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
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

ALK breakapart: 3′ (telomeric)
5′ (centromeric)

Courtesy of Dr. Michelle Dolan – University of Minnesota Medical Center
Bone marrow aspirate

ALK breakapart: 3' (telomeric)
5' (centromeric)

Courtesy of Dr. Michelle Dolan – University of Minnesota Medical Center
47,XX,+X,t(2;5)(p23;q35)
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 inter trabecular 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