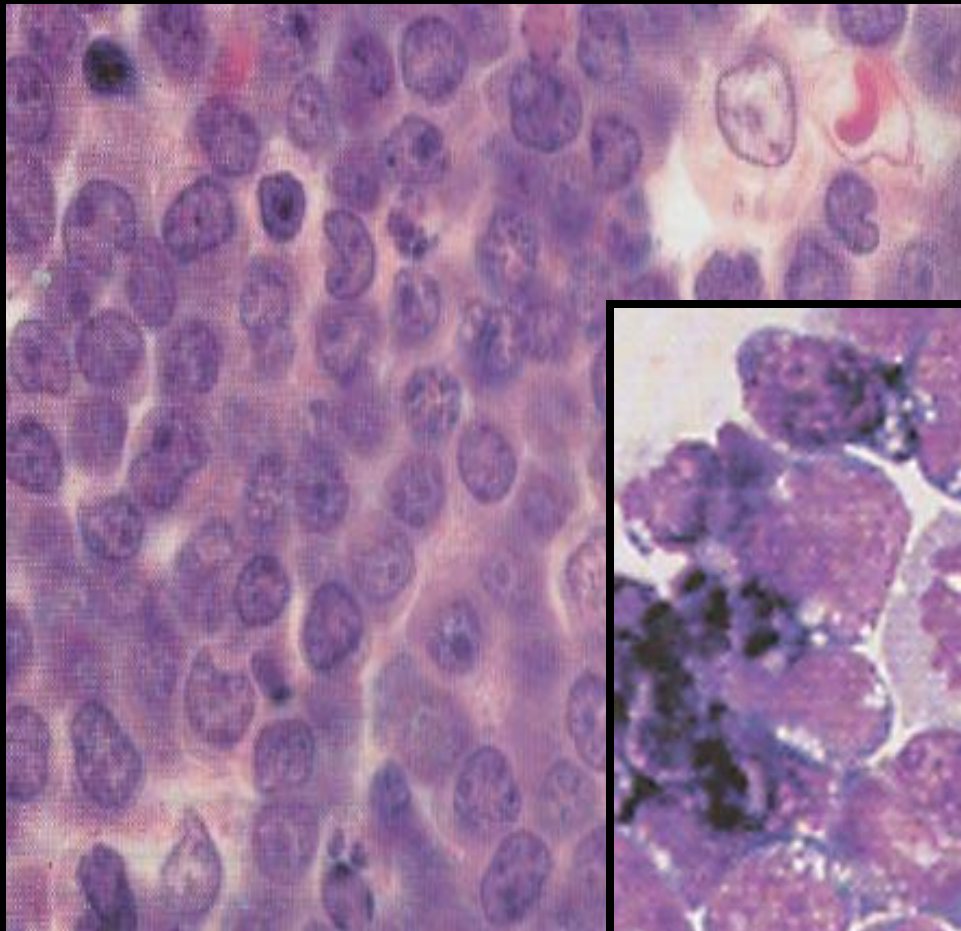
Breast

Morphology

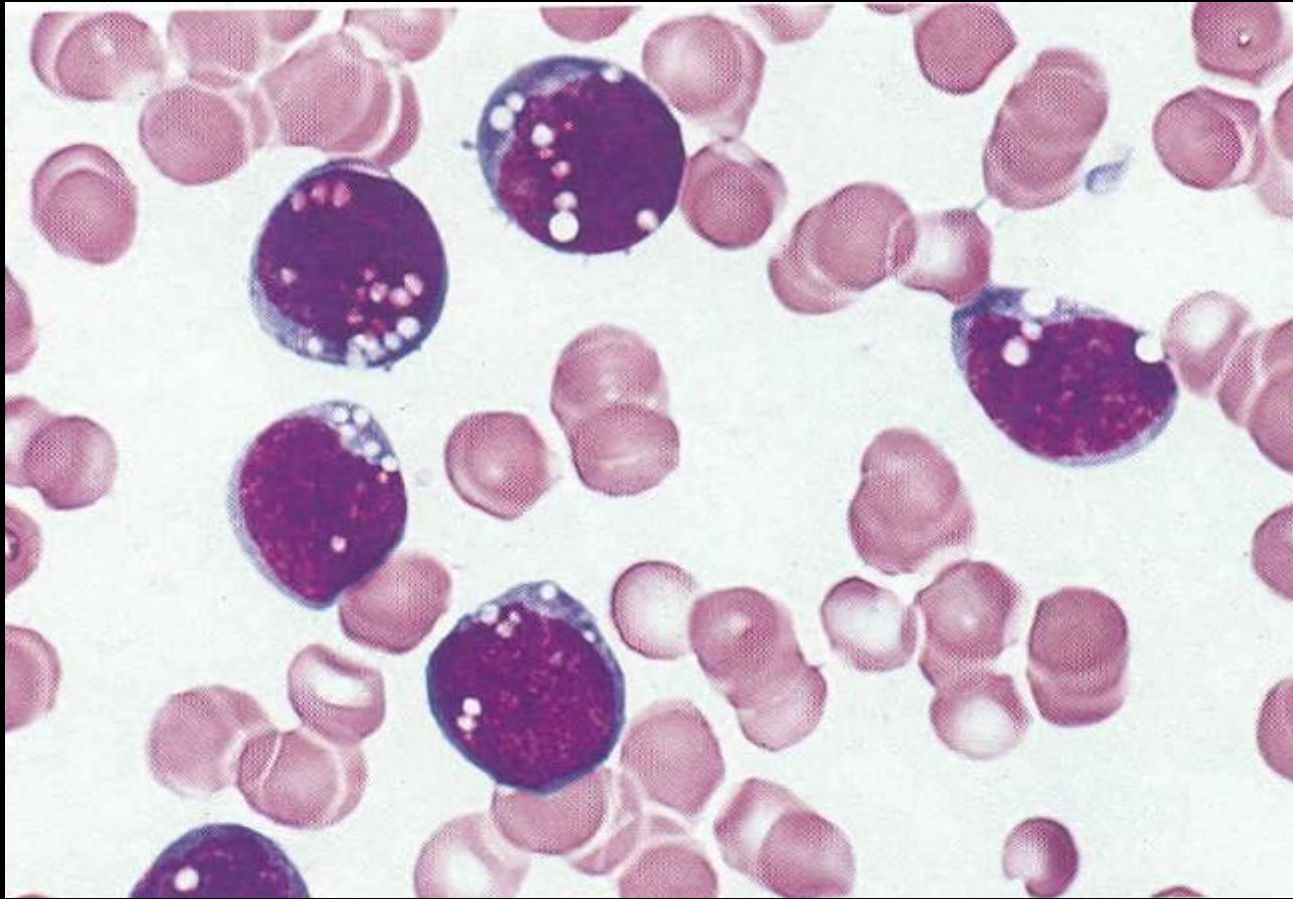
- Classical BL: observed in endemic and sporadic cases
 - Medium-sized cells show a diffuse monotonous pattern of infiltration
 - Sometimes after fixation the cells exhibit squared off borders of retracted cytoplasm and may appear cohesive
 - The nuclei is round with clumped chromatin and relatively clear parachromatin
 - The nuclei contain multiple basophilic medium-sized, centrally located nucleoli

Morphology

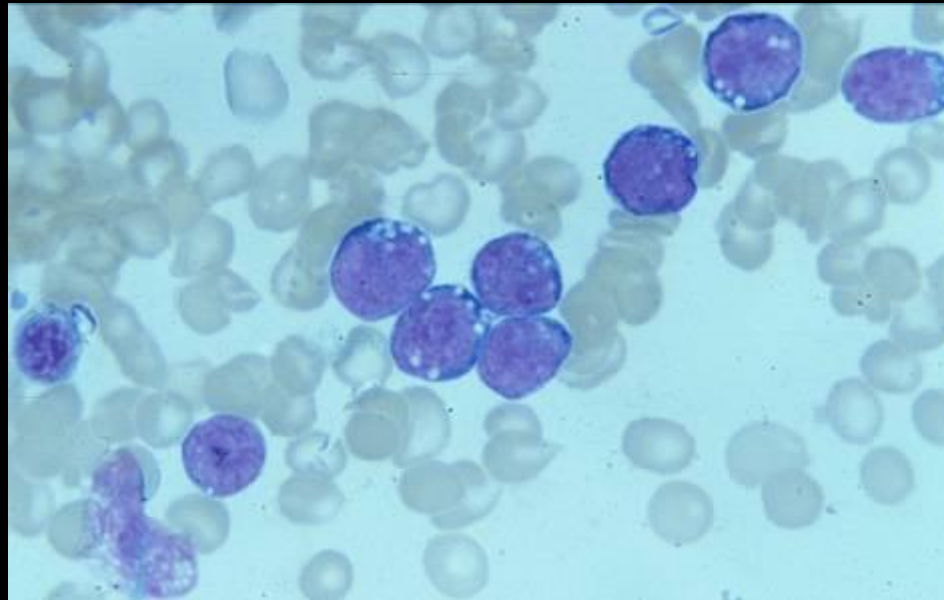
- The cytoplasm is deeply basophilic and usually contains lipid vacuoles
- The tumor has an extremely high proliferation rate (many mitotic figures)
- High rate of spontaneous cell death
- A “starry sky” pattern is usually present
- The nuclei of the tumor cells approximate in size those of the admixed starry-sky histiocytes



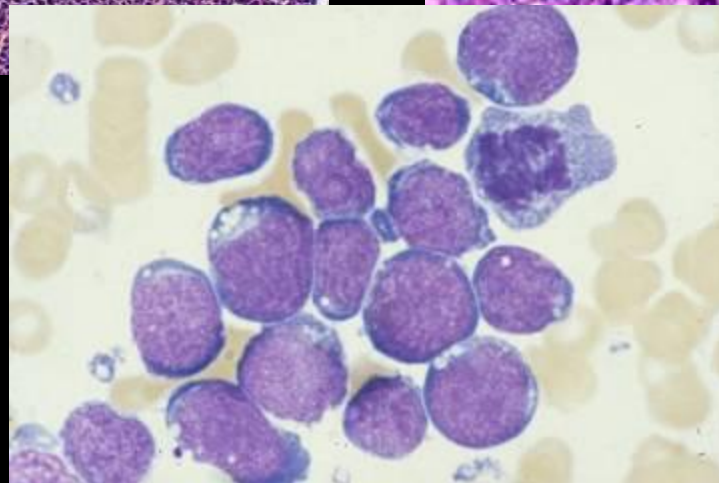
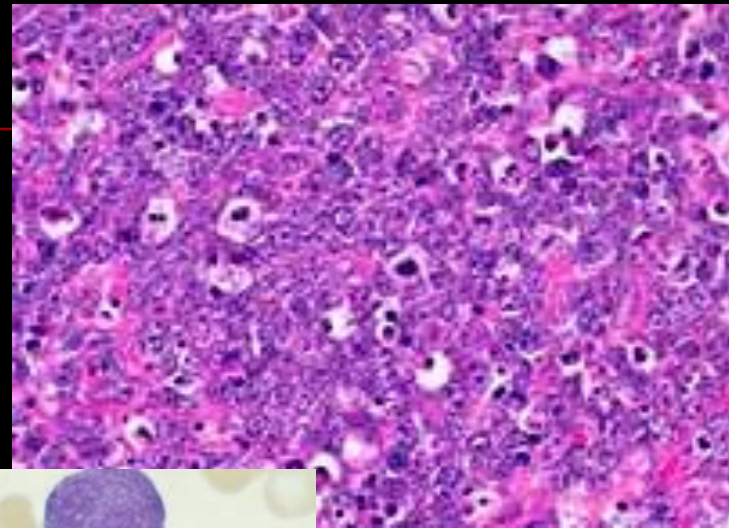
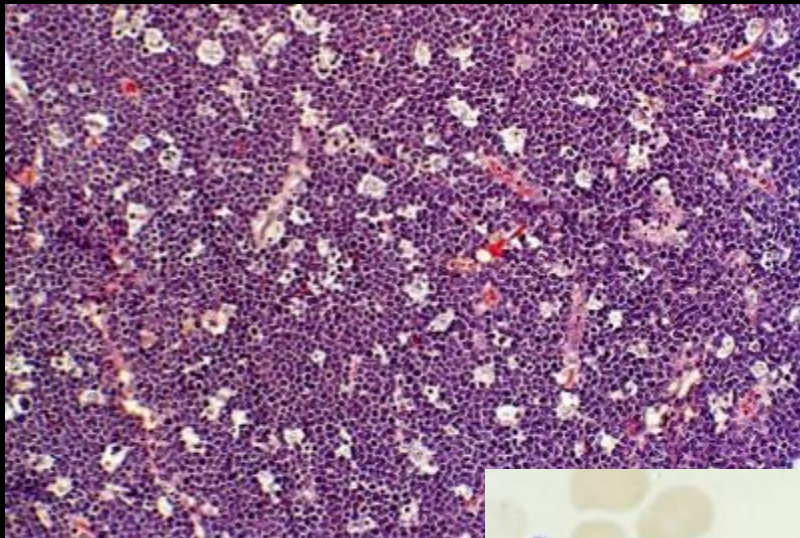
Burkitt's lymphoma



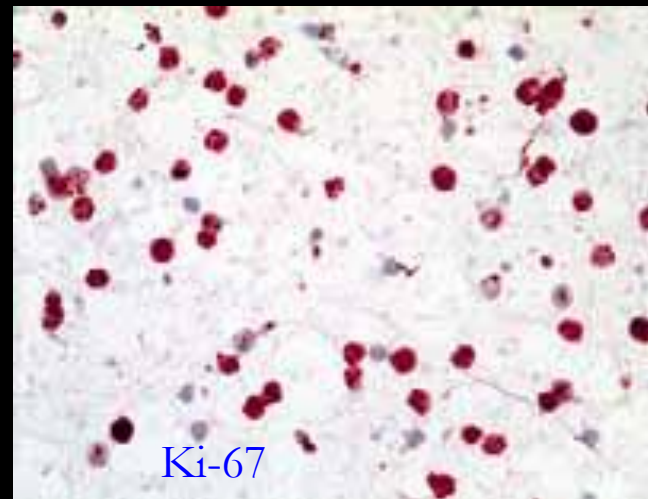
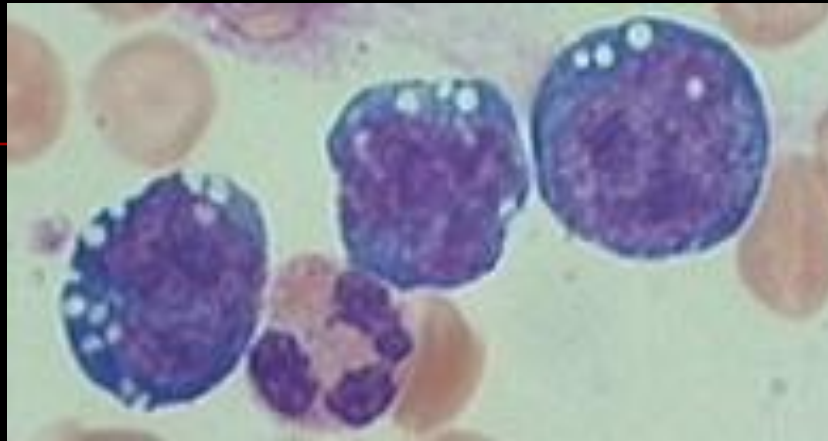
Burkitt Lymphoma



Burkitt Lymphoma



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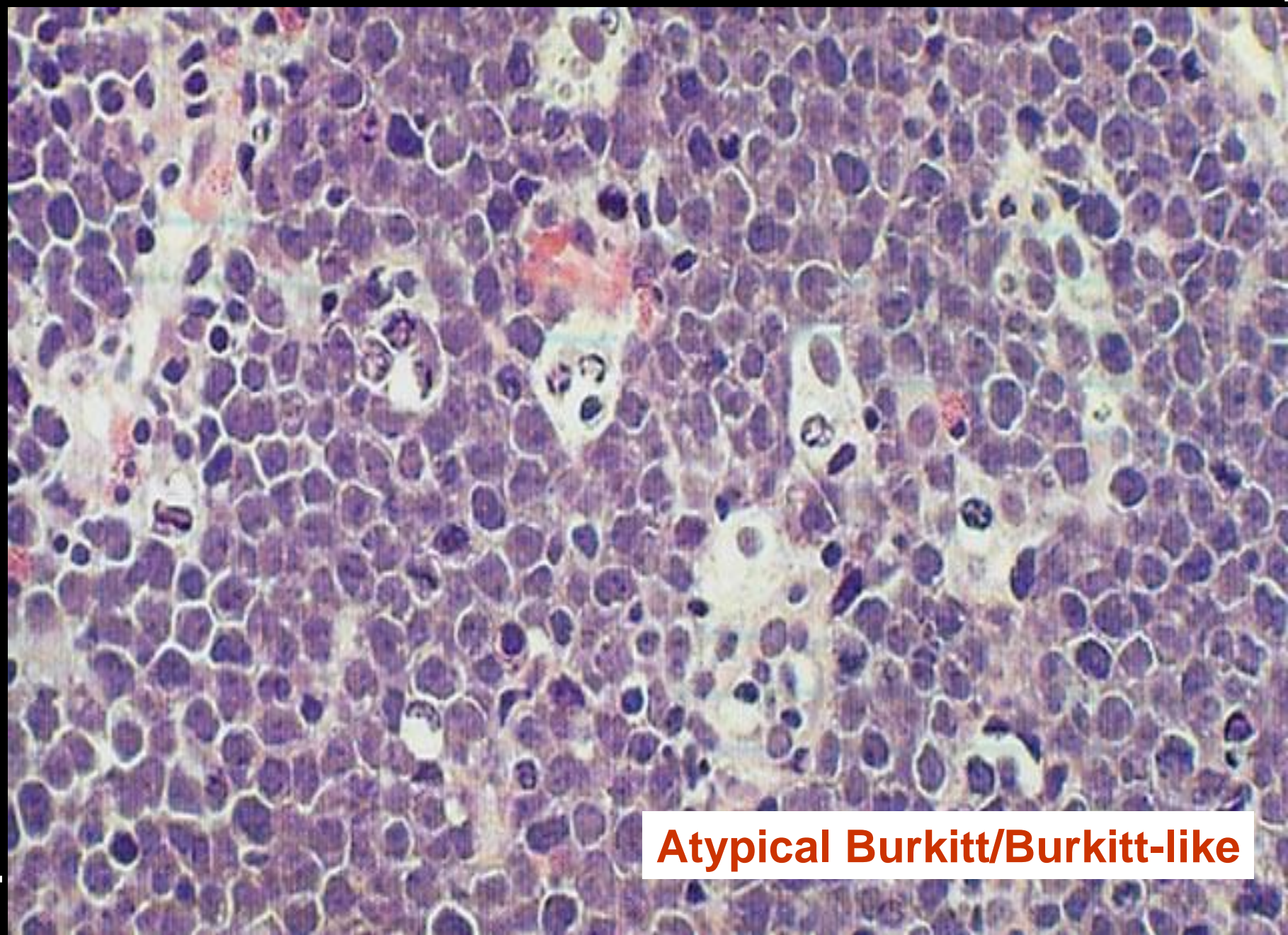
Variants

- BL with plasmacytoid differentiation
 - Eccentric basophilic cytoplasm
 - Single central nucleolus
 - Monotypic intra-cytoplasmic Ig can be demonstrated
 - Certain degree of pleomorphism in nuclear size and shape can be recognized
 - This variant can be observed in children, but is more common in immunodeficiency states

Variants

■ Atypical Burkitt/Burkitt-like

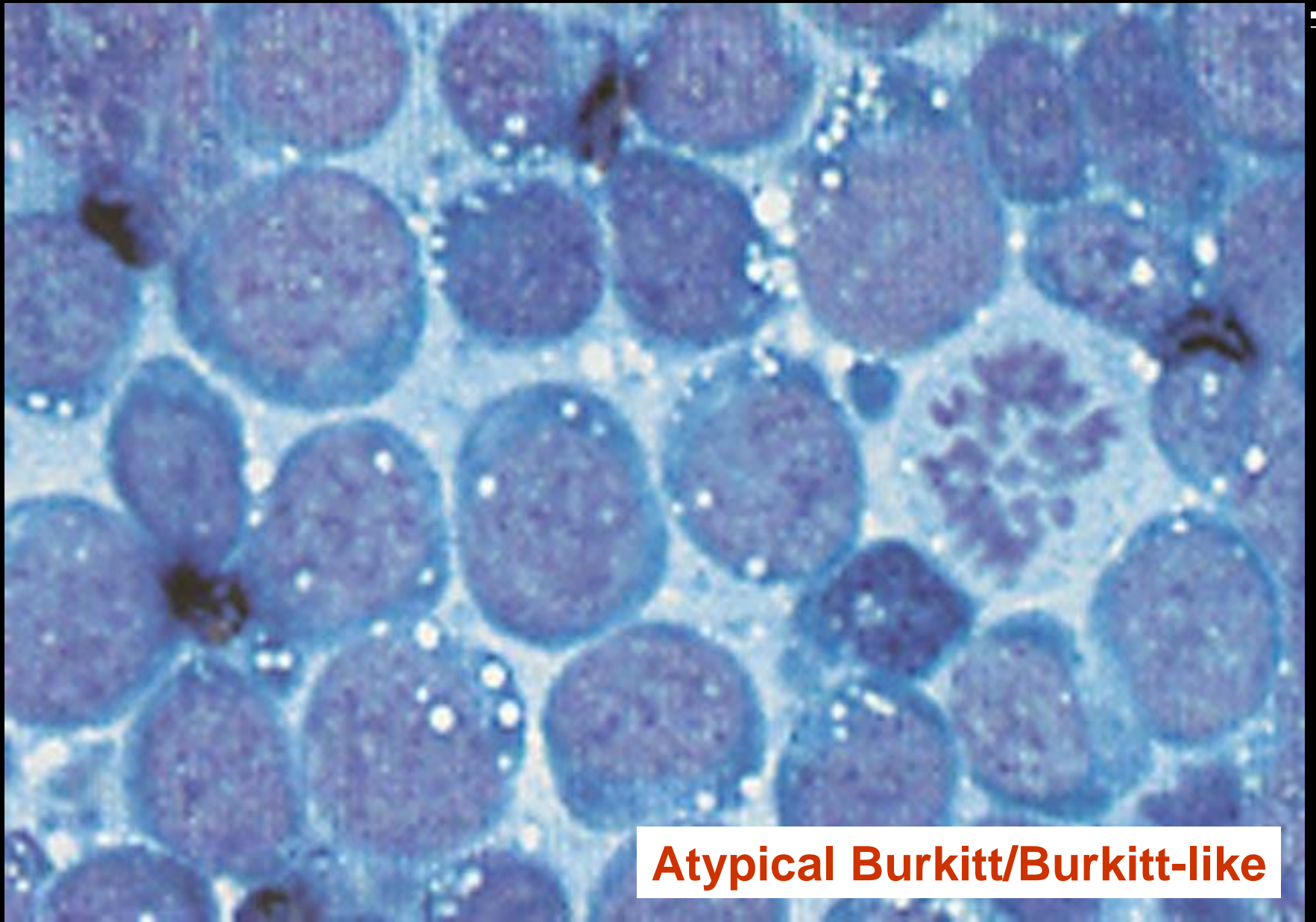
- Composed of medium-sized Burkitt cells and shows other features of BL
- The dx requires a growth fraction of 100%
- This variant shows greater pleomorphism in nuclear size and shape
- Nucleoli are more prominent
- Nucleoli are larger and fewer in numbers
- The term “atypical Burkitt” and “Burkitt-like” are reserved for cases with proven or strong presumptive evidence of MYC translocation



Atypical Burkitt/Burkitt-like



Atypical Burkitt/Burkitt-like



Atypical Burkitt/Burkitt-like

Immunophenotype

- Tumor cells express IgM with light chain restriction and B-cell associated antigens (CD19, CD20, CD22, CD10 and BCL6)
- Negative for CD5, CD23 and TdT
- BCL2 is not expressed
- The expression of CD10 and BCL6 point towards follicle center origin
- CD21 can be expressed in the endemic form

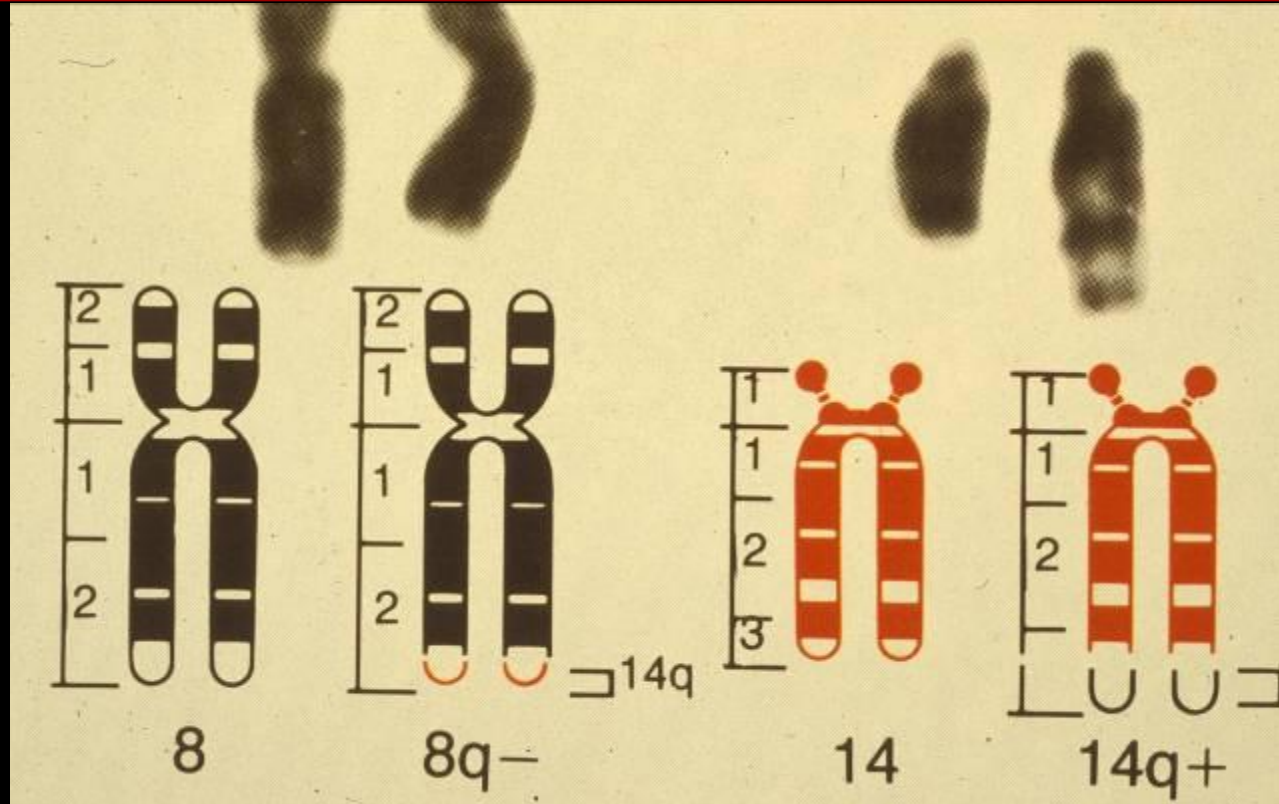
Immunophenotype

- Monotypic cytoplasmic Ig can be demonstrated in the plasmacytoid variant
- A high growth fraction is observed: nearly 100% of tumor cells are positive for Ki-67
- Blasts of BL presenting with leukemia have a mature B-cell phenotype

Genetics

- Clonal rearrangements of the Ig heavy and light chains genes
- Somatic mutations of the Ig genes are found
- All cases have the translocation of MYC at band q24 from chromosome 8 to the Ig heavy chain region on chromosome 14 [t(8;14)] at band q32
- Less commonly to a light chain loci on 2q11 [t(2;8)] or 22q11 [t(8;22)]

Burkitt Lymphoma



Genetics

- In endemic cases, the breakpoint on chromosome 14 involves the heavy chain joining region (early B-cell), whereas in sporadic cases, the translocation involves the Ig switch region
- The MYC gene is constitutively expressed secondary to the influence of the promoters of the Ig genes
- The deregulation of MYC plays a decisive role in lymphogenesis by driving the cells through the cell cycle

Genetics

- MYC also activates target genes specifically involved in apoptosis
- Other genetic lesions include inactivation of TP53 in up to 30% of sporadic and endemic cases
- The MYC translocation is not specific for BL
- The MYC translocation has been reported in secondary precursor B-lymphoblastic leukemia/lymphoma following follicular lymphoma

Genetics

- EBV genomes can be demonstrated in nearly all cases of endemic BL and in about 25-40% in immunodeficiency states and less common in sporadic cases (less than 30%)

Postulated cell of origin

Germinal centre B-cell

Prognosis and Predictive factors

- In endemic and sporadic cases the tumor is very aggressive but potentially curable
- Tx should begin as early possible
- Staging is performed by the scheme proposed by Murphy
- Staging is largely related to tumor burden
- Reduction of tumor by surgery has been shown to have some value

Prognosis

- BM and CNS involvement, unresected tumor greater than 10 cm and high LDH are recognized as poor prognostic factors
- Endemic BL is highly sensitive to polychemotherapy
- Intensive chemotherapy combination regimens result in cure rates up to 90% in pts with low stage disease and 60-80% in pts with advanced disease
- The results are better in children than in adults

Prognosis

- Pts with advanced stage disease, including BM and CNS involvement may be cured with high dose tx
- Relapse, when occur is usually during the first year after dx
- Pts without relapse for 2 years can be regarded as cured
- In Burkitt leukemia, the tx consists of very intensive chemotherapy of relatively short duration and with such a tx most pts have a very good prognosis with 80-90% survival