Case of the Month

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Case History

- 61 year old female
- Persistent asymptomatic lymphocytosis since 1 year

Examination

- Oriented to time, place and person
- Mild pallor present, no icterus, afebrile
- Pulse 78/min, BP 118/76mm Hg
- No lymphadenopathy
- P/A examination: no hepato-splenomegaly

Investigations

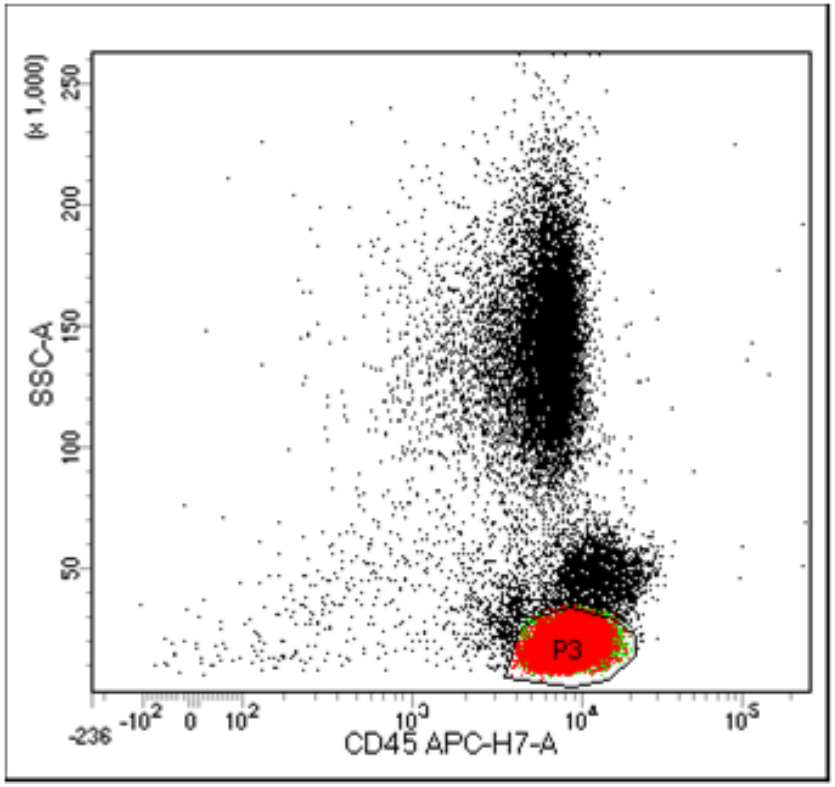
- CBC
  - Hb - 10.8 gm%, TLC – 6610/cumm, Platelets: 2.06 lakh/cumm
  - Differential count showed 71% lymphocytes with predominance of granular lymphocytes
  - Immunophenotyping by flow cytometry was advised to rule out lympho-proliferative disorder
- ANA was negative
- No organomegaly on imaging

Flow cytometry

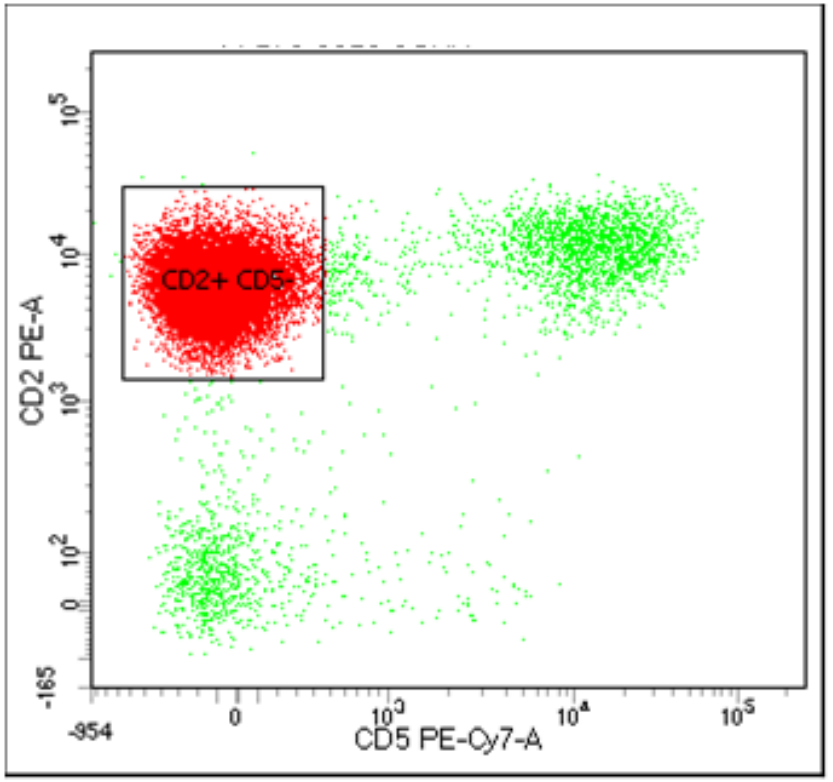
- Lymphocytes constituted 66% of Non Debris singlets
- Mature T cells: Constituted 3% of all lymphocytes
- An abnormal population was identified which was 80% of all lymphocytes

Immunophenotype

SSC Vs CD45

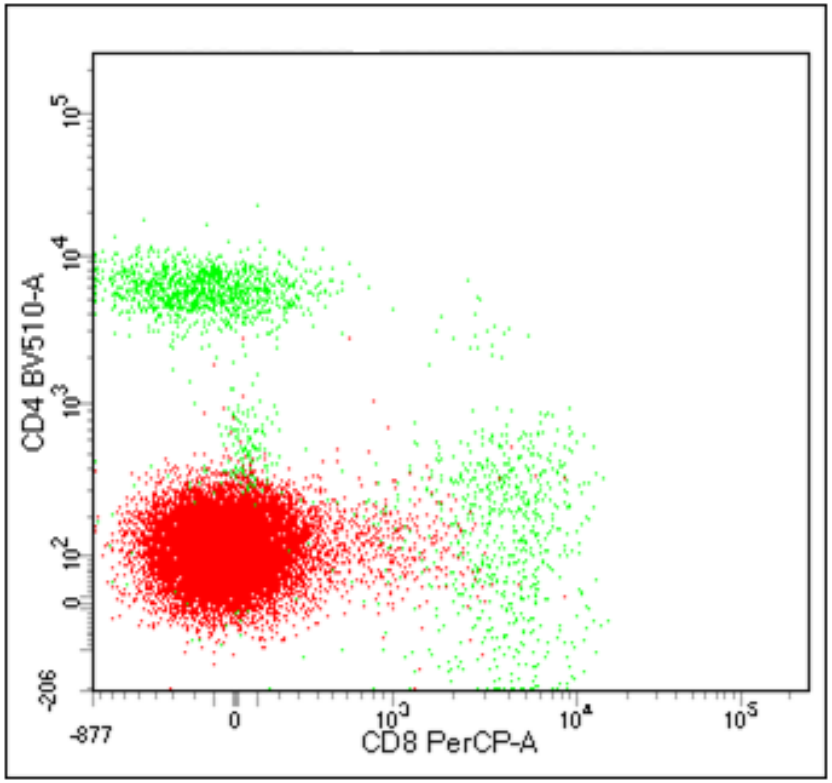


CD2 Vs CD5

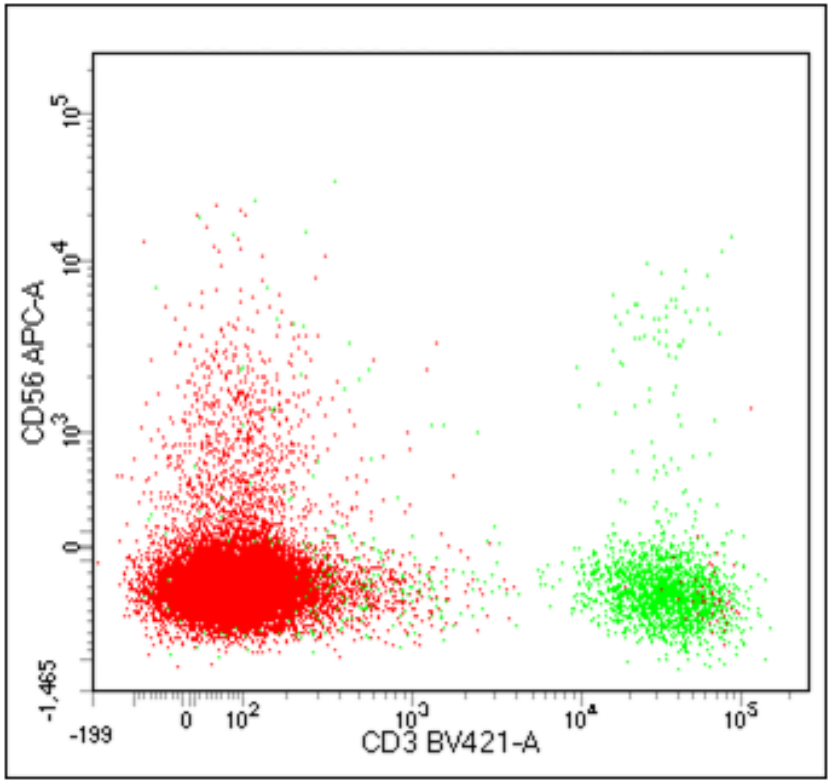


Immunophenotype

CD4 Vs CD8

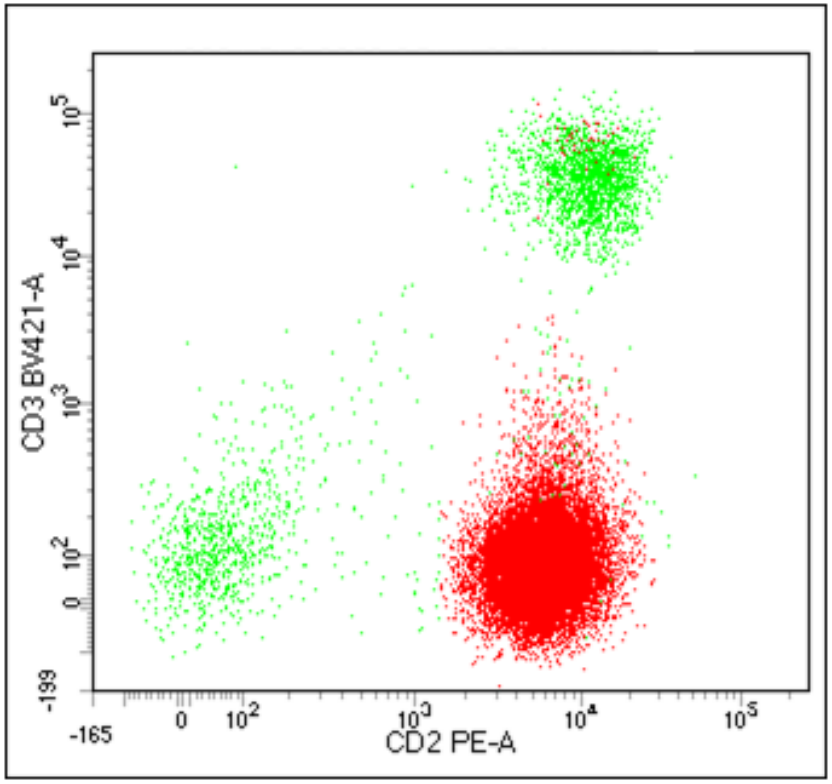


CD56 Vs CD3



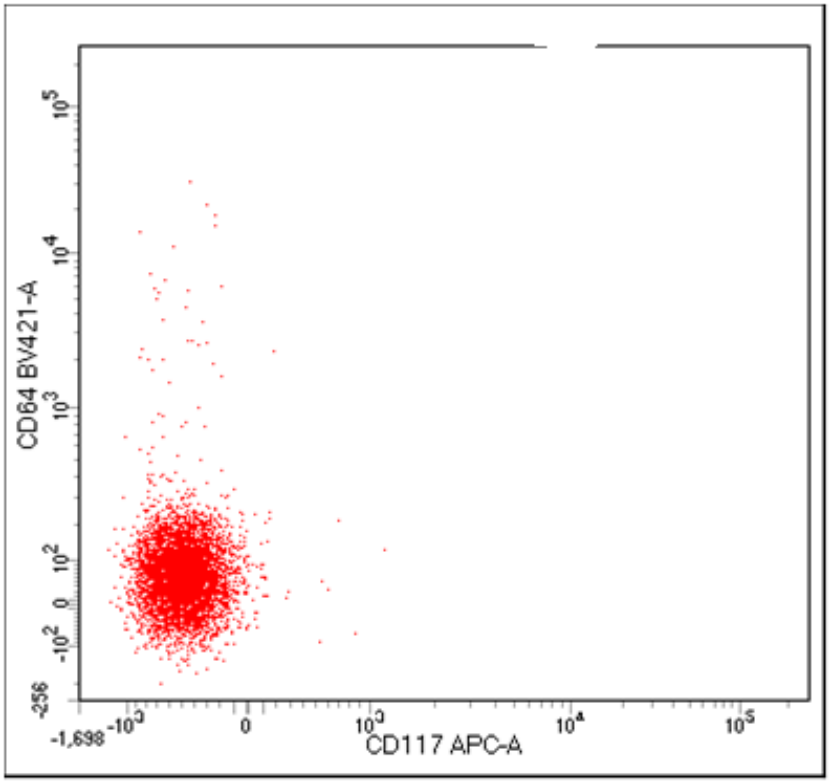
Immunophenotype

CD3 Vs CD2

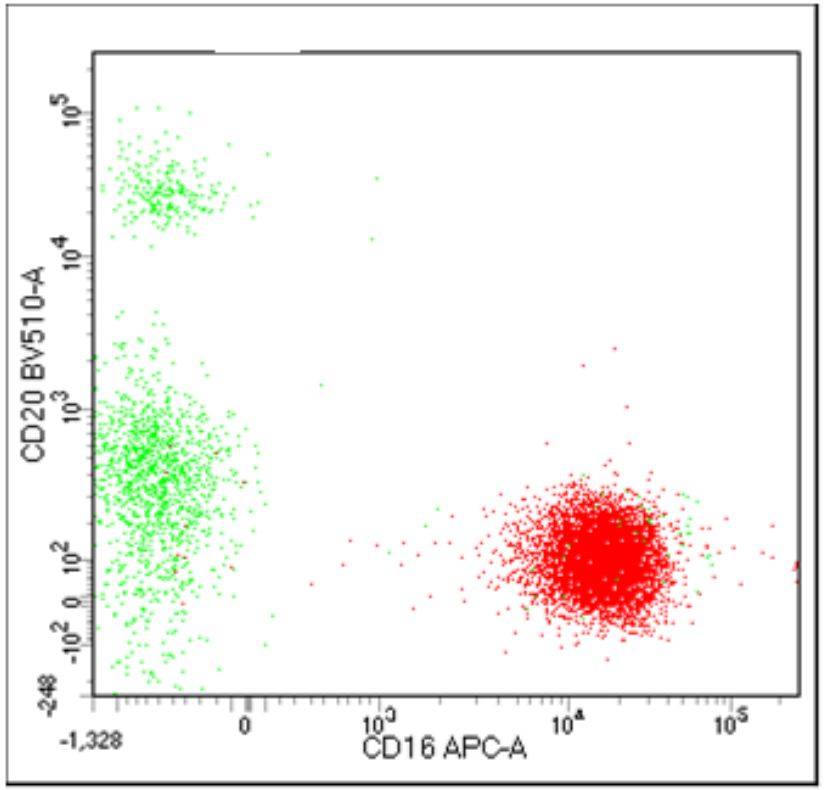


Immunophenotype

CD64 Vs CD117

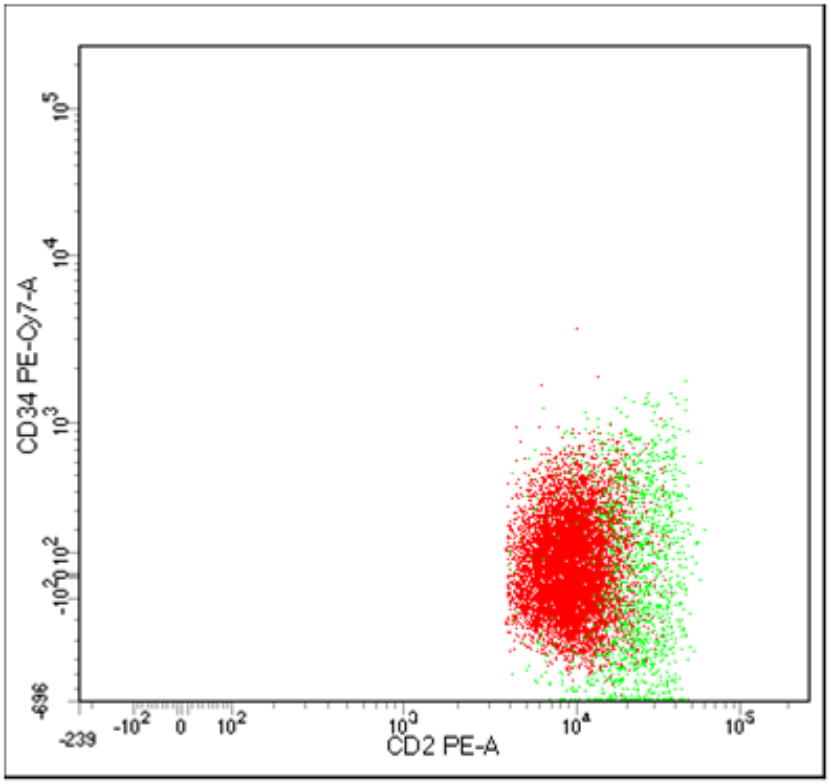


CD20 Vs CD16

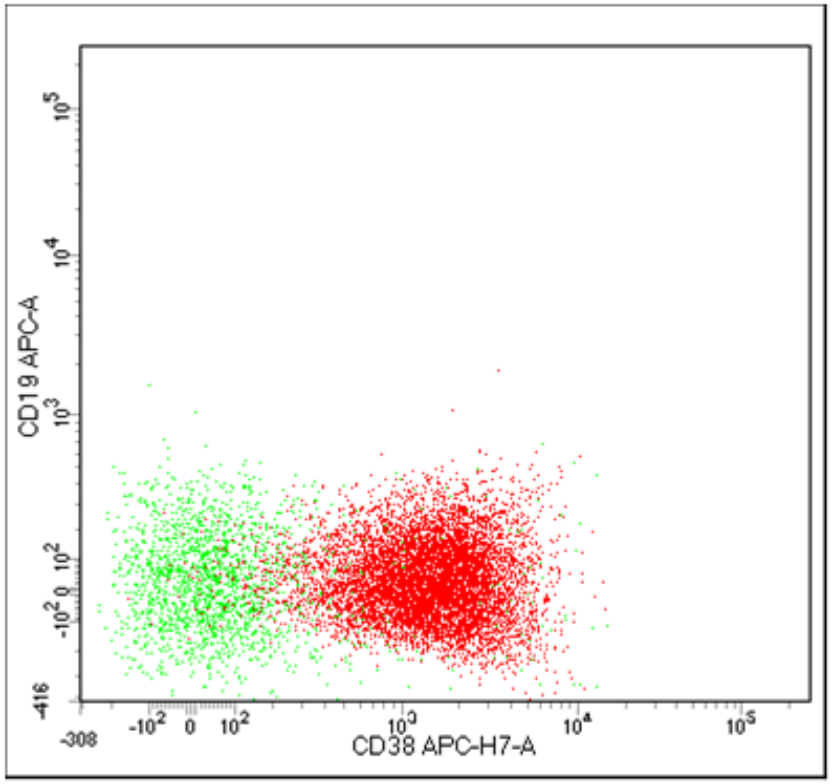


Immunophenotype

CD34 Vs CD2

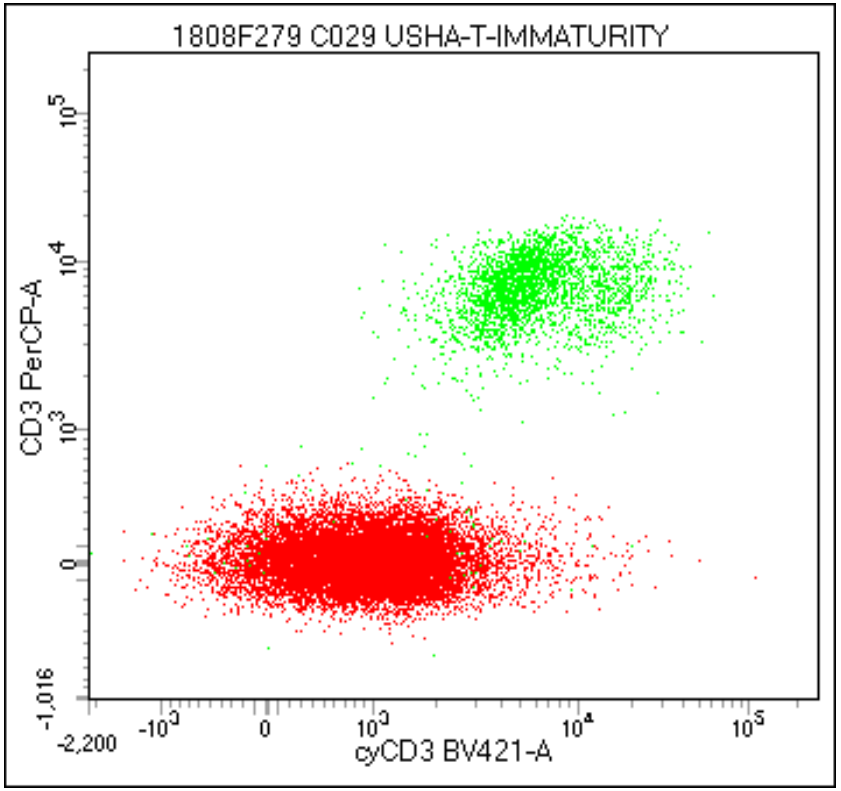


CD19 Vs CD38

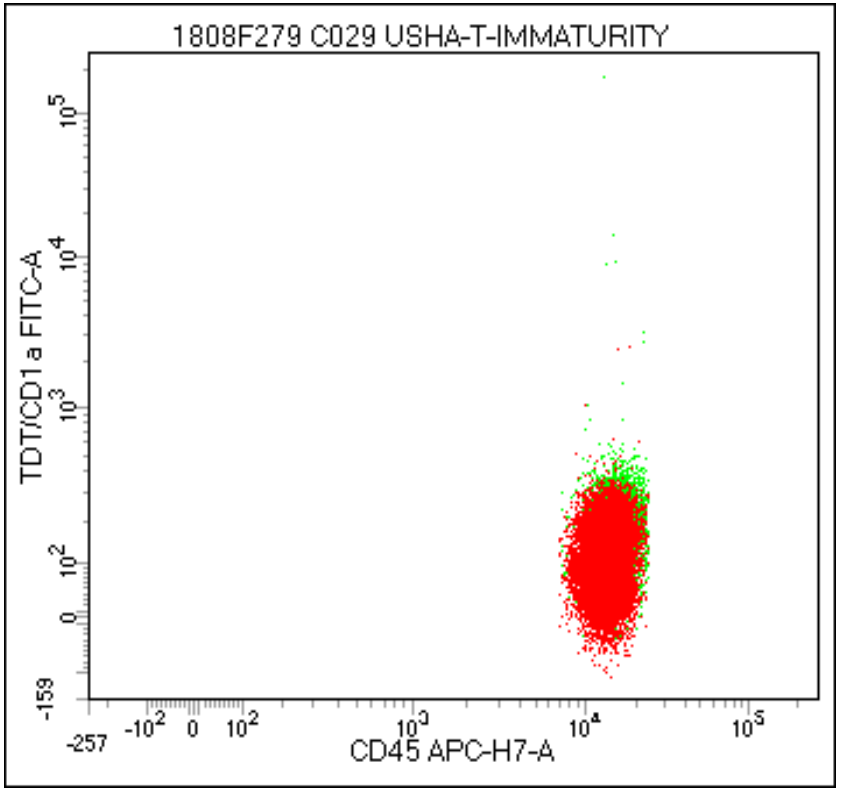


Immunophenotype

Surf Vs Cyto CD3



Tdt/CD1aVs CD45



Flow cytometry (Summary)

- Positive Markers: CD45(Bright), CD2(Bright), CD7(Dim), CD16(Bright), CD38(Bright), Cyto CD3 (Dim, UCTH1 clone Epsilon chain specific)
- Negative markers: CD5, CD56, CD4, CD8, Surface CD3, B-Cell markers, Myeloid Markers & Immaturity markers

Final Diagnosis

Chronic lymphoproliferative disorder of NK cells (CLPD-NK)

Discussion

- Chronic lympho-proliferative disorders of NK cells (CLPD-NKs) are rare CLPD considered as a provisional entity in WHO 2016 classification
- Characterised by persistent peripheral blood leukocytosis of NK cell origin without an identifiable chronic infectious or other reactive cause

Etiopathogenesis

- Age of Onset:
  - median patient age 60 years
  - no sex predominance
- Etiology
  - NK-cell activation due to an unknown stimulus, presumably viral
  - Although no evidence of direct NK-cell infection has been observed
- Organs involved
  - Peripheral blood and bone marrow

Clinical Presentration

- Usually insidious onset with incidental detection on routine blood counts
- Presence of lymphadenopathy and systemic symptoms are rare
- Presence of systemic symptoms should raise possibility of NK cell proliferation secondary to other neoplastic, autoimmune or infectious conditions

Peripheral Blood findings

- Peripheral blood lymphocytosis of predominantly small to intermediate sized lymphocytes with fine azurophilic granules
- The counts should be persistently increased for > 6 months
- Absolute NK cell count > 2000 per cumm

Bone Marrow Findings

- These cases usually have interstitial and intra-sinusoidal predominantly small cells with moderate pale cytoplasm and are difficult to identify on light microscopy
- Bone marrow aspiration and biopsy was not done in the present case

Immunophenotype

- T cell markers
  - Cyto CD3 with epsilon chain
  - Variable expression of CD2, CD5, CD7
  - CD8 is usually expressed uniformly (absent in current case)
  - CD4 and Surface CD3 are negative
- NK cell markers
  - CD16 is positive and CD56 is frequently absent or underexpressed
  - Granzyme B and TIA1 are positive

Molecular and Cytogenetics

- Cytogenetics is frequently normal
- STAT3 activating mutations are described in upto 1/3rd of the cases
- EBV negativity and benign clinical profile are the important differentiating features from Aggressive NK cell leukemia

Clinical Course

- In most patients, the clinical course is indolent over a prolonged period
- No therapy is needed
- The management of CLPD-NKs is similar to that of T-cell large granular lymphocytic leukemia
- Disease progression with increasing lymphocytosis and worsening of cytopenia is observed in some cases

Clinical Course

- Cytopenia, recurrent infections and co-morbidity→ harbingers of worse prognosis
- Rare cases
  - spontaneous complete remission
  - transformation to an aggressive NK-cell disorder
- Cytogenetic abnormalities may imply a worse prognosis and could be associated with rare transformations

Take Home Message

- Persistent asymptomatic peripheral blood lymphocytosis should raise a suspicion for underlying lympho-proliferative disorder
- In addition to CLL other rare CLPDs like LGL leukemia and CLPD-NK may have similar presentation
- These indolent cases of NK cell malignancies may be missed if isolated CD56 is used as primary gating marker

Take Home Message

- Other NK cell markers like CD16 and T cell markers for aberrant expression should be used in clinically suspected cases
- Before signing out a diagnosis of CLPD-NK a thorough clinical and radiological examination is required to rule out underlying neoplastic, Infectious or chronic inflammatory disorder

THANKS