Anaplastic Large Cell Lymphoma, ALK-positive, Small Cell Variant, with Leukemic Presentation and Rare CD8-positive Phenotype

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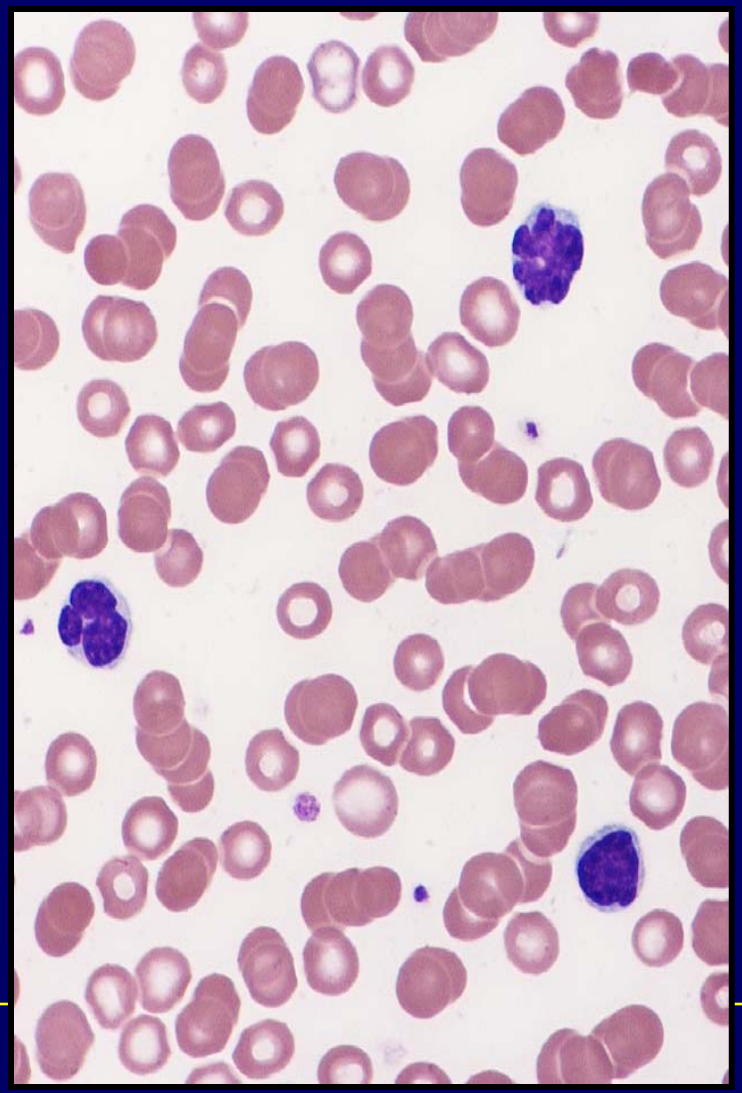
Anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive

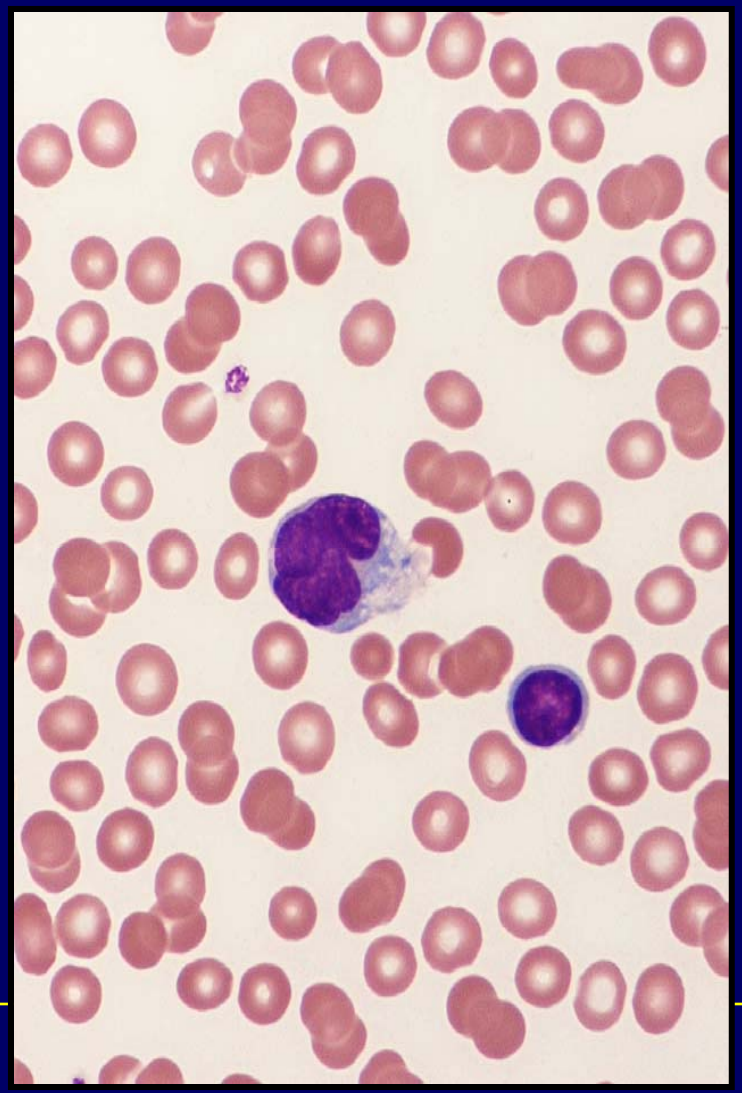
- T-cell lymphoma
- Usually large and pleomorphic lymphoid cells
- Characteristic genetic abnormality:
  - Translocations involving the ALK gene
- Frequent involvement of nodal & extranodal sites
- Cohesive growth pattern preferentially invading the LN sinuses
- A leukemic presentation is quite rare.
- Broad morphologic spectrum:
  - Common pattern (60%) – CV
  - Lymphohistiocytic pattern (10%) – LHV
  - Small cell pattern (5-10%) – SCV
  - Hodgkin-like pattern (3%) – HLV
  - Composite pattern
- SCV-ALCL – leukemic presentation with PB involvement

Clinical presentation

- 16-year-old female
- 2-week history of hives, persistent fever, fatigue, night sweats, weight loss, abdominal pain
- Splenomegaly, lymphadenopathy
- Leukocytosis (58,600/μL), anemia, thrombocytopenia
- Extensive infectious & rheumatologic work-up negative
- Initially, peripheral blood smear examination suggestive of leukemia

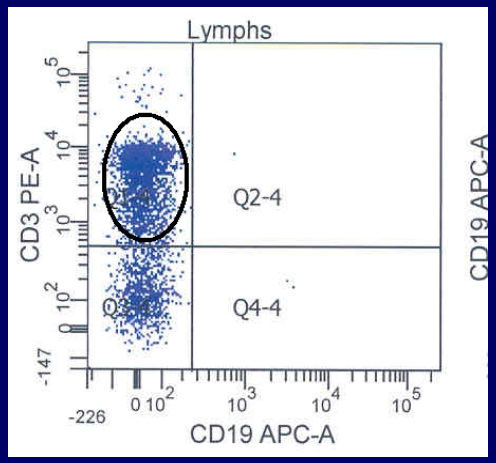
Peripheral blood morphology

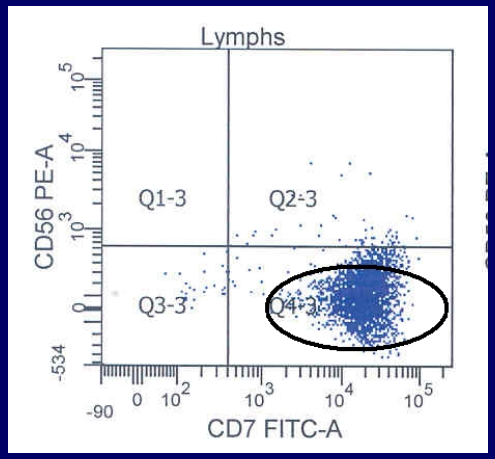


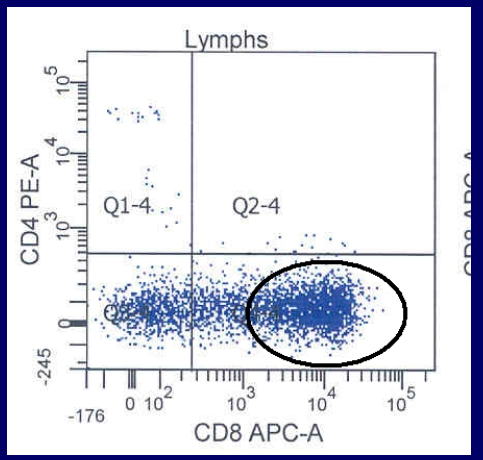


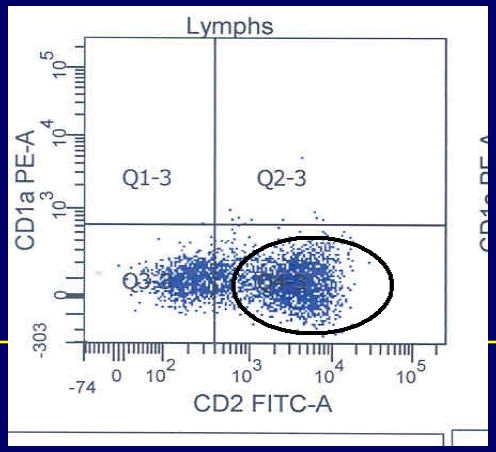
Peripheral blood flow cytometry

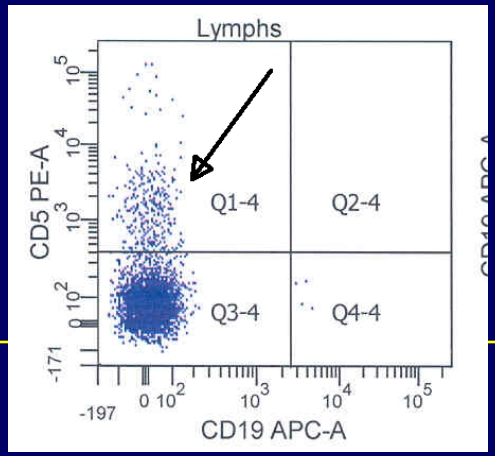
- Aberrant T-cell population: CD2, 3, 7, 8; loss of 5; aberrant 13
- Not specific for any type of T-cell leukemia (T-cell prolymphocytic leukemia, adult T-cell leukemia, Sezary syndrome, etc.)

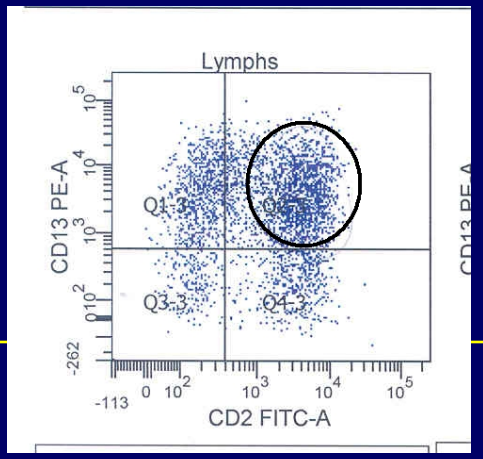






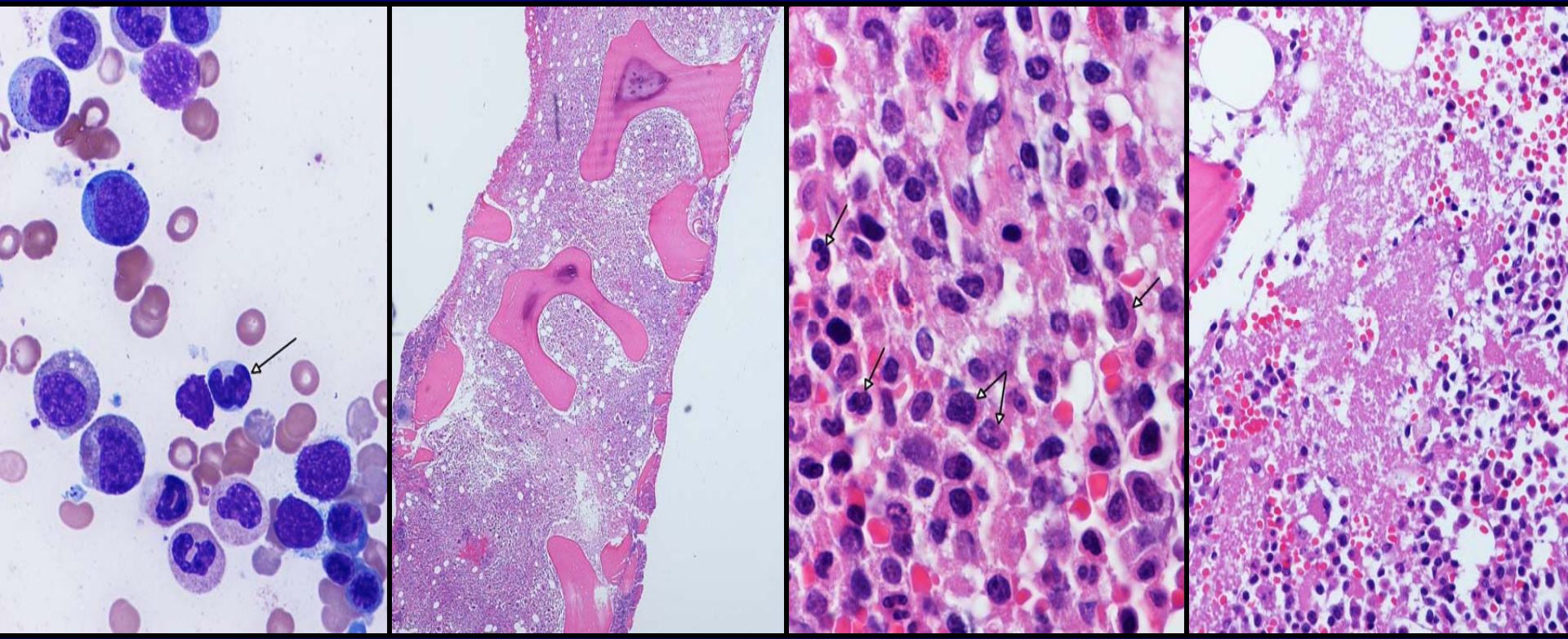


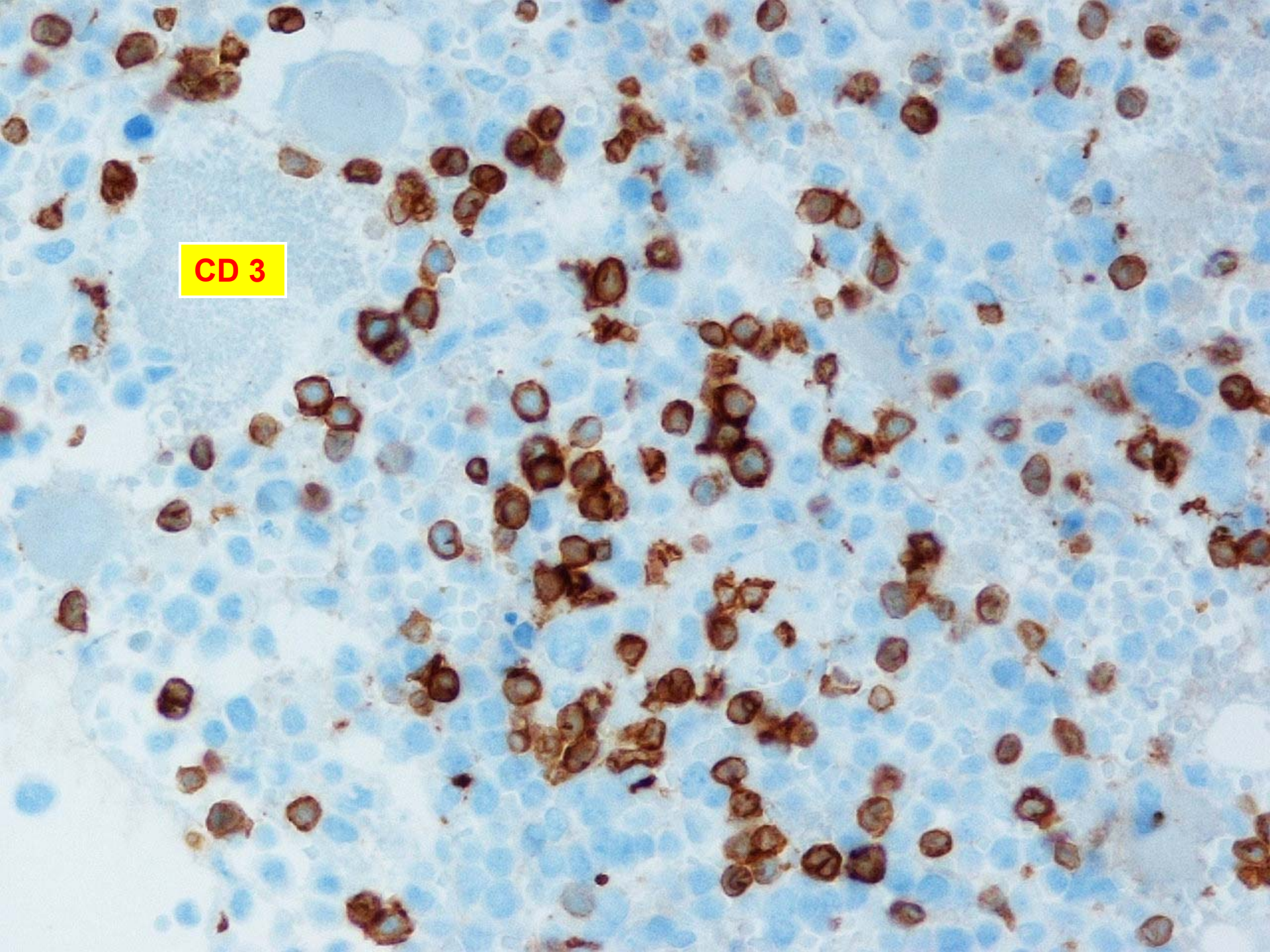




Bone marrow morphology

- Smaller population of similar atypical cells



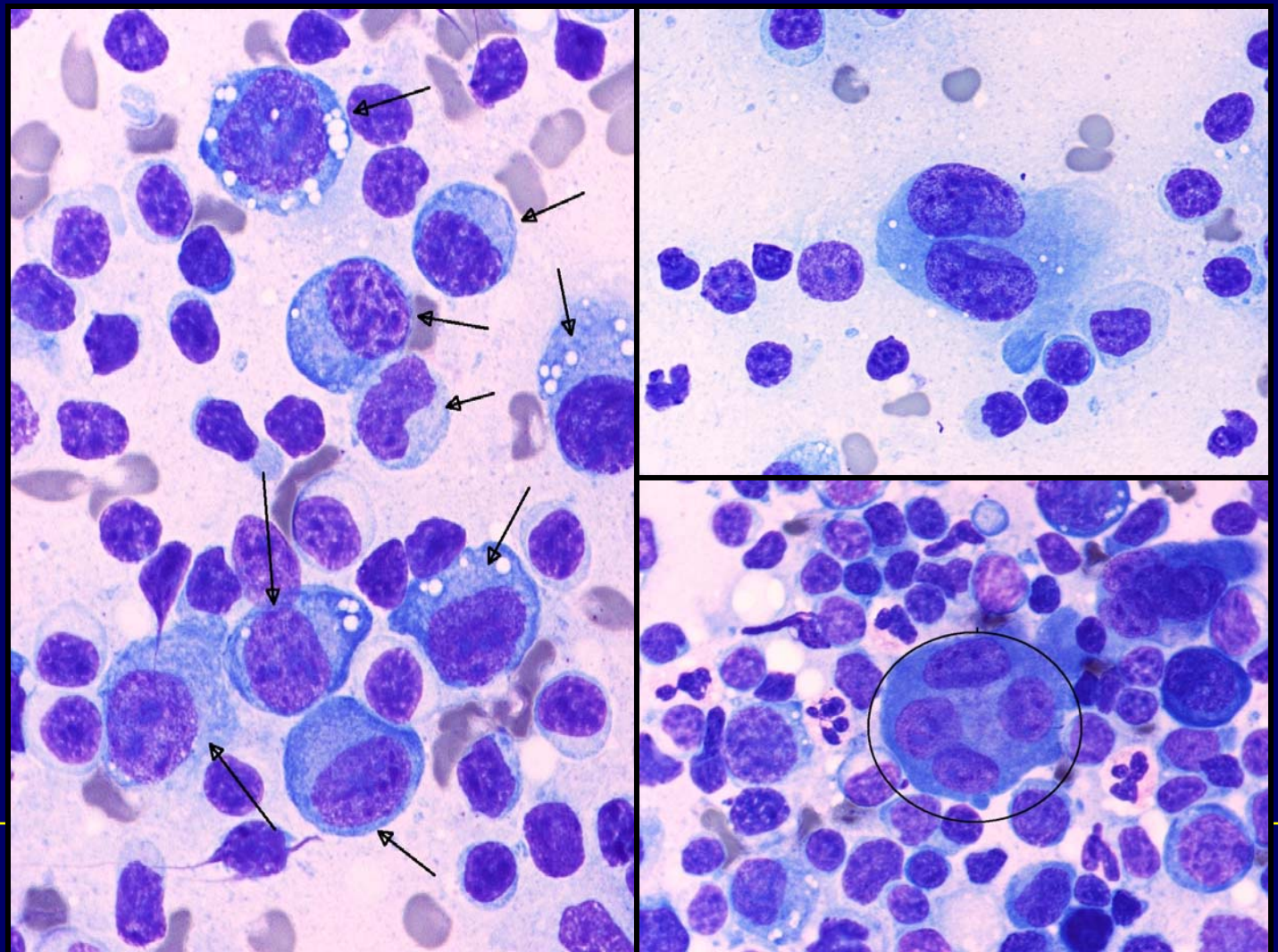

CD 3

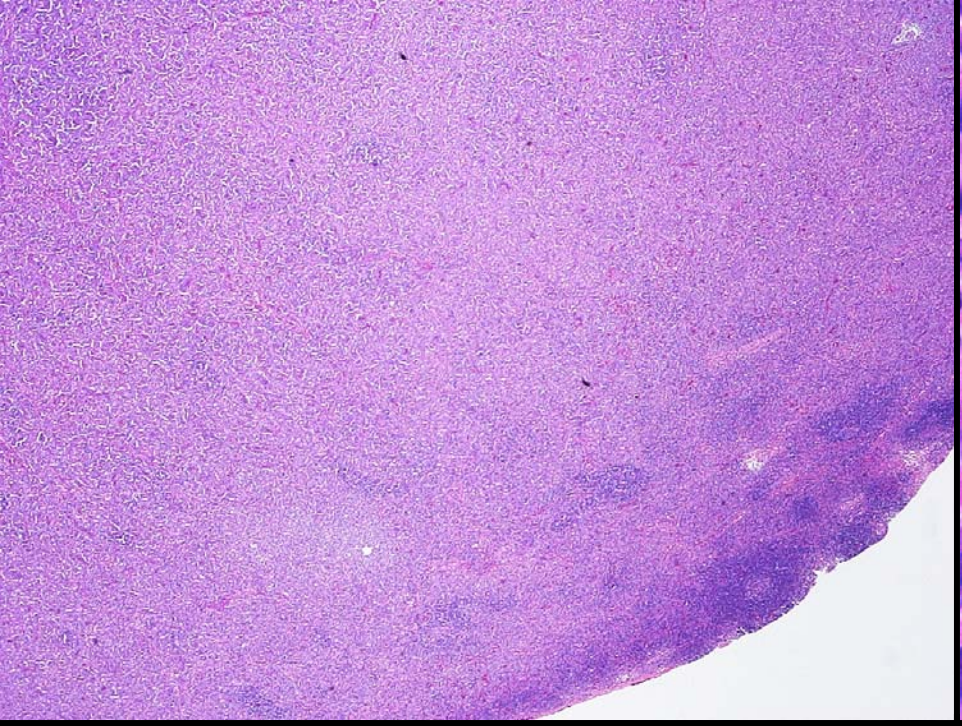
Lymph node biopsy

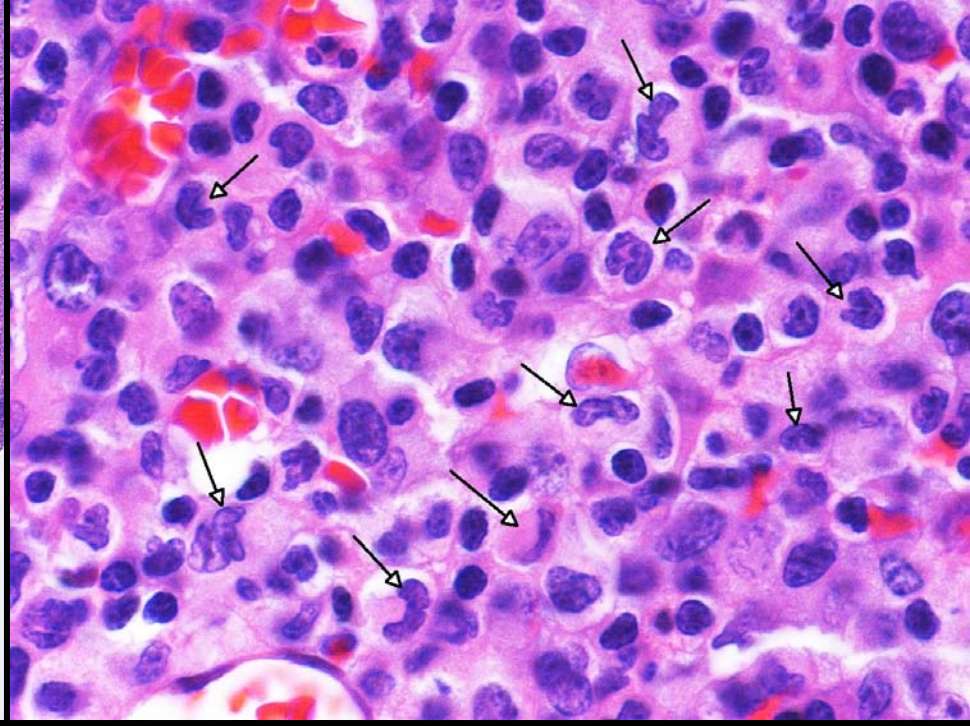
- Peripheral blood and bone marrow findings not definitively diagnostic of a specific entity
- Decision made to obtain a lymph node biopsy

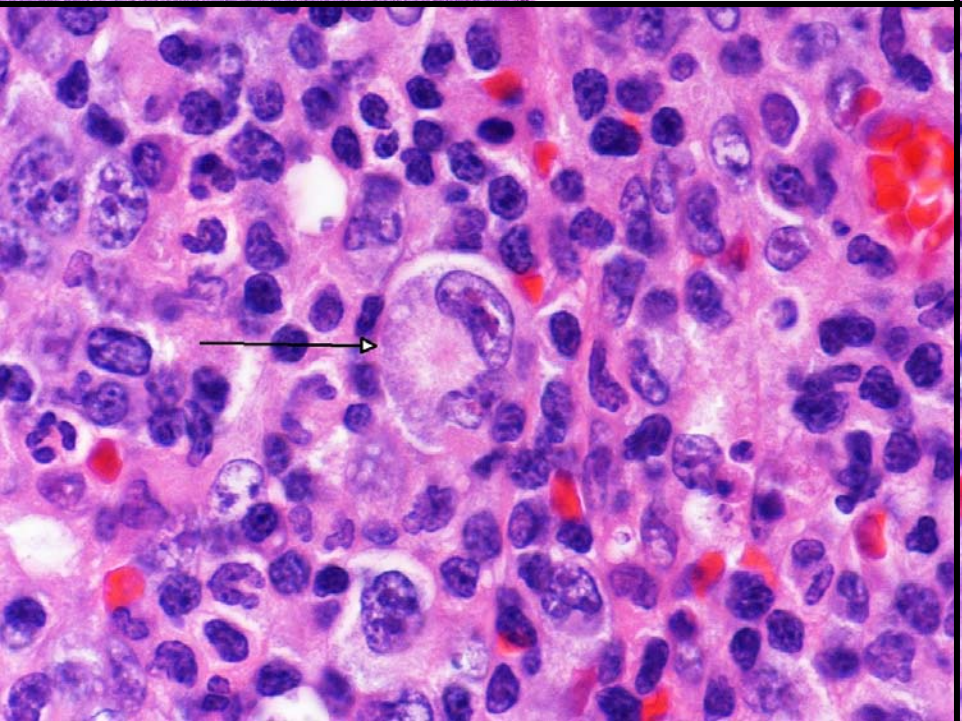
Lymph node biopsy

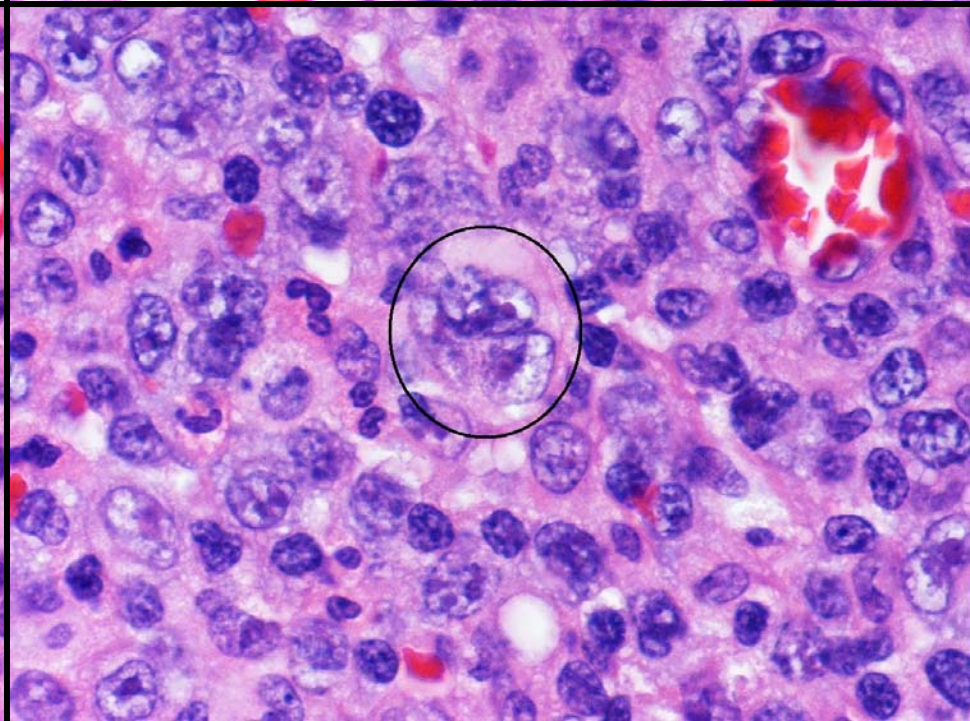
- Touch imprints: Large cells including wreath-like cells









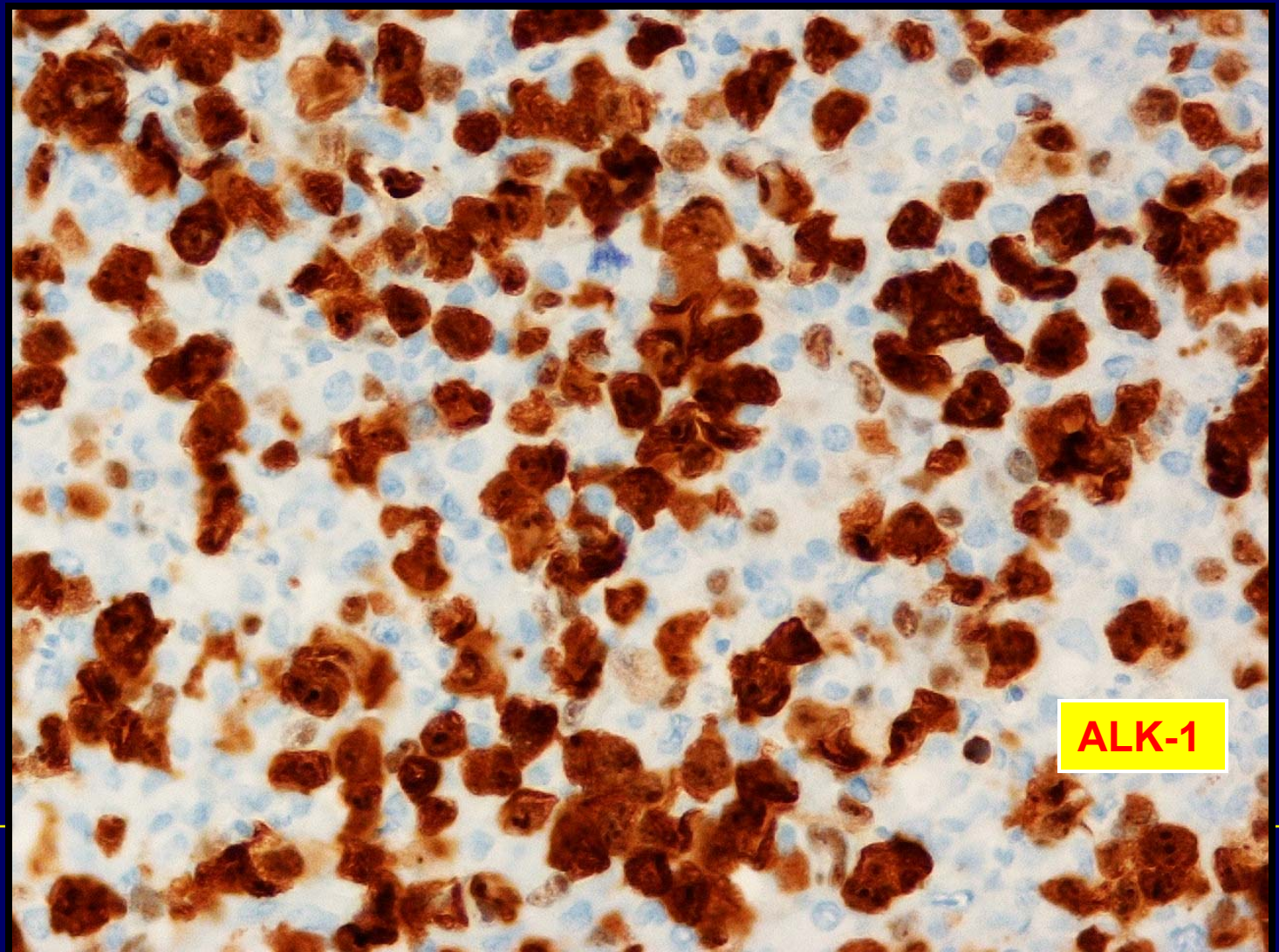


Lymph node biopsy

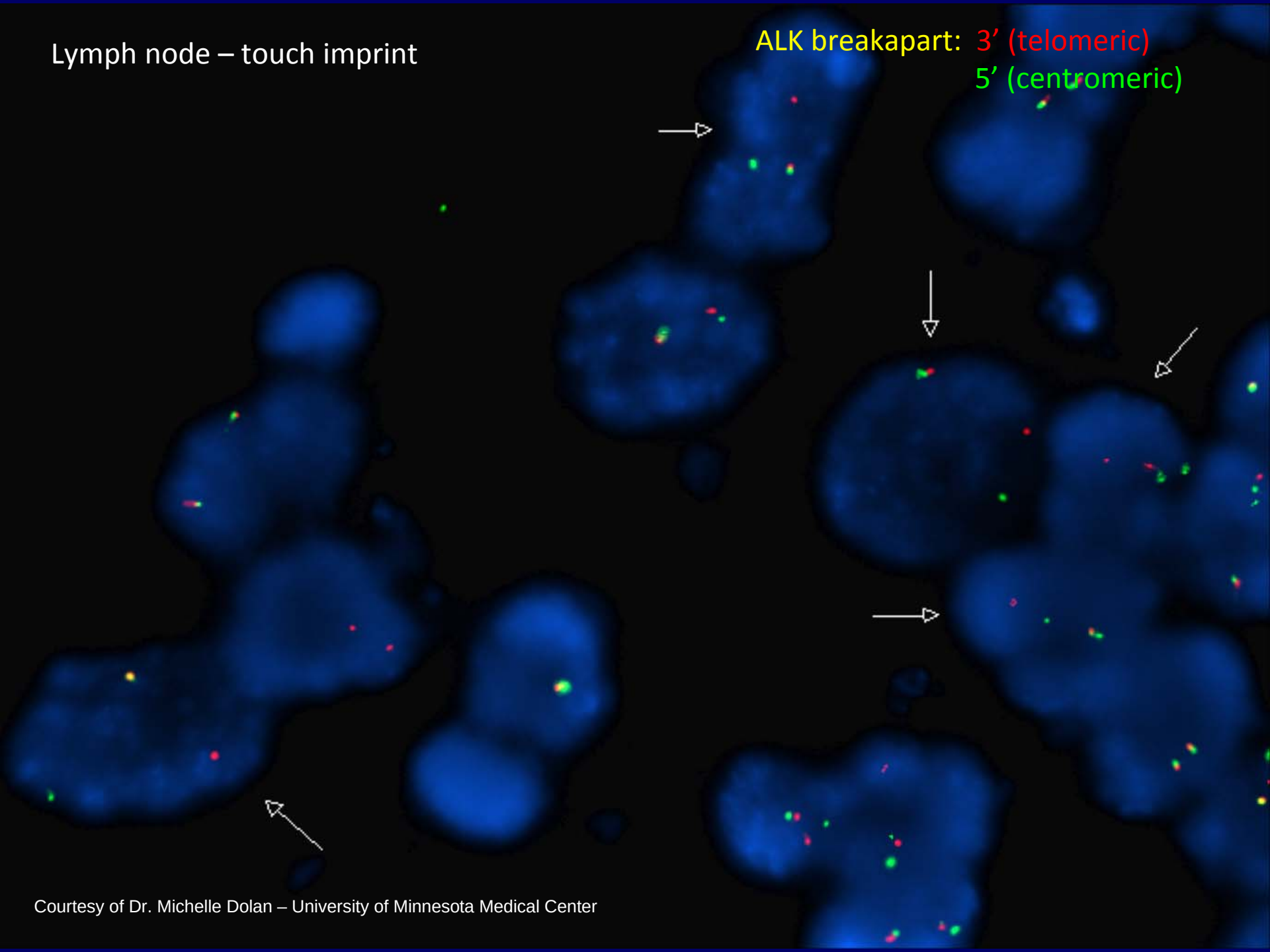
- Almost completely effaced normal lymphonodular architecture
- Majority of neoplastic cells – small
- Larger cells including "hallmark" and wreath-like cells – easily identifiable
- Also noted Reed-Sternberg-like cells
- Strongly suggestive now of ALCL

Lymph node biopsy

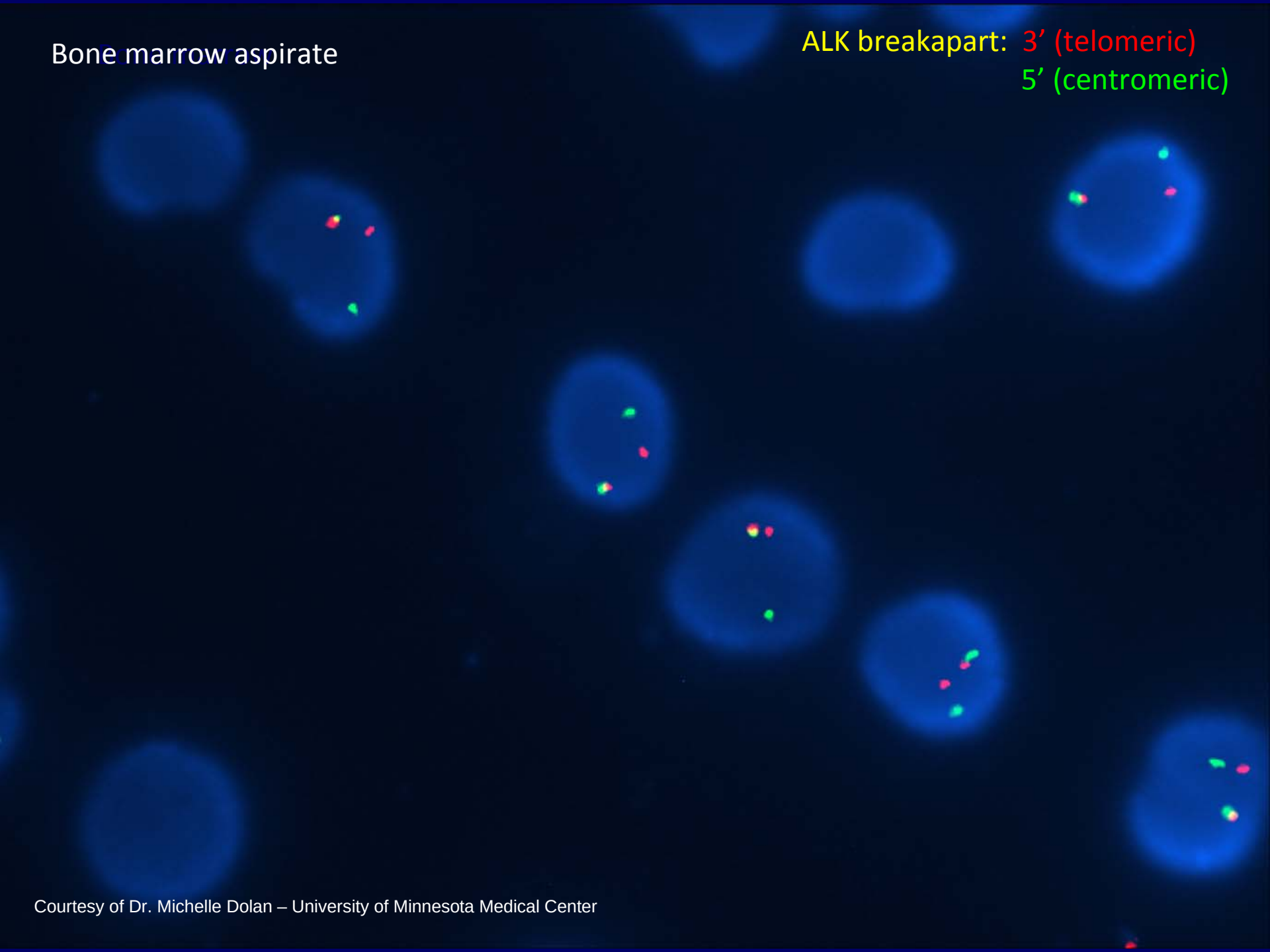
- Confirmed by ALK-1 IHC and FISH



Lymph node – touch imprint



Courtesy of Dr. Michelle Dolan – University of Minnesota Medical Center



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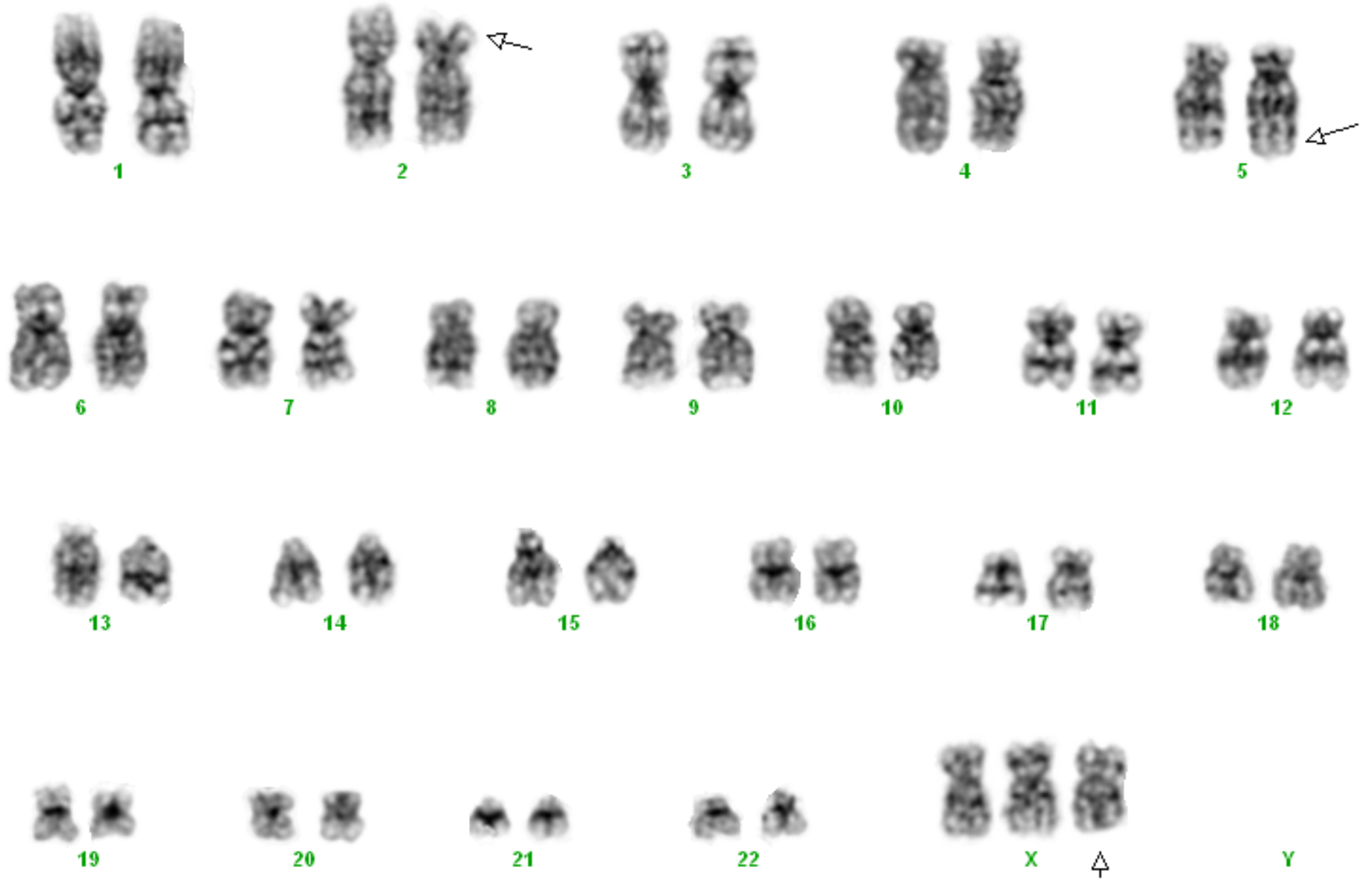

47,XX,+X,t(2;5)(p23;q35)

Courtesy of Dr. Michelle Dolan – University of Minnesota Medical Center

Diagnosis

- **Anaplastic large cell lymphoma, ALK-positive, small cell variant, with leukemic presentation**
  - Malignant cells: BM – 12%, PB – 44%
  - FISH positive for t(2;5)
  - Rare CD8-positive phenotype

Epidemiology & sites of involvement

Epidemiology:

- Median age: 14 years (range, 4 months–40 years)
- 5-10% of ALCL morphologic variants

Sites of involvement:

- Peripheral blood (leukemic presentation)
- Lymph nodes (prominent adenopathy)
- Skin (macular eruptions or subcutaneous nodules)
- Other extranodal sites: bone and soft tissue
- Bone marrow involvement: ~20% (IHC)
- Pleural and cerebrospinal fluid involvement possible

Clinical features

- Most patients – constitutional symptoms
- Common presentation with disseminated disease
- Peripheral and/or abdominal lymphadenopathy
- Extranodal infiltrates including skin lesions
- Often stage III/IV disease at initial diagnosis

Morphology

Peripheral blood – markedly atypical lymphoid cells:

- Prominent nuclear irregularities
- Dense, lobulated nuclei
- Azurophilic cytoplasmic granules
- Similar to ‘‘cerebriform’’cells (SS) or ‘‘flower’’ cells (ATLL)
- Abundant basophilic cytoplasm with small vacuoles

Bone marrow:

- Often very subtle
- Small clusters of small lymphocytes
- Only rare, scattered, large tumor cells
- Mass lesions uncommon
- More advanced lesions (much less common):
  - often lytic
  - fibrosis of the intertrabecular spaces
  - numerous small lymphocytes
  - scattered large transformed cells

Morphology - continued

Skin:

- Superficial dermis to subcutis
- Predominantly diffuse infiltrate within tumor nodules
- Perivascular and periadnexal distribution in macular eruptions
- Overlying epidermal hyperplasia
- Focal epidermotropism

Solid organ:

- Small irregular lymphocytes and rare large lymphocytes
- May be subtle - IHC
- “Fried egg” cells, “signet ring” cells
- Large cell component frequently and characteristically surrounding small vessels

Immunophenotype

- Characteristic differential staining of the small, medium, and large cells:
  - **CD30:**
    - large cells - cell membrane and Golgi region, prominent
    - small- and medium-sized cells - weak or negative
  - **EMA:**
    - positive in essentially all cases of the SCV
    - cell membrane and Golgi staining pattern similar to CD30
    - usually only a subset of malignant cells
  - **ALK:**
    - present in all reported cases (usually nuclear):
    - may be heterogeneous (similar to CD30)
    - large cells – strong and diffuse
    - small cells – only a subset, may be weaker
- T-cell phenotype in all reported cases of the SCV
- ‘‘Null-cell’’ phenotype may still exist (similar to other variants of ALCL)
- CD3 – commonly negative (similar to other variants of ALCL)
- CD8 – commonly negative
- CD2, CD5, and CD4 – positive in most cases
- At least one cytotoxic marker (TIA1, granzyme B, or perforin)
- Epstein-Barr virus – virtually always negative

Genetics

- 80-85% of ALK+ ALCL cases:
  - Characteristic t(2;5)(p23;q35) translocation
  - Fusion of the *NPM* and *ALK* genes
- 15-20%:
  - Variant translocations of *ALK* to a gene other than *NPM*
- Uncertain underlying cause for the more prevalent nuclear staining of ALK in SCV
- Clonal *TCR* gene rearrangements in most cases (similar to other variants of ALCL)

Treatment & prognosis

- **Currently no standardized therapy for ALCL-SCV:**
  - Combination chemotherapy
  - High-dose chemotherapy with stem cell support
  - Bone marrow transplantation
  - Hematopoietic stem cell transplantation
  - Other adjuvant therapies
- **Two-year survival: ~50% (73% in the common type)**
- **SCV may be very aggressive (despite being ALK+):**
  - Disseminated nature of the tumor?
  - Truly more aggressive tumor biology?
- **Reported in association with the CV, the LHV, as well as in association with the dual occurrence of the two variants**
- **Also reported – transformation of the SCV to CV and vice versa:**
  - Sign of a rapidly deteriorating clinical course?
  - 75% of patients in one study dying in less than a year
- **Anti-CD30:**
  - Brentuximab
  - Approved for ALCL
- **ALK inhibitors:**
  - Presently approved for NSCLC
  - Crizotinib – reports of sensitivity in ALCL

Summary

- SCV-ALCL – a disease often difficult to recognize
- In the differential diagnosis of any young patient presenting with constitutional symptoms and prominent adenopathy, with or without associated skin findings
- Subtle – major role for CD30 and ALK IHC:
  - May be confused with reactive processes
  - Often misdiagnosed as PTCL, NOS
- High propensity to disseminate – examination of PB
- Distinct association of SCV with leukemic presentation
- SCV – possibly a more aggressive lymphoma than other types of ALCL, ALK+

Follow-up on our patient

- Initially stage IV-B, CSF negative (7/11)
- Treated according to ANHL0131:
  - APO (doxorubicin, prednisone, vincristine/vinblastine)
  - Vincristine-associated neuropathy
  - Completed 6/12
  - End-of-therapy scans and BM – negative
- 10/12:
  - Relapse (right wrist) – biopsy proven
  - Negative scans, BM, and CSF
  - Brentuximab added (4 doses) – NED
- 3/13:
  - 8/8 HLA-matched HSCT (brother) after TBI
  - Uncomplicated post-HSCT course; no GVHD
- 6/13:
  - Day 100 – 100% engraftment
  - Second relapse (left inguinal) – biopsy proven
  - Crizotinib added
  - Brentuximab every 3 months
  - Scans negative since

References

- Delsol G, Jaffe ES, Falini B, et al. Anaplastic large cell lymphoma (ALCL), ALK-positive. In: Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: IARC Press; 2008:312–316.
- Summers TA, Moncur JT. The small cell variant of anaplastic large cell lymphoma. Arch Pathol Lab Med. 2010 Nov;134(11):1706-10.
- Ok CY, Wang SA, Amin HM. Leukemic phase of ALK(+) anaplastic large-cell lymphoma, small-cell variant: clinicopathologic pitfalls of a rare entity. Clin Lymphoma Myeloma Leuk. 2014 Aug;14(4):e123-6.
- Spiegel A, Paillard C, Ducassou S, Perel Y, Plantaz D, Strullu M, Eischen A, Lutz P, Lamant L, Le Deley MC, Brugières L. Paediatric anaplastic large cell lymphoma with leukaemic presentation in children: a report of nine French cases. Br J Haematol. 2014 May;165(4):545-51.
- Kinney MC, Collins RD, Greer JP, Whitlock JA, Sioutos N, Kadin ME. A small-cell–predominant variant of primary Ki-1 (CD30)+ T-cell lymphoma. Am J Surg Pathol. 1993;17(9):859–868.
- Bayle C, Charpentier A, Duchayne E, et al. Leukeamic presentation of small cell variant anaplastic large cell lymphoma: report of four cases. Br J Haematol. 1999;104(4):680–688.
- Onciu M, Behm FG, Raimondi SC, et al. ALK-positive anaplastic large cell lymphoma with leukemic peripheral blood involvement is a clinicopathologic entity with an unfavorable prognosis. Am J Clin Pathol. 2003;120(4):617–625.
- Grewal JS, Smith LB, Windegarden JD III, Krauss JC, Tworek JA, Schnitzer B. Highly aggressive ALK-positive anaplastic large cell lymphoma with a leukemic phase and multi-organ involvement: a report of three cases and a review of the literature. Ann Hematol. 2007;86(7):499–508.
- Hodges KB, Collins RD, Greer JP, Kadin ME, Kinney MC. Transformation of the small cell variant of Ki-1+ lymphoma to anaplastic large cell lymphoma: pathologic and clinical features. Am J Surg Pathol. 1999;23(1):49–58.
- Greer JP, Batt MA, Whitlock JA, et al. Clinical features of the small cell variant (SCV) of Ki-1+ anaplastic large cell lymphoma (ALCL). Blood. 1995; 86(suppl 1):532a.