Hematologic malignancies

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Blood cell lines

Lymphoid vs myeloid

Malignant vs Benign

Morphology.

Metastasis.

Clonality.

Leukemia vs Lymphoma

Location

Phenotype.

MDS

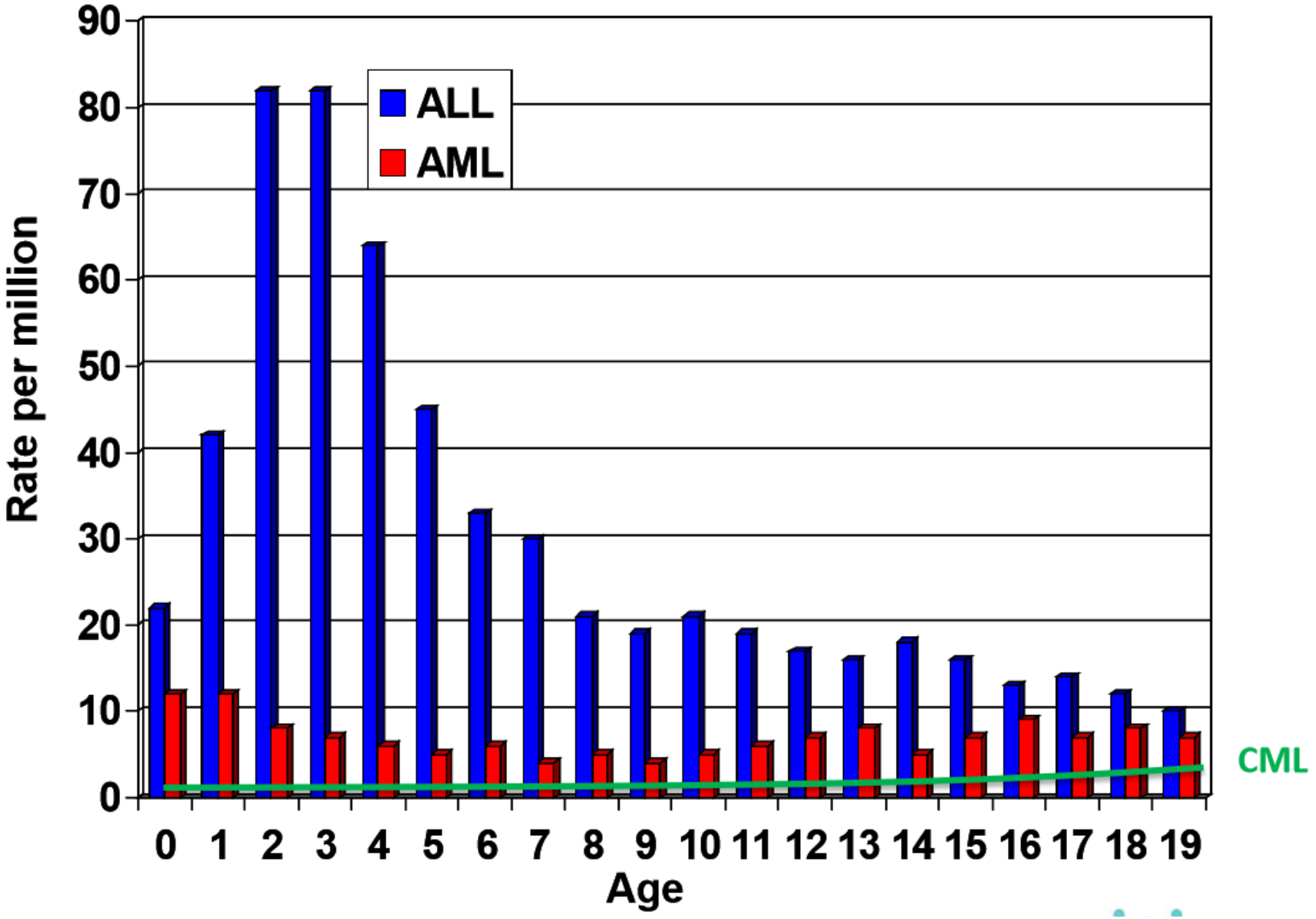
Defined by:

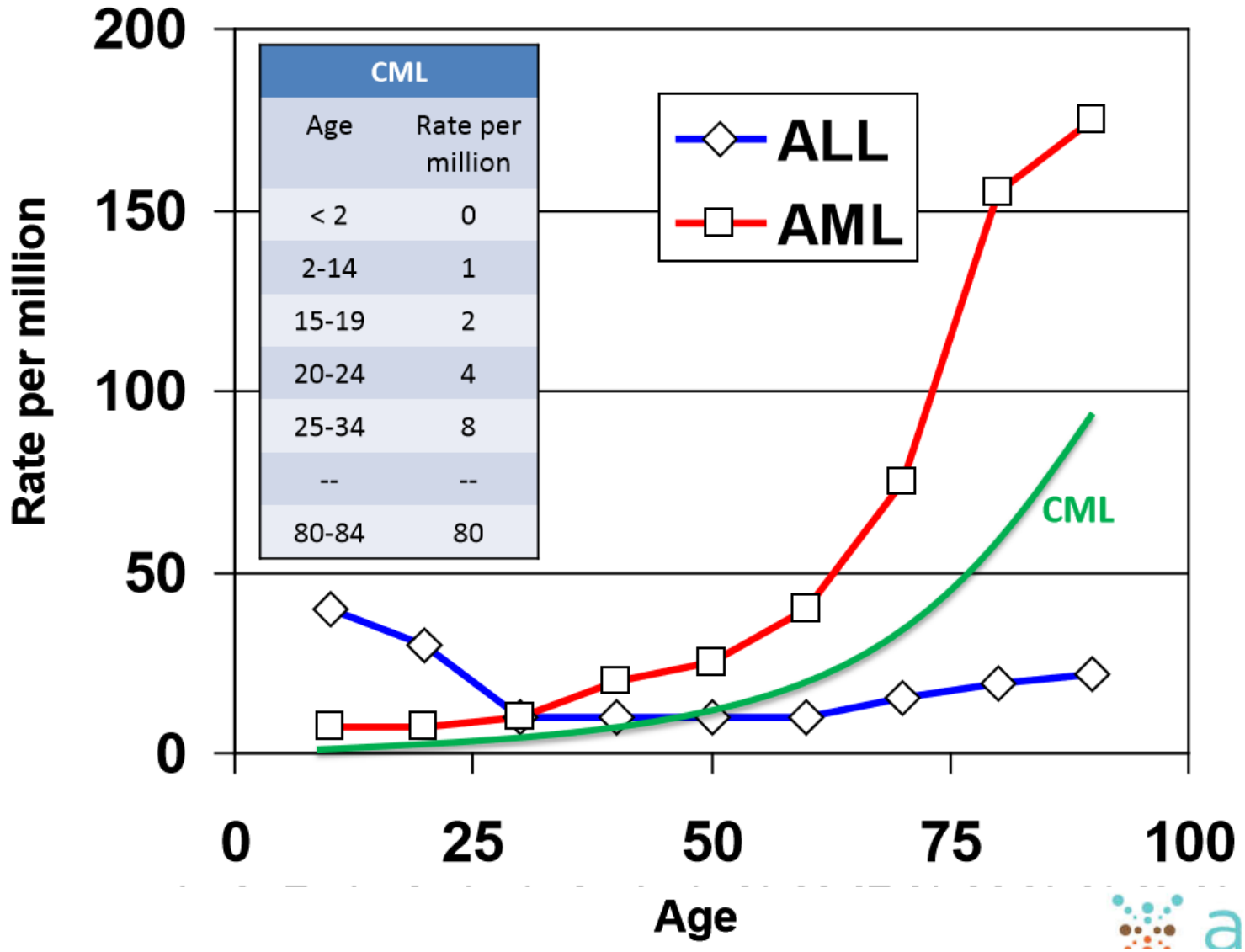
- Dysplastic bone marrow changes.
- Increased blast population.
- Cytogenetic abnormalities.

MDS

- De-novo vs Secondary.
- Natural history.
- Treatment.

AML


90
80
70
60
50
40
30
20
10
0
Rate per million
ALL
AML
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Age
CML


CML
Age
Rate per million
< 2
0
2-14
1
15-19
2
20-24
4
25-34
8
--
--
80-84
80
ALL
AML
CML
Rate per million
200
150
100
50
0
0
25
50
75
100
Age

AML

- Concordance studies

- Congential Bone marrow failure syndromes predispose to AML

FAB: morph/phenotype; 30% blasts

AML Subtype		Comments
M0	**AML without differentiation**	Difficult to distinguish from ALL; diagnosis requires expression of surface markers such as CD13, CD33 and CD117 (c -kit) in the absence of lymphoid differentiation
M1	**AML with minimal differentiation**	Myeloperoxidase detectable by special stains/flow cytom etry
M2	**AML with differentiation**	Auer rods; common t(8;21) -> AML1 -ETO fusion, good prognosis , chloromas
M3	**Acute promyelocytic leukemia (APL), hypergranular type**	Auer rods; DIC/bleeding;; t(15;17) -> PML-RARα fusion, good prognosis with ATRA therapy
M3v	**APL, microgranular variant**	Cytoplasm of promyelocytes demonstrates a fine granularity, and nuclei are often folded. Same clinical, cytogenetic and therapeutic implications as FAB M3.
M4	**Acute myelomonocytic leukemia (AMML)**	Mixture of myeloblasts (at le ast 20%) and monocytic blasts; often with peripheral monocytosis
M4Eo	**AMML with eosinophilia**	AMML with >5% abnormal eosinophil precursors in marrow (with basophilic granules), common inv(16), good prognosis
M5	**Acute monocytic leukemia**	>80% of bone marrow non-erythroid cells are monocytic; M5a: monoblastic; M5b: monocytic (more differentiated); ***for both M4 and M5***: infant age, MLL 11q23 rearrangements, CNS involvement, chloromas, gingival hyperplasia
M6	**Acute erythroblastic leukemia**	Rare in children
M7	**Acute megakaryoblastic leukemia**	Seen mostly in children with Down syndrome (good prognosis if ≤ 2 years old; GATA1 mutations) or mosaicism for trisomy 21; rare in normal children (poor prognosis , t(1;22) -> OTT-MAL fusion, often infants); myelofibrosis commo n

WHO: clinical/molecular; 20% blasts

- Is the AML due to prior XRT/chemo?
  - If yes: Dx is Therapy-related AML (t-AML)
- Is the AML in a child with Down syndrome?
  - If yes: Dx is DS-related AML
- Is major ("Big 4") recurring abnormality present?
  - If yes: Dx is AML w/ t(8;21); inv(16); t(15;17); MLL-r
  - *NOTE: No minimum blast % needed*
- Is there dysplasia, prior MDS and/or MDS-related mutation (-7, del(5q), etc.)?
  - If yes, Dx is AML with MDS-related changes
  - ***If no to all: Dx is AML, NOS - use FAB to subclassify***

t-AML

APML or AML M3

Cytogenetic	Molecular	FAB	Characteristics
t(8;21)	*AML1-ETO (RUNX1-RUNX1T1)*	M2	Auer Rods Chloromas Good px
t(15;17), variants	*PML-RARA* *{variant}-RARA*	M3	Granules/Auer rods DIC/bleeding Good px (with ATRA/Arsenic)
inv(16)/ t(16;16)	*CBFB-MYH11*	M4Eo	Eos w/ baso granules Chloromas Good px
abnormal 11q23	*MLL-{partner}*	M4 M5	Infant WBC/skin/CNS/gums t-AML after topo II inh

Treatment

CML

Ph+ (9;22) BCR-ABL

Chronic, accelerated and blast crisis phases.

Treatment options.

ALL

AML vs ALL

Predisposing conditions: TP53 mutations, immunodeficiencies.

May involve CNS or testis.

Ph+ ALL.

Mainstay of treatment is chemotherapy with overall long term survival over 90%.

Some high risk patients proceed to BMT.

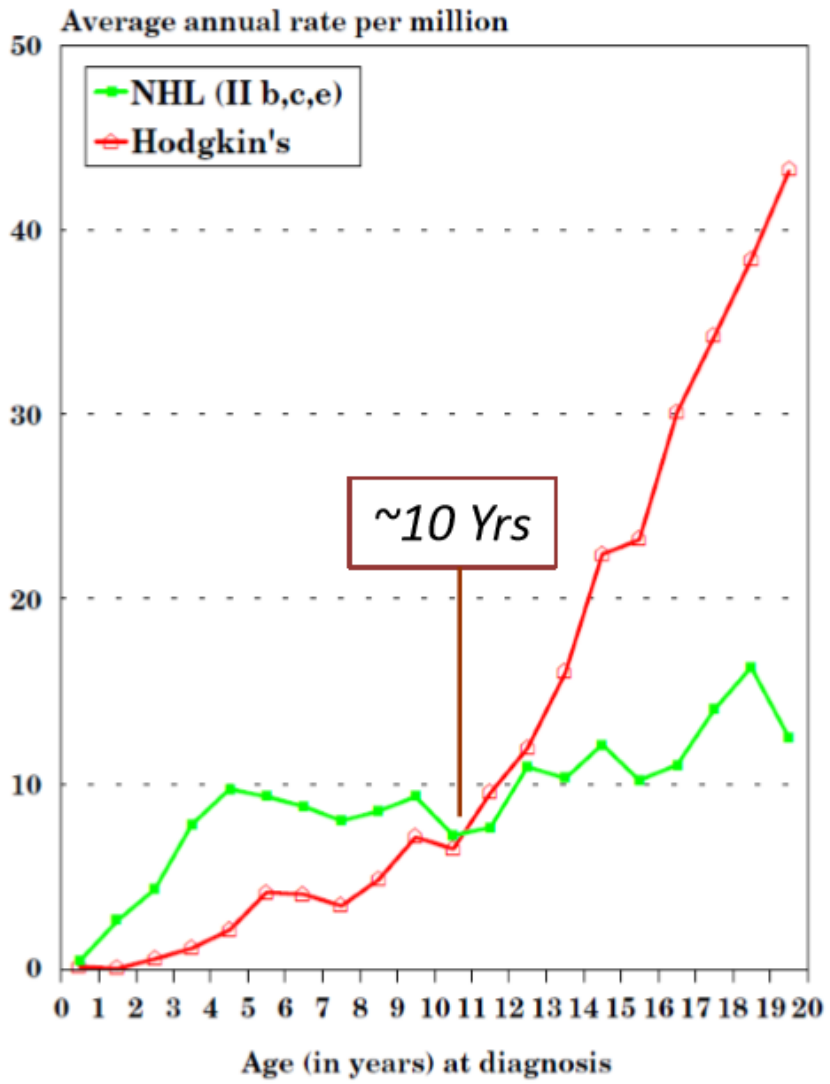
Age 0-14

Leukemia	32%
CNS	20
Lymphoma	11
Neuroblastoma	8
Rhabdo/STS	7
Kidney	6
Bone	6
Germ-cell	4
Retinoblastoma	3
Liver	1

Age 15-19

Lymphoma	25%
Germ cell	14
Leukemia	12
CNS	10
Soft-tissue Sarcoma	8
Bone	8
Thyroid carcinoma	7
Melanoma	7

	T cell derived	B cell derived
Immature	T-lymphoblastic	B-lymphoblastic
Mature	Anaplastic Large Cell	Burkitt Diffuse Large B cell Hodgkin


Average annual rate per million
50
40
30
20
10
0
NHL (II b,c,e)
Hodgkin's
~10 Yrs
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (in years) at diagnosis

Hodgkin Lymphoma

Most commonly presents with painless neck or chest adenopathy.

Many cases are associated with EBV infection.

B symptoms.

Classic (most common) and NLPHL

Excellent outcomes in low stage disease.

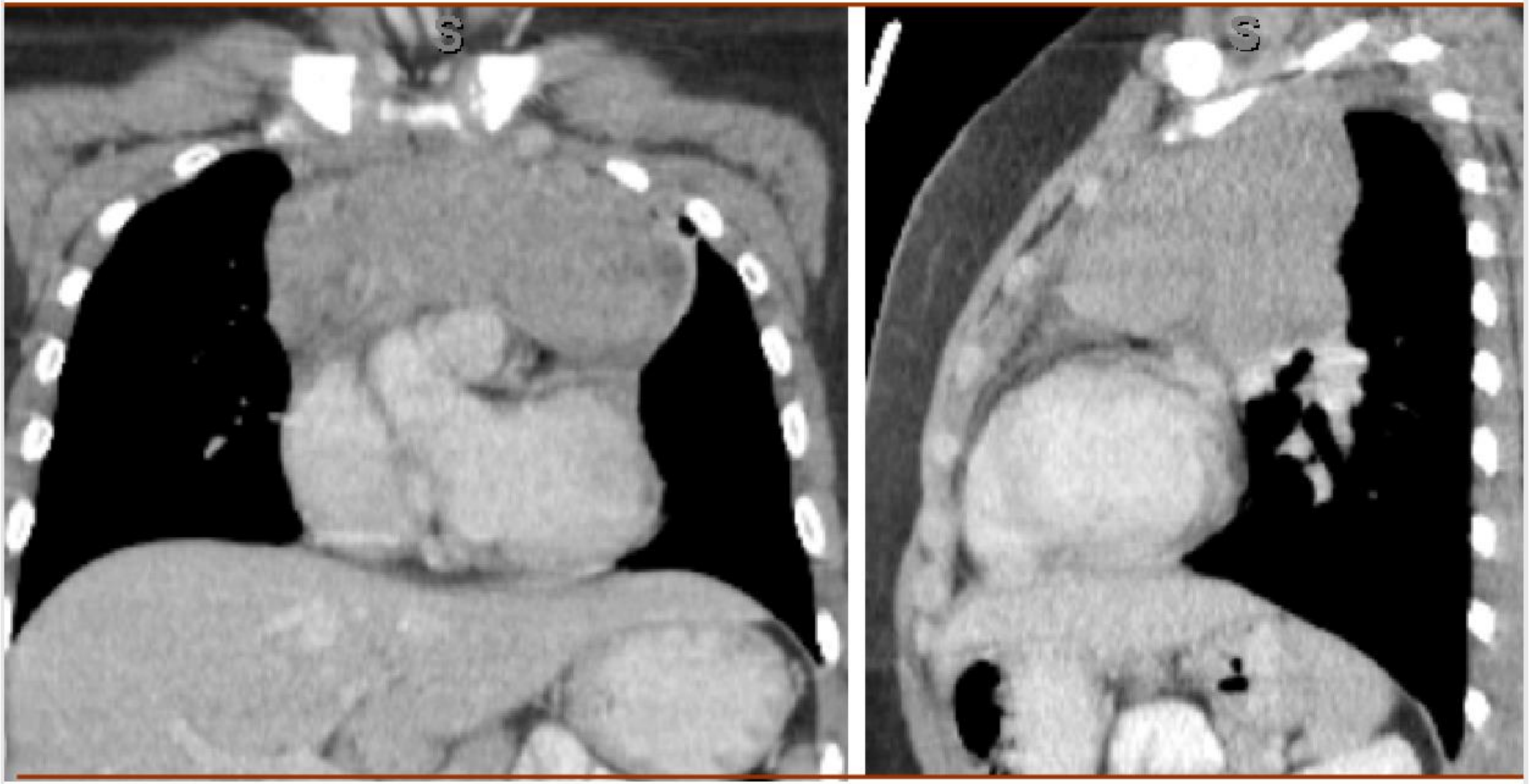
Malignant cell of classic Hodgkin is Hodgkin Reed-Sternberg (owl eye)

Clinical Presentation of Hodgkin Lymphoma

1. Painless lymphadenopathy
2. Mediastinal mass (~2/3)
3. Constitutional symptoms

- B symptoms are prognostic
  - Weight loss of 10% in 6 months
  - Drenching night sweats
  - Unexplained fevers >38°C for 3 consecutive days
- Others are not prognostic
  - Fatigue, anorexia, mild weight loss
  - Pain immediately following alcohol
  - Pruritus: generalized, can be severe, more often in advanced disease

- Markers of inflammation and RES activation (↑CRP, ESR, ferritin, copper)
- Anemia of chronic inflammation
- Immune dysregulation: autoimmune neutropenia, AIHA, ITP, nephrotic syndrome



Burkitt Lymphoma

- Mature NH B cell lymphoma.
- Very high proliferation rate, early diagnosis and treatment matters.
- High risk for tumor lysis syndrome.
- Most famous associated genetic abnormality t(8;14).
- Excellent prognosis if treatment not delayed.

	Sporadic	Endemic
EBV	15%	95%
Geography	North America, Europe	Equatorial Africa, Brazil Turkey, New Guinea
Incidence	0.2/100,000	10/100,000
Location	Abdominal mass LN, Marrow, CNS ovaries	Jaw mass, abdomen, CNS in 1/3

Anaplastic Large cell Lymphoma

Is a mature T cell Lymphoma.

Most common genetic abnormality is t(2;5) or ALK (anaplastic lymphoma kinase)