Vanquishing the Hydra: A Novel Therapeutic Approach in Multi-Refractory T-Cell Prolymphocytic Lymphoma/Leukaemia (T-PLL)

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Clinical Case - Referral

- ***Lymphocytosis*** x 2 Months – Please see (June 2022)
- 68-year-old male
- **PMHx:**
  - Tonsillectomy
  - Previous clavicular & tibial fractures
  - Hypercholesterolaemia
  - COVID-19 (Dec 2021)
- **Medications**
  - Rosuvastatin 20mg Nocte (NKDA)
- **Social Hx:**
  - Retired marine engineer. Married with 4 children
  - Ex-Smoker. Alcohol 4 Unit/week

Parameters	Value
Haemoglobin	12.5 g/dL
White Cells	22.0 x 10^9/L
Neutrophils	1.9 x 10^9/L
Lymphocytes	19.1 x 10^9/L
Monocytes	0.1 x 10^9/L
Eosinophils	0.1 x 10^9/L
Platelets	162 x 10^9/L
MCV	91 fL
LDH	283 U/L

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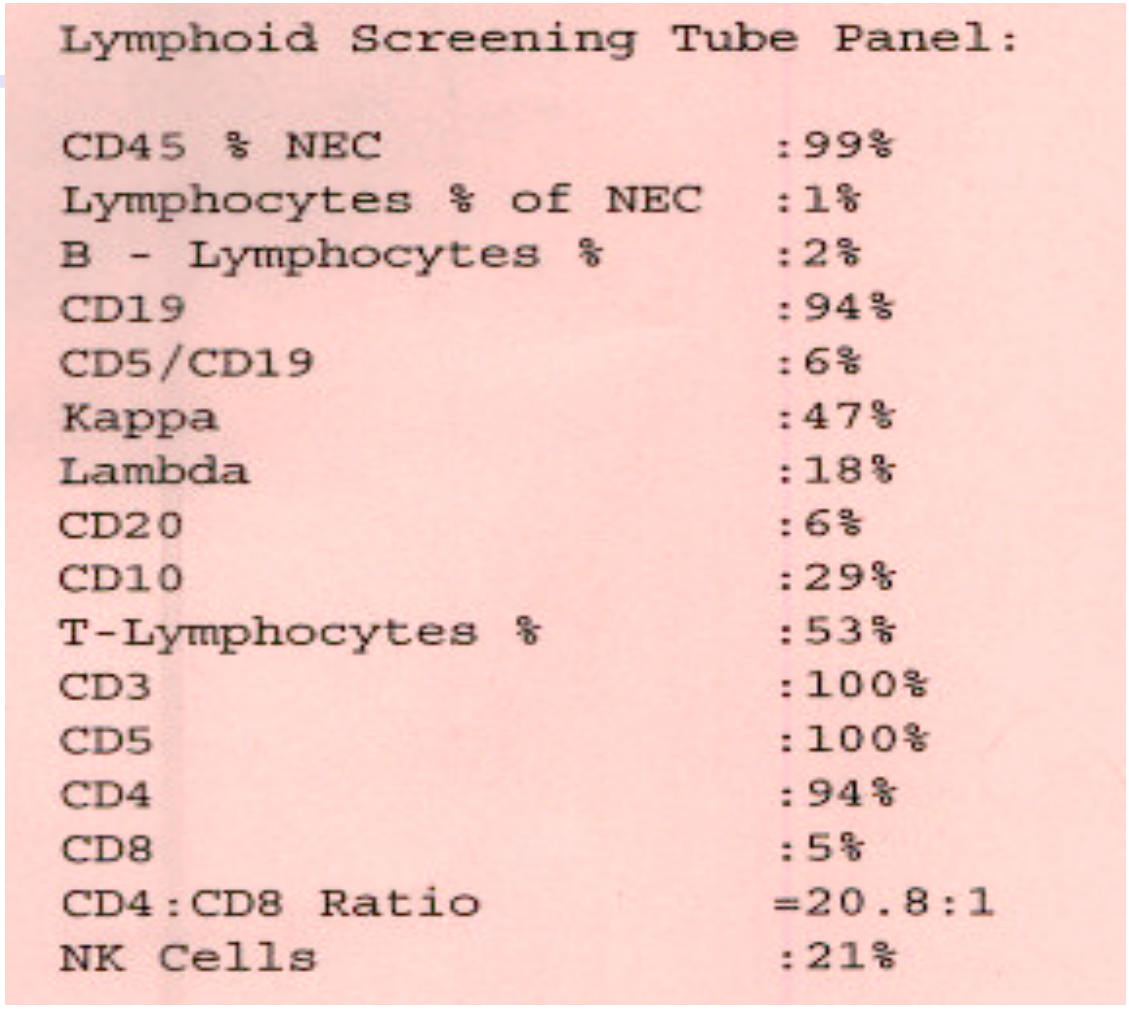
Assessment

- **Clinical:**
  - Asymptomatic
  - No B Symptoms
- **Examination:**
  - Palpable liver and spleen on inspiration.
  - Bilateral post auricular nodes, axillary nodes and inguinal nodes.
- **Immunophenotyping:**
  - No evidence of B-cell monoclonality
  - Referred for TCRs
- **CT TAP**
  - Diffuse low volume cervical, axillary, retroperitoneal and external iliac lymphadenopathy
  - Largest (1.2cm) – Right Inguinal



Lymphoid Screening Tube Panel:

CD45 % NEC	:99%
Lymphocytes % of NEC	:1%
B - Lymphocytes %	:2%
CD19	:94%
CD5/CD19	:6%
Kappa	:47%
Lambda	:18%
CD20	:6%
CD10	:29%
T-Lymphocytes %	:53%
CD3	:100%
CD5	:100%
CD4	:94%
CD8	:5%
CD4:CD8 Ratio	=20.8:1
NK Cells	:21%

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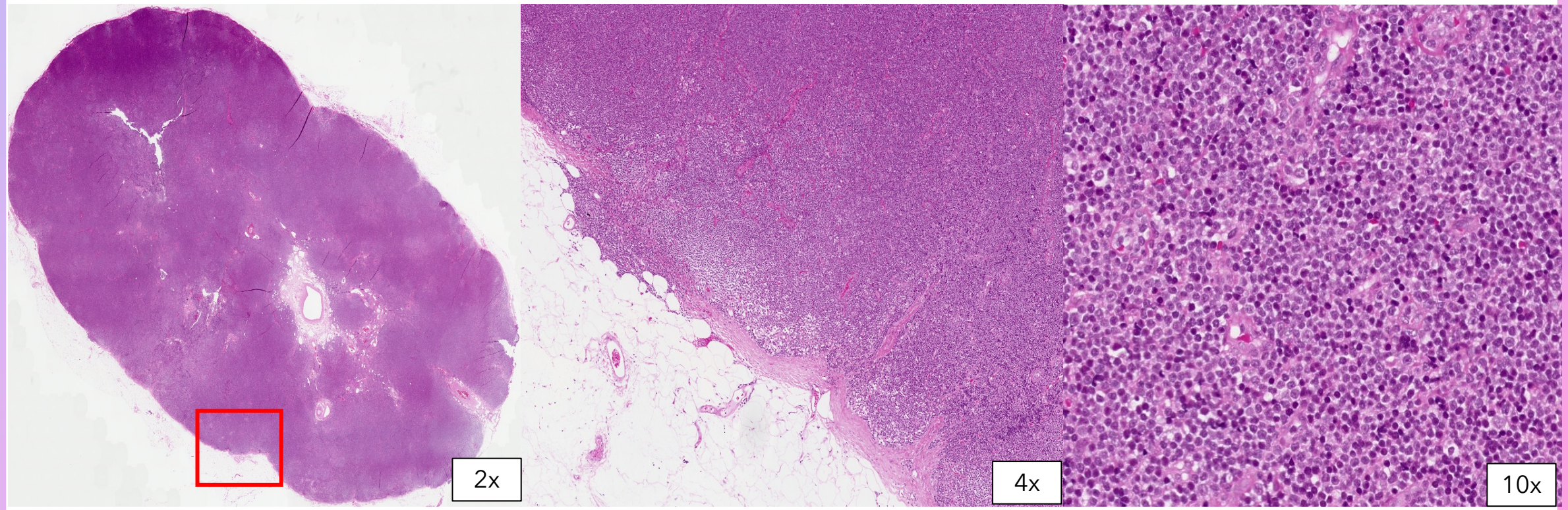
Histology – Inguinal Node



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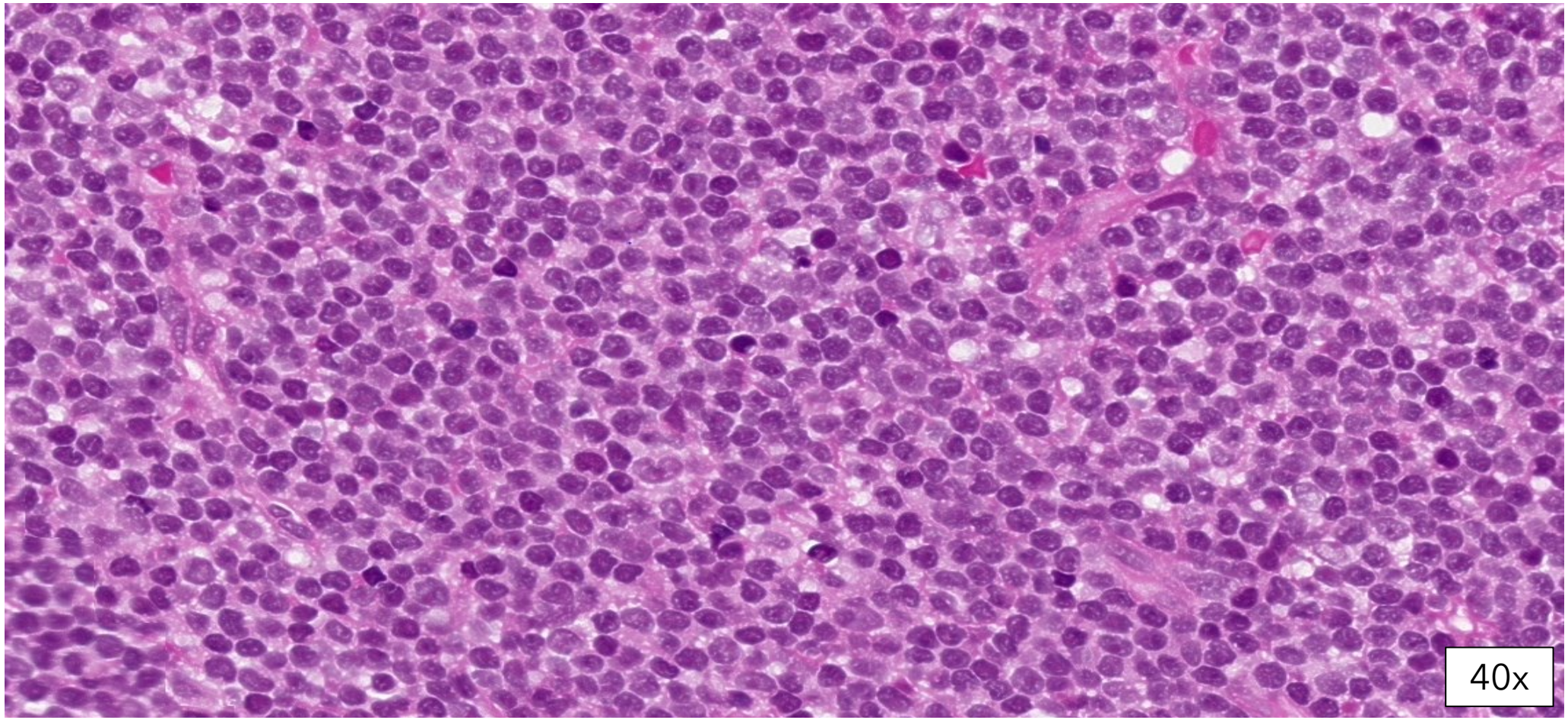
Histology



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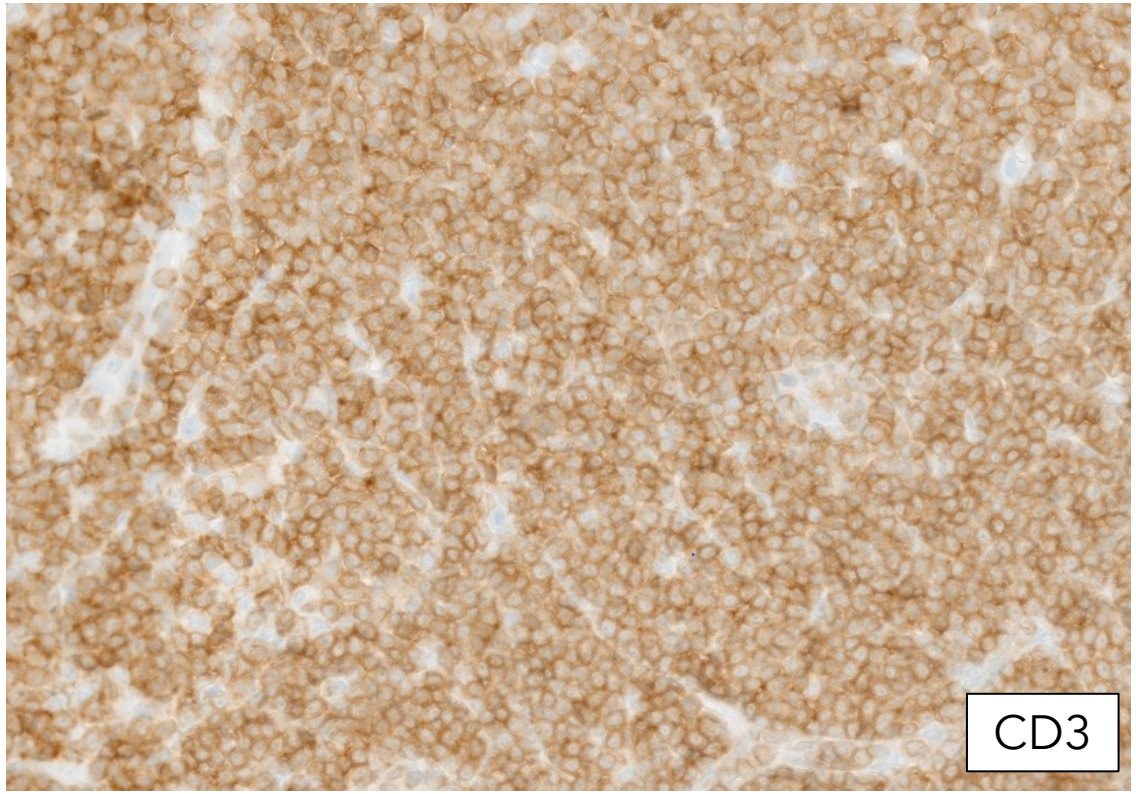
Immunohistochemistry

- **Positive:**
  - CD3
  - CD4
  - CD5
  - CD7
  - CD8 (Highlights a smaller proportion of cells)
  - GATA-3



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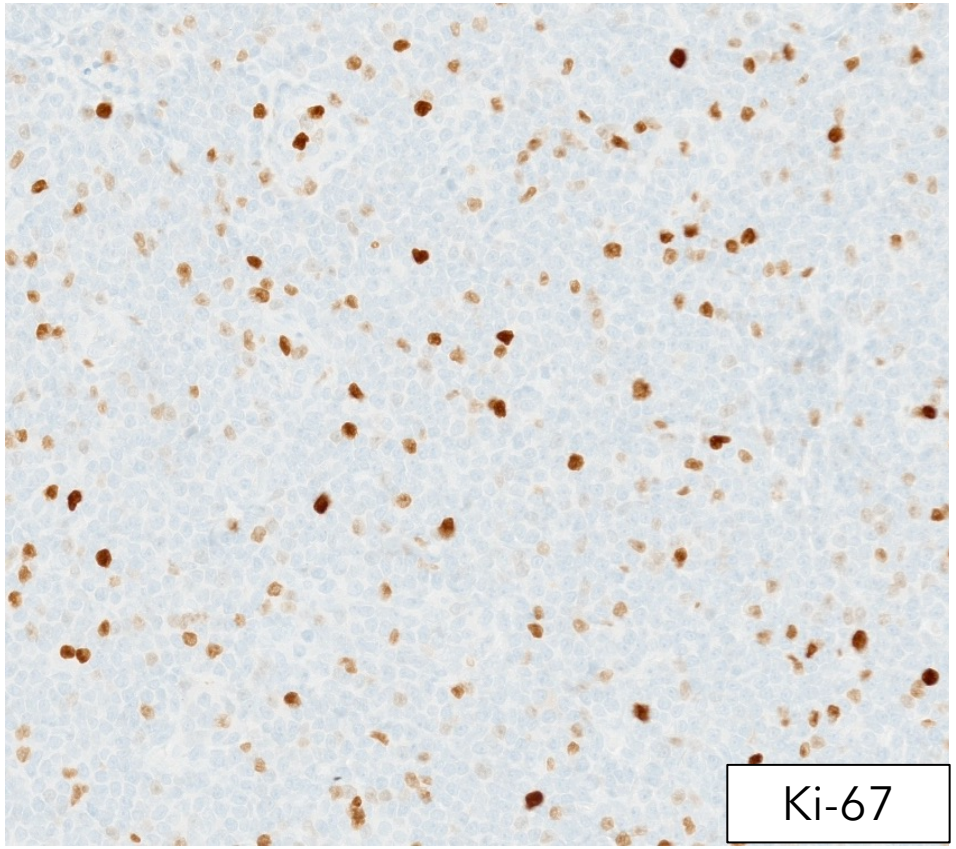
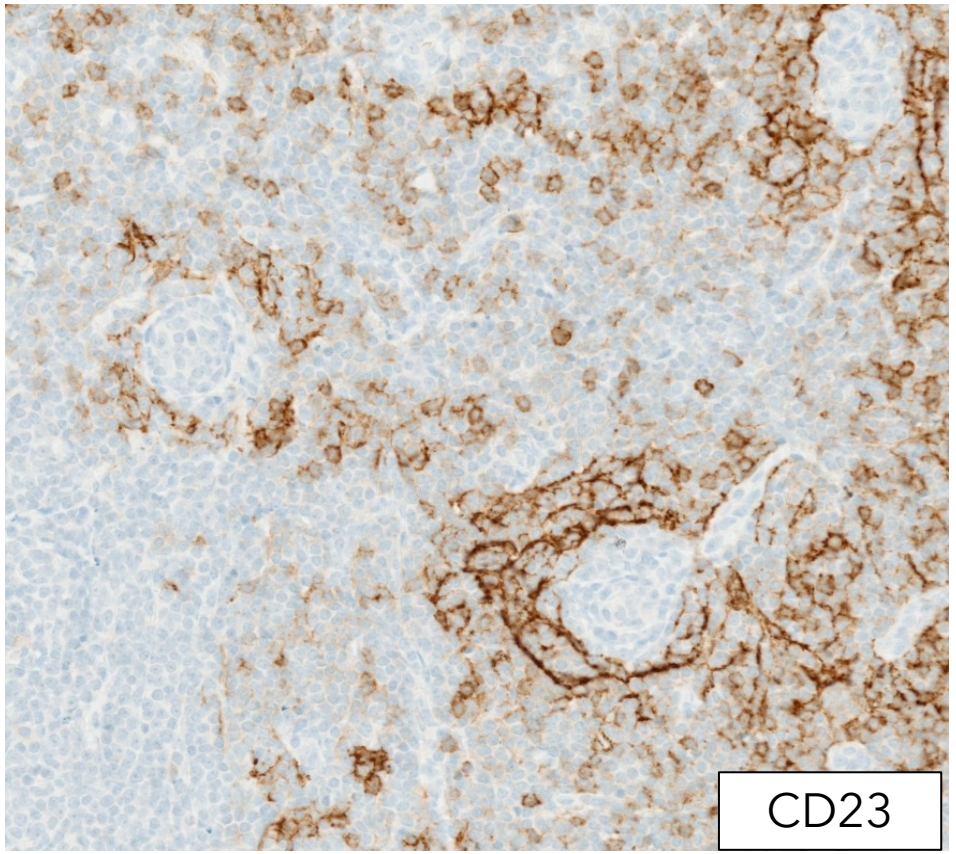
Immunohistochemistry





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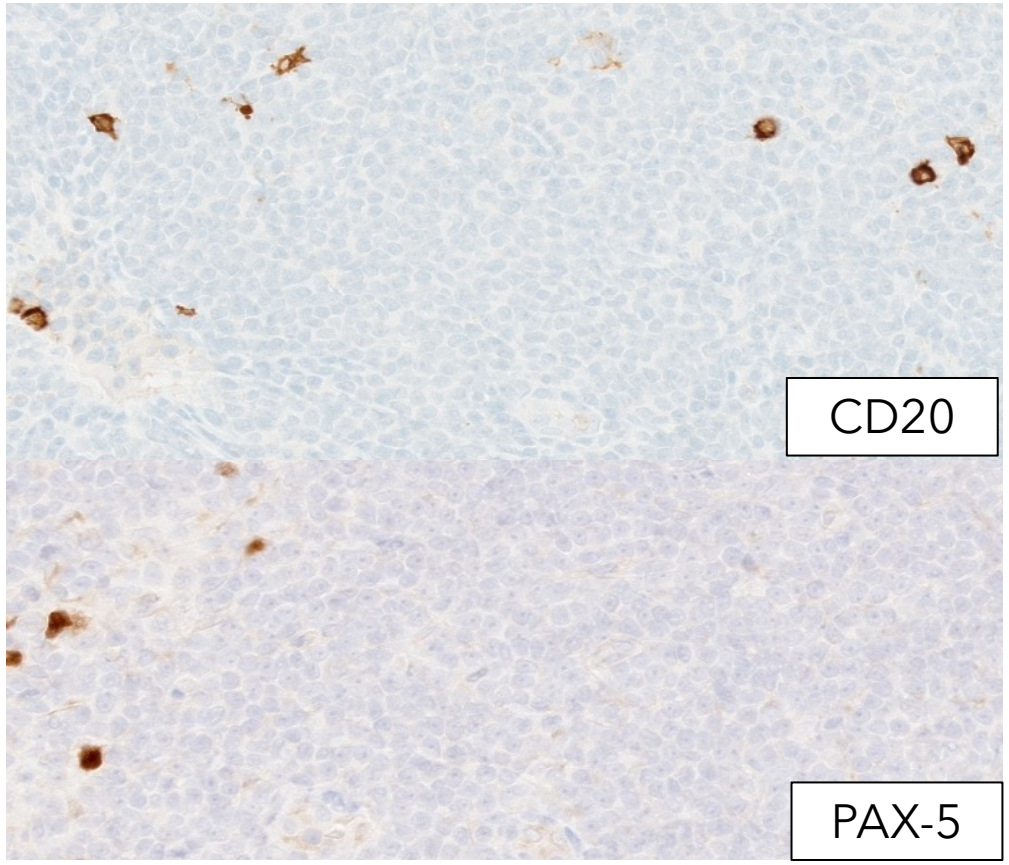
Immunohistochemistry

- **Negative:**
  - CD20
  - PAX-5
  - CD56
  - TIA-1
  - Granzyme B
  - Perforin
  - CD30
  - CD15
  - CD34
  - TdT
  - CD1a
  - ALK-1
  - EBER
  - Cyclin D1



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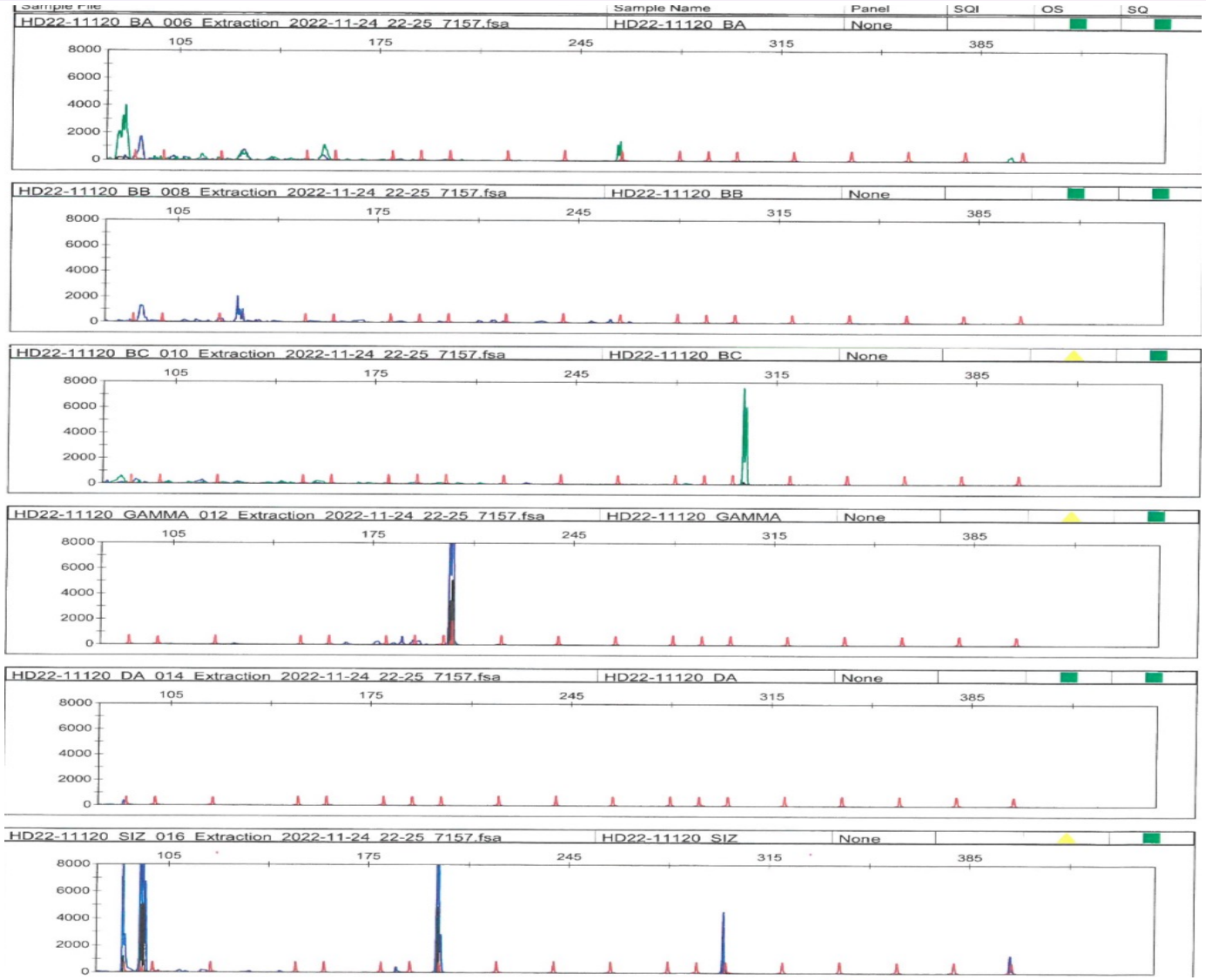
PCR

- Detected a ***clonal T-cell prolife with similar beta-gamma TCR gene rearrangements*** to that detected in peripheral blood.



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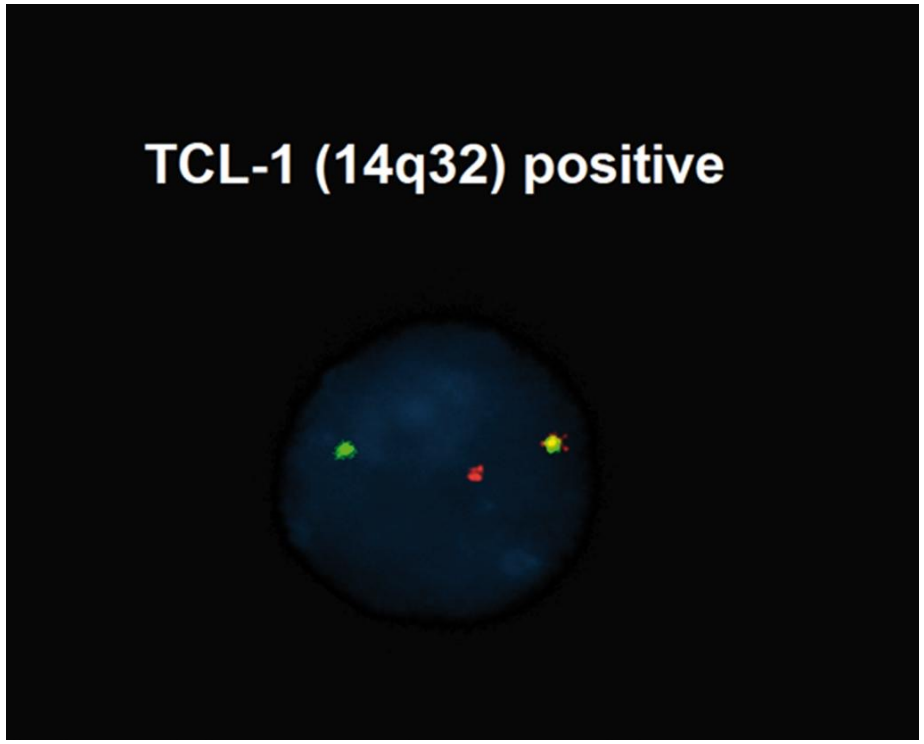
Fluorescent-in-Situ Hybridisation (FISH)

- FISH showed a clear break in TCL-1 gene locus confirming the diagnosis of ***T-Cell Prolymphocytic Leukaemia/Lymphoma (T-PLL)***



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Treatment Course

- ***Oct 2022:*** Periorbital and facial oedema
  - Empiric steroid therapy
- ***Nov 2022:*** Diffuse erythematous rash
  - Lymphoma MDT – Second opinion
  - ***MLL*** – Consistent with T-PLL

1st Line Therapy:

- Alemtuzumab (Campath®):
  - Excellent clinical response (EOT March 2023)
  - Post treatment BMAT – Confirmed morphological response
  - Patient preference not to proceed to HSCT

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1st Relapse

- **Oct 2023:**
  - Presented with cyst-like lesion on his back
  - Progressive enlargement with associated colour change
  - Generalised oedema
- Referred for surgical opinion for excisional biopsy
  - Suspected involvement by T-PLL
- **2nd Line Therapy:**
  - Alemtuzumab & Pentostatin
  - Complicated Listeria spp. PICC line infection

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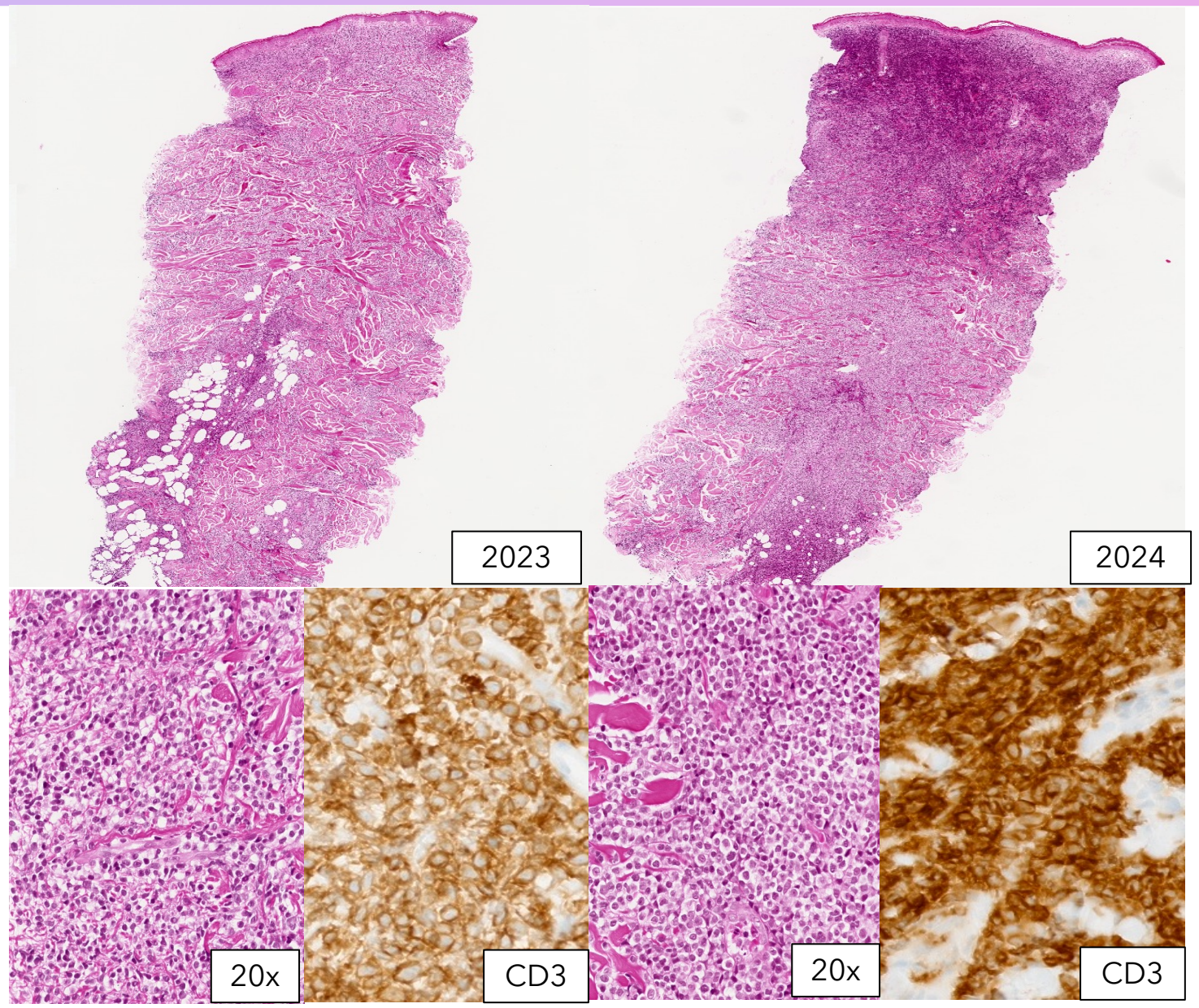
Skin Biopsy

- Punch biopsies of skin plaques and nodules on:
  - Mid thorax (2023)
  - Upper back (2024).



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Relapsed Disease

- ***March 2024:***
  - Overt cutaneous disease relapse - Large plaques affecting face and back.
  - ***3rd Line Therapy:***
    - Gemcitabine (Bridging)
    - Symptomatic Radiotherapy – 2Gy 4 Fractions
    - Compassionate access – Ibrutinib + Venetoclax (Phase II Trial data)
- ***May 2024:***
  - Rapid disease relapse
  - ***4th Line Therapy:***
    - Pembrolizumab & Brentuximab Vedotin (Phase II Trial data)
    - Complete cutaneous and clinical response
    - Complicated by episode of septic shock
    - Patient elected not to proceed with further therapy – RIP June 2024

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Relapsed Disease

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T-Cell Prolymphocytic Leukaemia/Lymphoma

Epidemiology[1,2]:

- Rare, mature T-cell neoplasm
- 2% Mature lymphocytic leukaemia
- Male predominance
- Median Age. = 62yrs
- Inherent chemoresistance
- Median OS <2yrs

Treatment[1]:

- IV Alemtuzumab remains the standard therapy to achieve CR.
  - ORR = 51-90%[2]
  - CR = 40-81%[2]
- Allogeneic transplant in 1st remission is advised as consolidative therapy to potential long-term remission[1].
  - TRM & Relapse rates remains high
- Relapsed disease carries a dismal prognosis and represents a significant area of unmet clinical need.

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Novel Therapies

- **Alemtuzumab + Pentostatin[1]:**
  - 1st line in relapsed disease post Alemtuzumab
  - ORR = 69%, Median OS 10.2 months (n=11)
- **Ibrutinib + Venetoclax (I+V)[3]:**
  - Evidence of BCL-2 primed apoptosis in Phase 1 in-vitro studies
  - Phase II studies subsequently demonstrated:
    - ORR = 7%
    - PD = 64.3%
- **Brentuximab Vedotin + Pembrolizumab (BV-Pembro)[4]:**
  - Evidence of PD-1 and CD-30 overexpression in proportion of relapsed refractory PTCL/CTCL as potential therapeutic targets.
    - ORR = 45.5% (15/34)
    - Non-Progressive Disease = 64.6% (21/34)

References

1. Fox CP et al. Guidelines for the management of mature T- and natural killer-cell lymphomas (excluding cutaneous T-cell lymphoma): a British Society for Haematology Guideline. 2021 Nov 22;196(3):507–22.
2. Philipp B. Staber et al; Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia. *Blood* 2019; 134 (14): 1132–1143. doi: https://doi.org/10.1182/blood.2019000402
3. Herling et al; Limited efficacy for ibrutinib and venetoclax in T-prolymphocytic leukemia: Results from a phase 2 international study. *Blood Adv* 2024; 8 (4): 842–845. doi: https://doi.org/10.1182/bloodadvances.2023012248
4. Pier Luigi Zinzani et al; Nivolumab plus brentuximab vedotin for relapsed/refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *Blood Adv* 2024; 8 (10): 2400–2404. doi: https://doi.org/10.1182/bloodadvances.2023011030

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Questions?

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