

CASE HISTORY: A 50 year old Chinese female presented with shortness of breath, and was found to have a 5cm anterior mediastinal mass, bilateral pleural effusions and pericardial effusion. Thoracentesis and pericardiocentesis showed atypical lymphocytosis with reportedly “indeterminate” flow findings and no evidence of T-cell receptor gene rearrangement. Bone marrow exam at the time was reportedly negative. Patient was treated with ALL chemotherapy for presumed lymphoblastic lymphoma. Six months later, 2 weeks after last chemotherapy, patient presented with sepsis and leukocytosis.

PATHOLOGY:

Microscopic:

Peripheral blood (Fig. 1 A,B): Leukocytosis with left shifted granulocytosis and occasional atypical circulating lymphocytes. The atypical lymphoid cells are large with clumped chromatin, prominent nucleoli and moderately abundant basophilic cytoplasm, with occasional plasmacytoid forms. A few have somewhat blastic chromatin and some cytoplasmic granules are seen.

Flow cytometry (Fig. 2): Only positive for CD3+ with high forward scatter.
Negative for CD2, CD4, CD8, CD5, CD7, CD56, CD34, CD1a, TdT, and all B-lineage and myeloid antigens

Molecular (blood): Positive for TCR-gamma gene rearrangement.

Bone Marrow (Fig. 1 C,D): Morphologically subtle interstitial infiltrate of large lymphoid cells, highlighted by CD3 immunostain (negative for CD2, CD5 and TdT by immunostains).

DISCUSSION:

IMMATURE VS MATURE

The differential diagnosis of T-cell disorders involving peripheral blood first requires a distinction between an immature or lymphoblastic process versus a mature T-cell disorder. The clinical history of a mediastinal mass would favor consideration of precursor T-lymphoblastic lymphoma/leukemia (T-ALL). Mature T-cell lymphomas involving thymus have been described, though much less commonly. Cytologically, T-ALL shows cells with immature “blastic” finely dispersed chromatin and prominent nucleoli; or, alternatively, the lymphoblasts may have very condensed chromatin without nucleoli. Mature T-cell lymphomas show considerable cytologic variation depending on type (see below) but tend to have more clumped chromatin. Phenotyping is critical diagnostically, with demonstration of TdT reactivity essential for establishing an immature or lymphoblastic phenotype. Other markers have been used to stratify T-ALL into phenotypic stages correlating with intrathymic differentiation (see Table 1), and may also indicate T-cell immaturity (e.g. CD1a). Aberrant expression of myeloid antigens is fairly common (20%) in T-ALL, and is not seen in mature T-cell neoplasms. TCR gene

rearrangements are seen in both immature and mature T-cell neoplasms, but are not lineage specific for immature blastic tumors (e.g. present in pre B-ALL). In this case, the lack of TdT and predominant non-blastic morphology argue against T-ALL.

MATURE T-CELL LEUKEMIAS:

The differential diagnosis of mature T-cell disorders with prominent leukemic phase typically includes T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia (T-LGL), Sezary syndrome/mycosis fungoides (SS/MF) and adult T-cell leukemia/lymphoma (ATLL). Other peripheral T-cell lymphomas may also have circulating tumor either at diagnosis (particularly peripheral T-cell lymphoma, NOS) or as a late complication. Distinguishing the mature T-cell leukemias, according to WHO schema, requires integration of clinical, phenotypic, cytologic/histologic and molecular/genetic data. Serologic or PCR study for HTLV-1 is also necessary if ATLL is suspected or in differential. Knowledge of the characteristic features of the various T-cell leukemias is important, as is recognition of areas of potential overlap, as most features are not entirely specific.

T-cell prolymphocytic leukemia (T-PLL):

- Marked lymphocytosis (>100K/uL)
- Generalized lymphadenopathy, hepatosplenomegaly
- May have skin involvement, effusions
- Medium sized lymphoid cells with prominent nucleolus (less often small cell or cerebriform morphology)
- HTLV-1 negative
- Most CD4+ CD8- (60%), with bright CD7 (negative for TdT, CD1a)
 - o Double positive CD4+ CD8+ in 25%; CD4- CD8+ in 15%
 - o CD3 expression variable, CD52 bright (Rx alemtuzumab)
- Common inv(14)(q11;q32) or t(14;14)(q11;q32)
- Reported TCL-1 positive, by immunohistochemistry
- Usually aggressive course with poor prognosis
- Subset of cases present with initially indolent course with lower WBC, with eventual progression

Adult T-cell leukemia/lymphoma (ATLL):

- endemic in SW Japan, Caribbean, SE U.S., Central and South America
- HTLV-1 +; long latency (10-30 years; median age at dx 58 years)
- Clinical subtypes: Acute, Lymphomatous, Smoldering, Chronic
- Lymphadenopathy, hepatosplenomegaly, skin lesion, osteolytic lesions, hypercalcemia, CNS lesions
- Blood involvement most marked in Acute subtype
- Peripheral blood shows medium to large lymphoid cells with polylobated or “flower”-like nucleus
- Helper phenotype (CD2+, CD3+, CD4+) with CD25 (CD7 often decreased/absent)

T-cell Large Granular Lymphocytic Leukemia (T-LGL):

- Clonal expansion of LGL cells
 - o Requires sustained increase in LGL (>2000/uL) OR demonstration of clonality (TCR rearrangement)
- Usually indolent course (median survival = 10 yrs), but may have significant associated cytopenias
 - o Many patients present with recurrent bacterial infections
 - o Neutropenia common (>80%)
 - o Anemia (50%) and thrombocytopenia (20%) common
 - May present as pure red cell aplasia
- Splenomegaly common; usually no LAN
- Autoimmune association (RA, AIHA, PRCA, ITP...)
- Cytotoxic phenotype most common: CD3+, CD8+, CD16+, CD57+
- TCR-rearrangements present in T-cell LGL

Mycosis fungoides/Sezary Syndrome (MF/SS):

- Sezary syndrome is clinicopathologic diagnosis, usually evident clinically
 - o Erythroderma, lymphadenopathy, numerous circulating T-cells with cerebriform nuclei (>1000/uL)
- Helper phenotype: CD3+, CD4+ with variable loss of CD7

Other peripheral T-cell lymphomas:

- Peripheral T-cell lymphoma, NOS, may show leukemic cells at presentation
- Leukemic phase of other T-cell lymphomas also occasionally occurs, more often as late complication (hepatosplenic TCL, AILT, extranodal NK/T –cell lymphoma)
- Diagnosis rests of prior history and/or exclusion of other more common T-cell leukemias
- Aberrant phenotypic loss of T-cell antigens common

FINAL DIAGNOSIS:

Peripheral T-cell lymphoma, NOS, involving peripheral blood and bone marrow

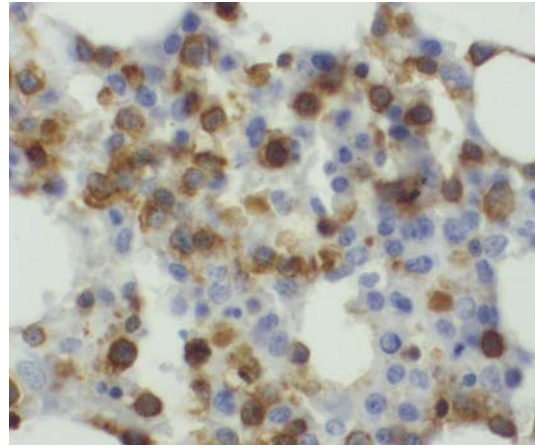
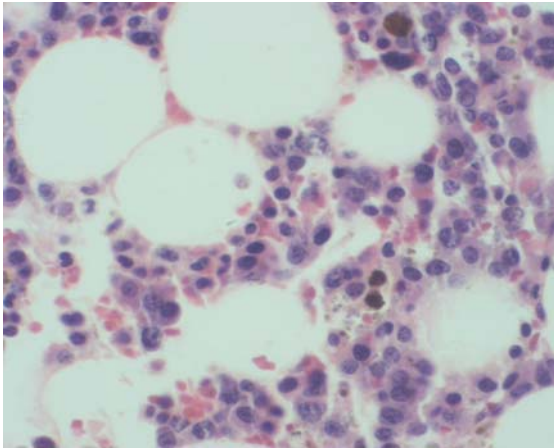
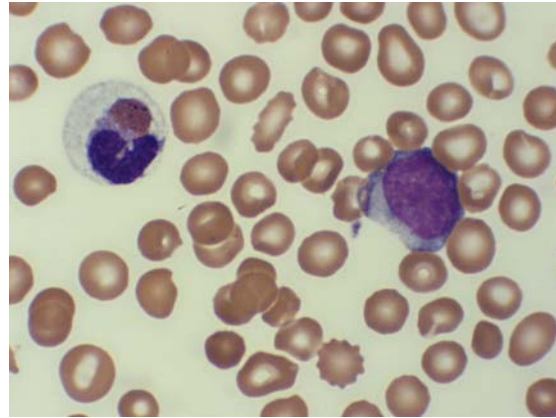
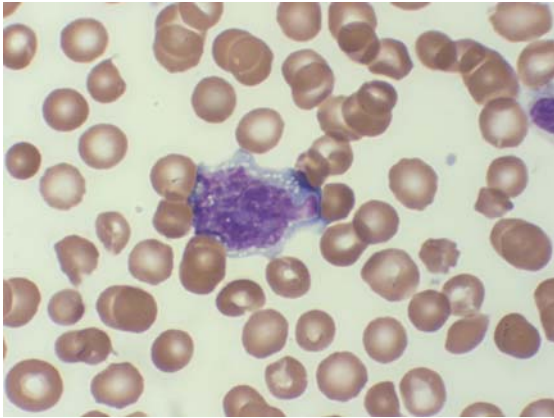
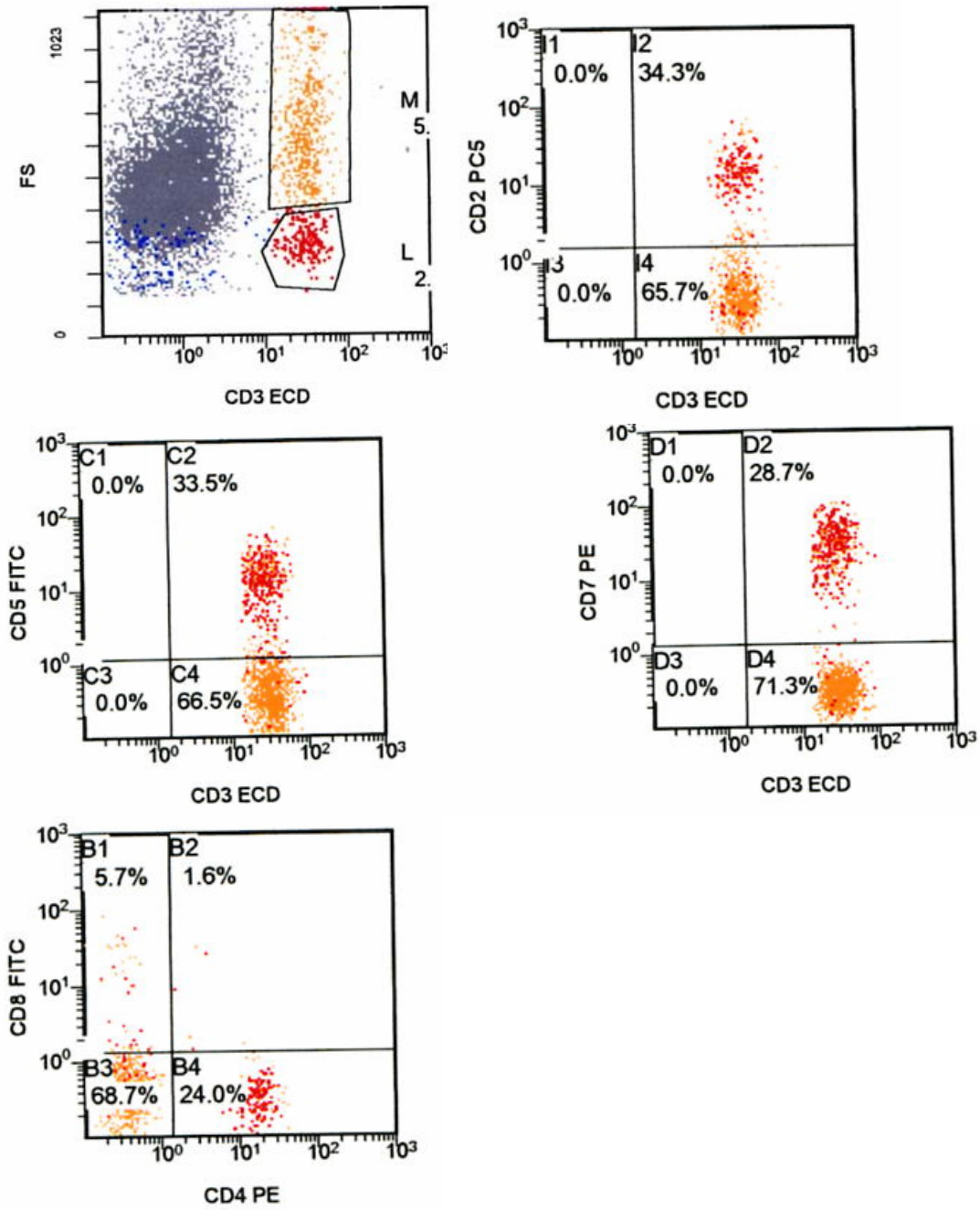


FIGURE 1:

A,B: Peripheral Smear with atypical circulating lymphocytes.

C,D: Bone marrow with CD3 immunostain highlighting atypical large cell infiltrate.

FIGURE 2:



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Figure 3

