Follicular Lymphoma With Associated Localised Amyloid Deposition

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Presented by: Samira Osman & Saad Sharif

Presentation

- 61-year-old female undergoing surveillance CT for breast cancer.

- Incidental finding - **diffuse omental and peritoneal disease**.
  - Complaining of RUQ and upper abdominal pain
  - No organomegaly or lymphadenopathy on exam
  - No neuropathy, normal cardiovascular and respiratory exam
  - No macroglossia

- **PMH**
  - Ductal Carcinoma in Situ – Rt lumpectomy and chest wall irradiation 2018
  - Hysterectomy
  - Appendectomy

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Laboratory findings

Hb	13.9 g/dL
Plt	206 x10^9/L
WCC	4.41 x10^9/L
ANC	2.84 x10^9/L
Lymph	1.01 x10^9/L
Creat	89 umol/L
LFTs	NAD

SPEP	No PP band
B2MG	2.4mg/L
Free Lambda	18.87mg/L
Free Kappa	13.04mg/L
FK/FL Ratio	1.447
LDH	187
NtproBNP	<100pg/mL
Troponin	<14ng/L

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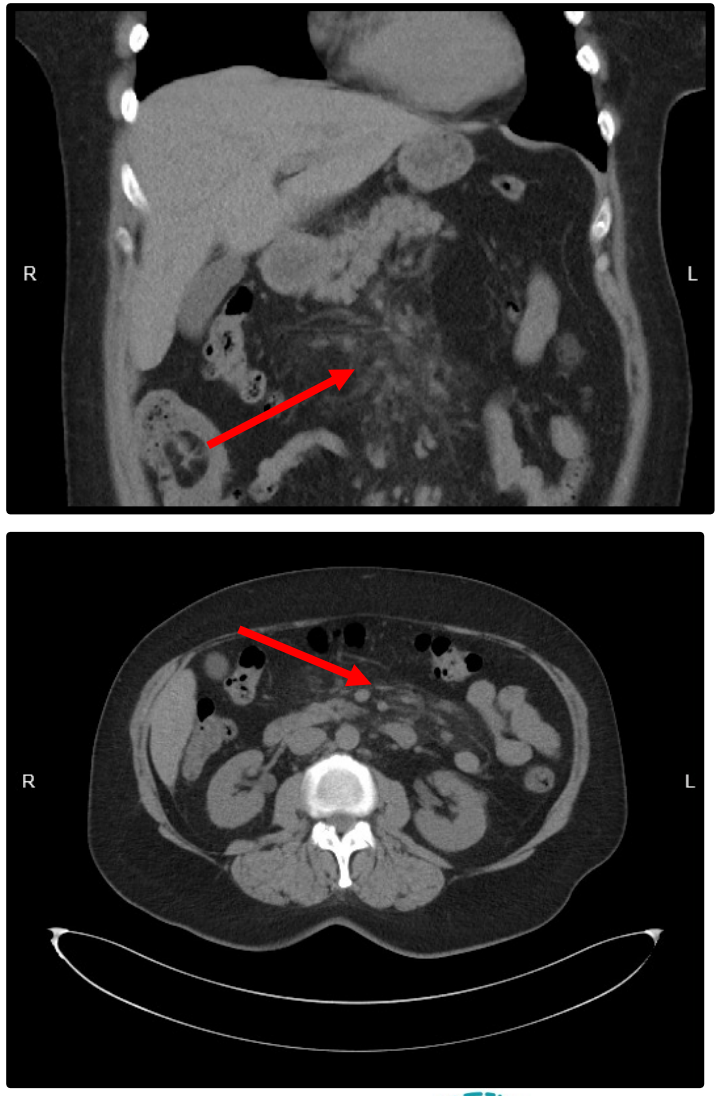
Investigations

- CT TAP- diffuse mesenteric thickening and nodularity.

- Incidental finding of bilateral pulmonary emboli.
  - Anticoagulated appropriately

- Diagnostic laparoscopy performed
  - Multiple biopsies taken from the nodules for histopathology



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Histology

- **Two specimens received in lab:**
- **A.** Specimen labelled “ small bowel mesenteric mass”: Multiple pieces of fibroadipose tissue with an aggregate measurement of 25mm x 30mm x 5mm.

- **B.** Specimen labelled “ peritoneal lesion”: An irregular piece of fibroadipose tissue with a measurement of 10mm x 8mm x 3mm.

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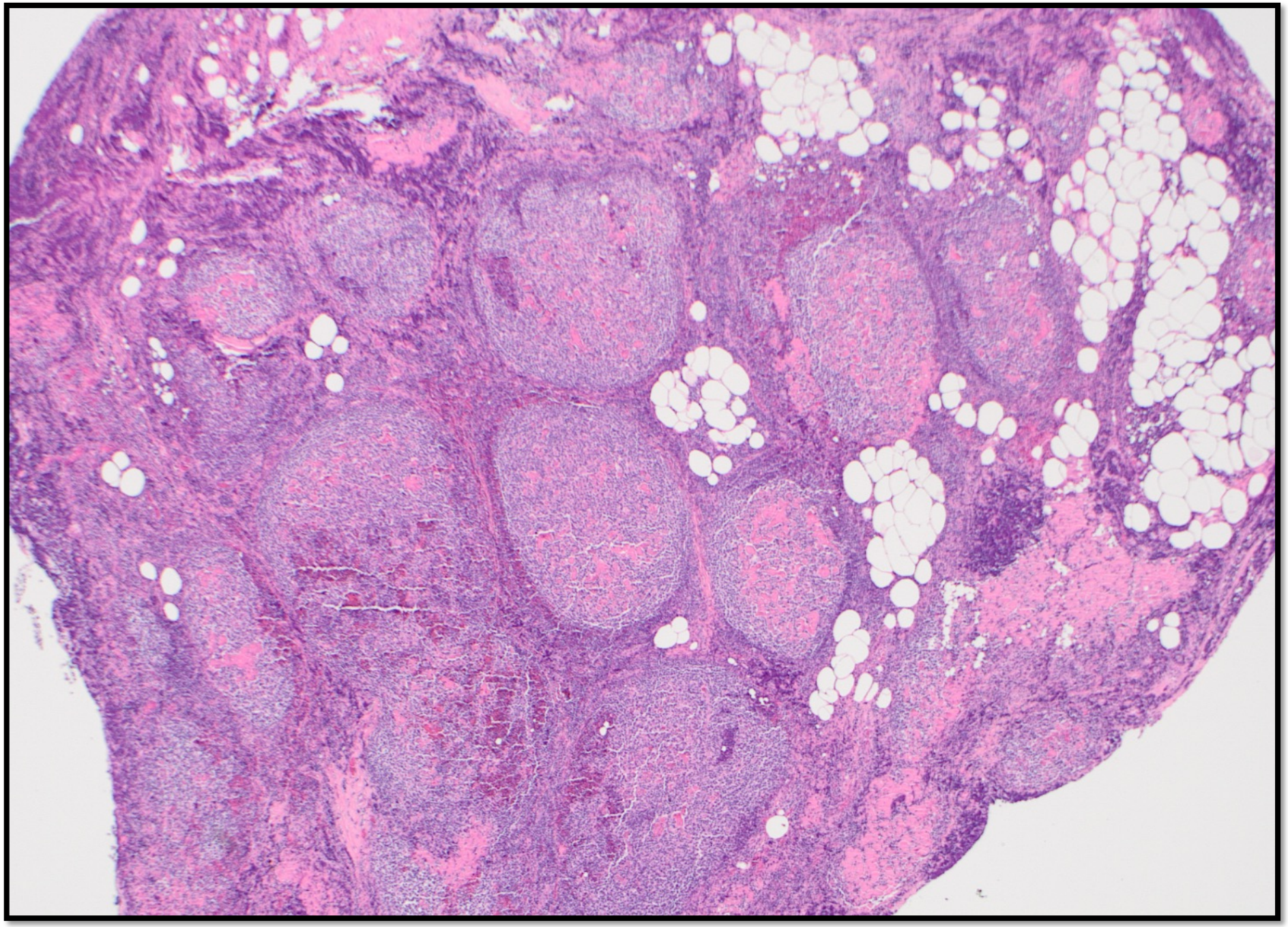

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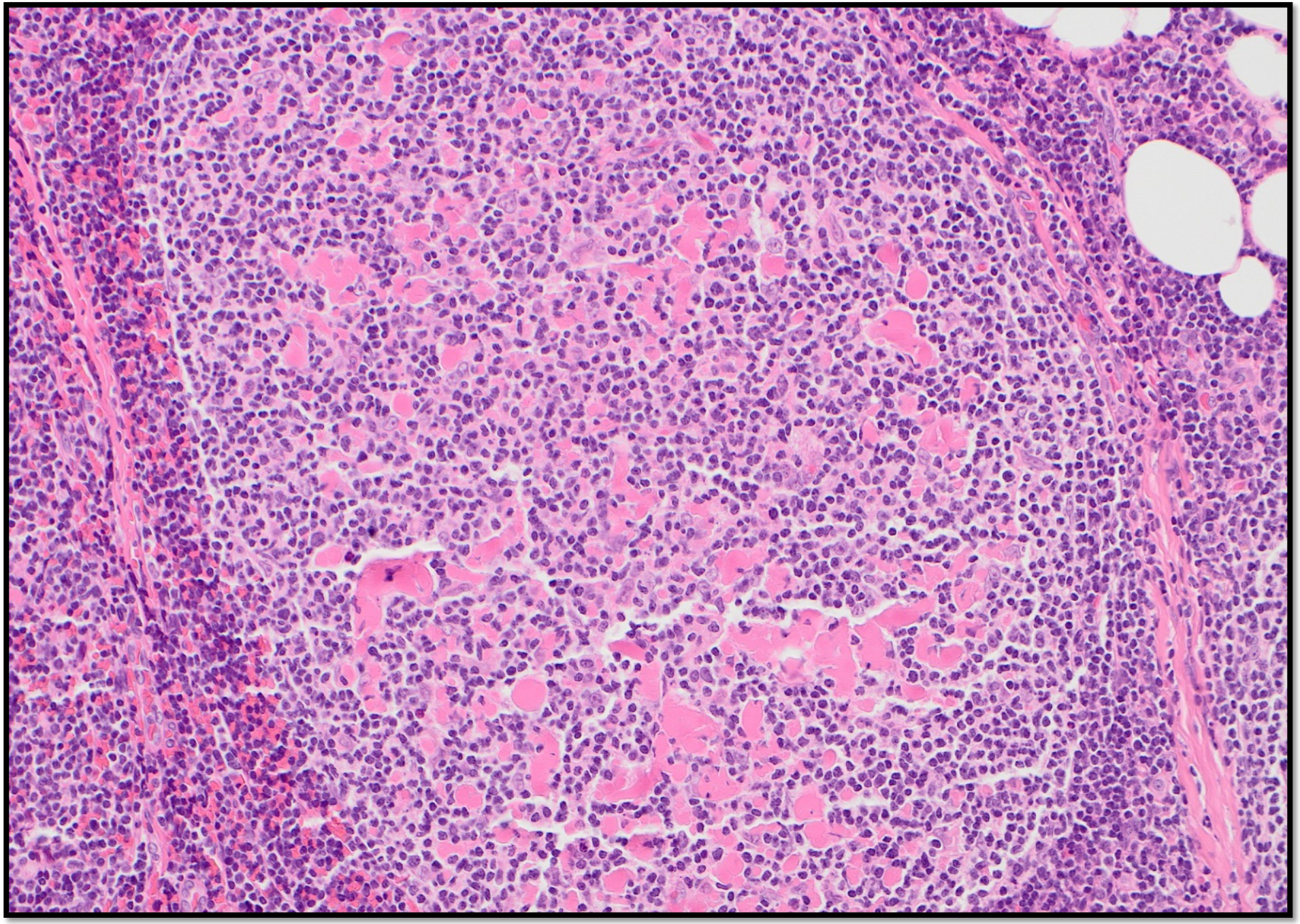

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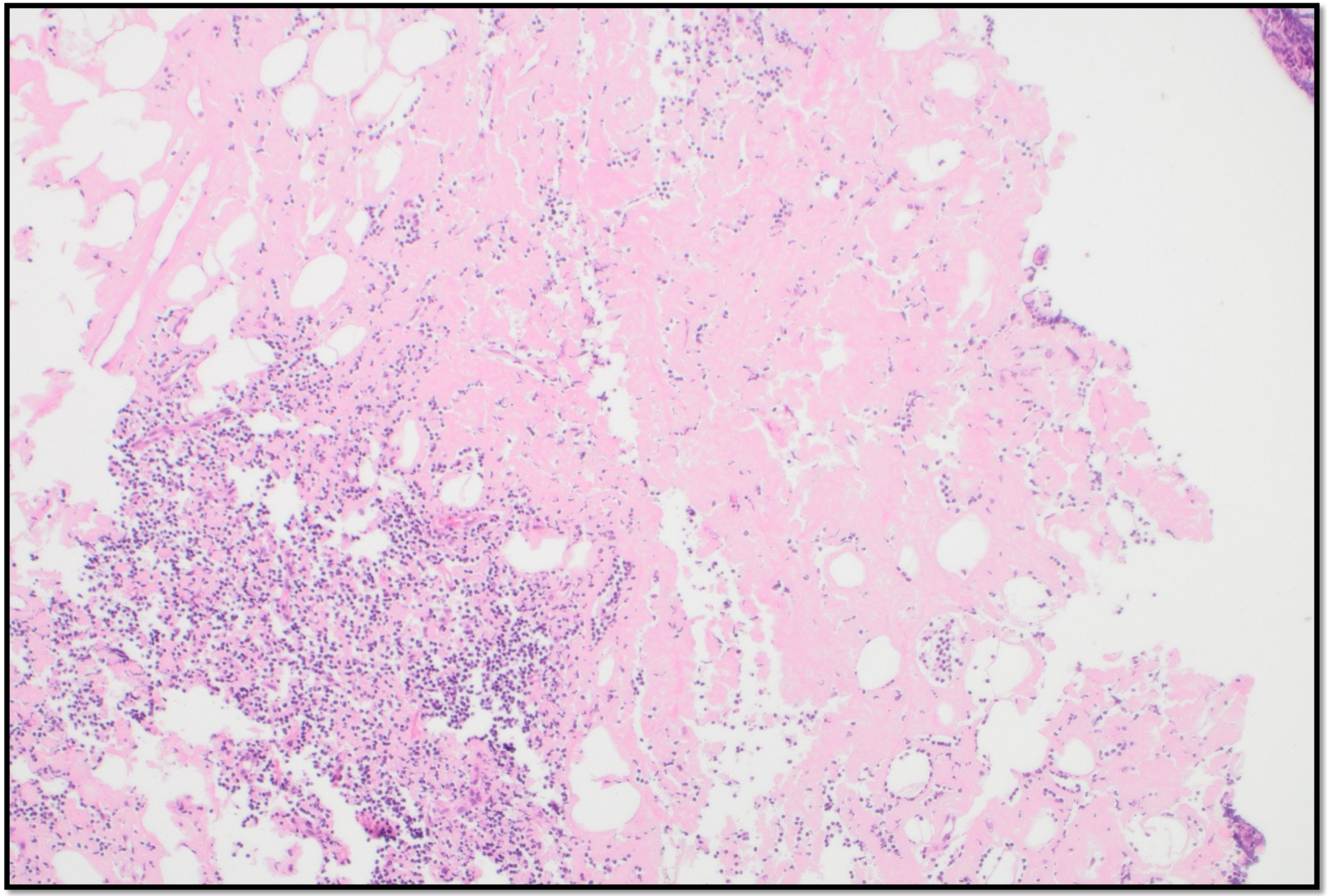

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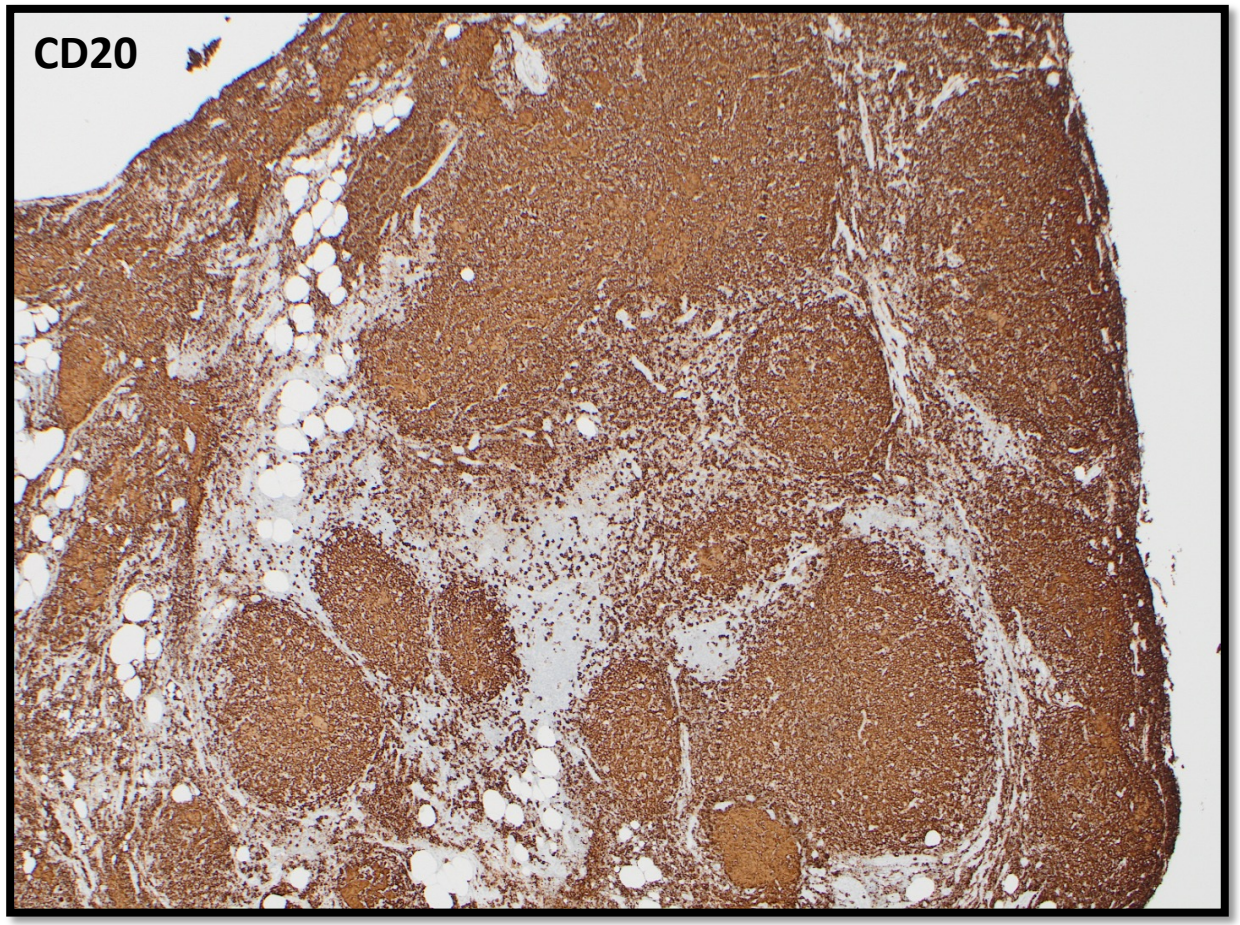

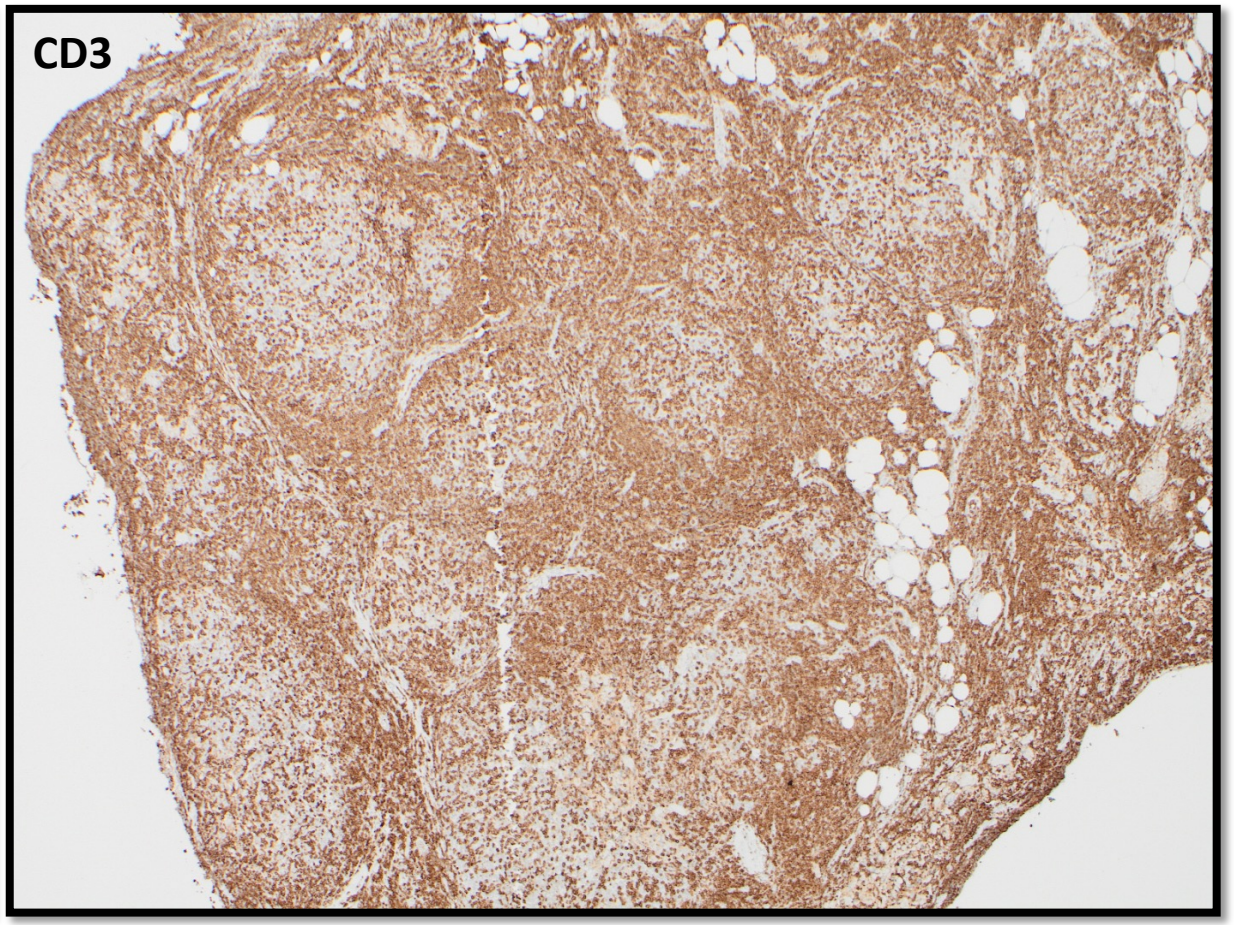

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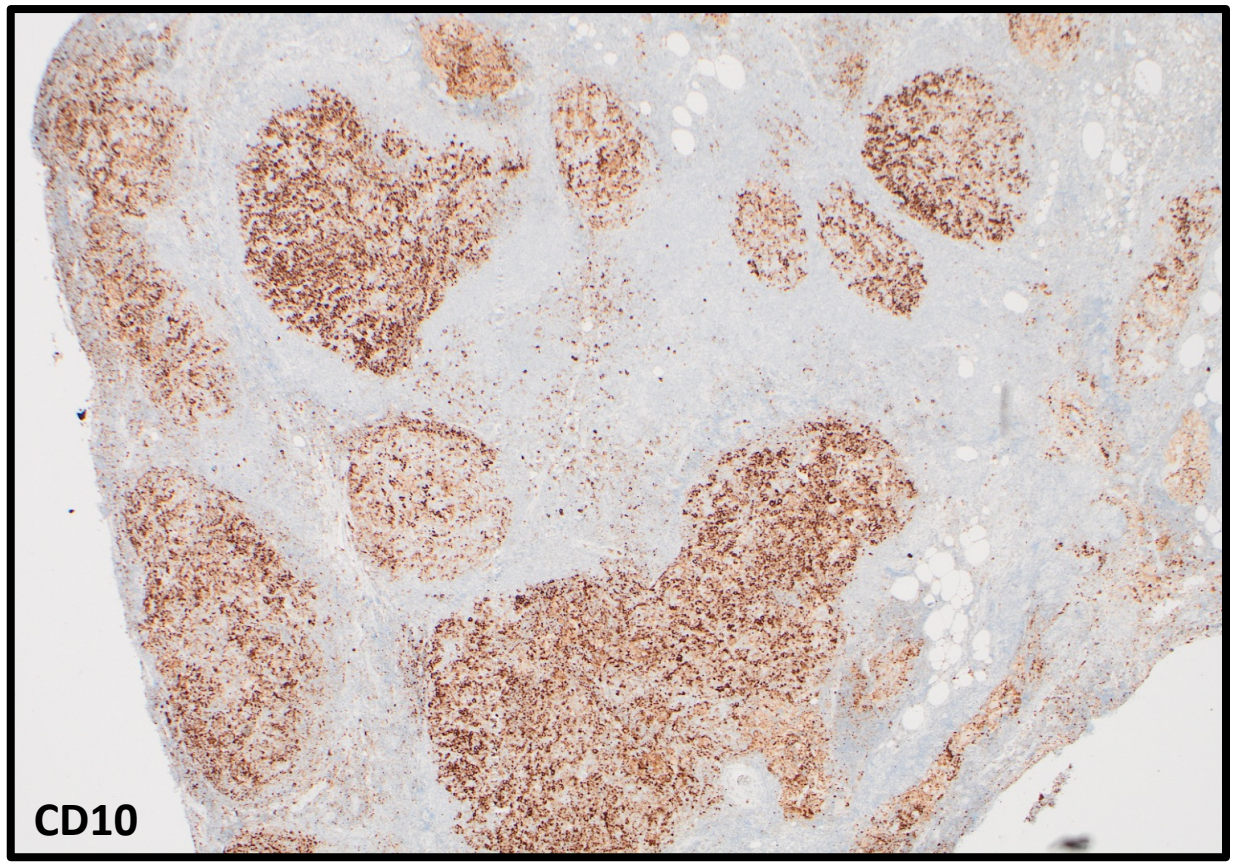

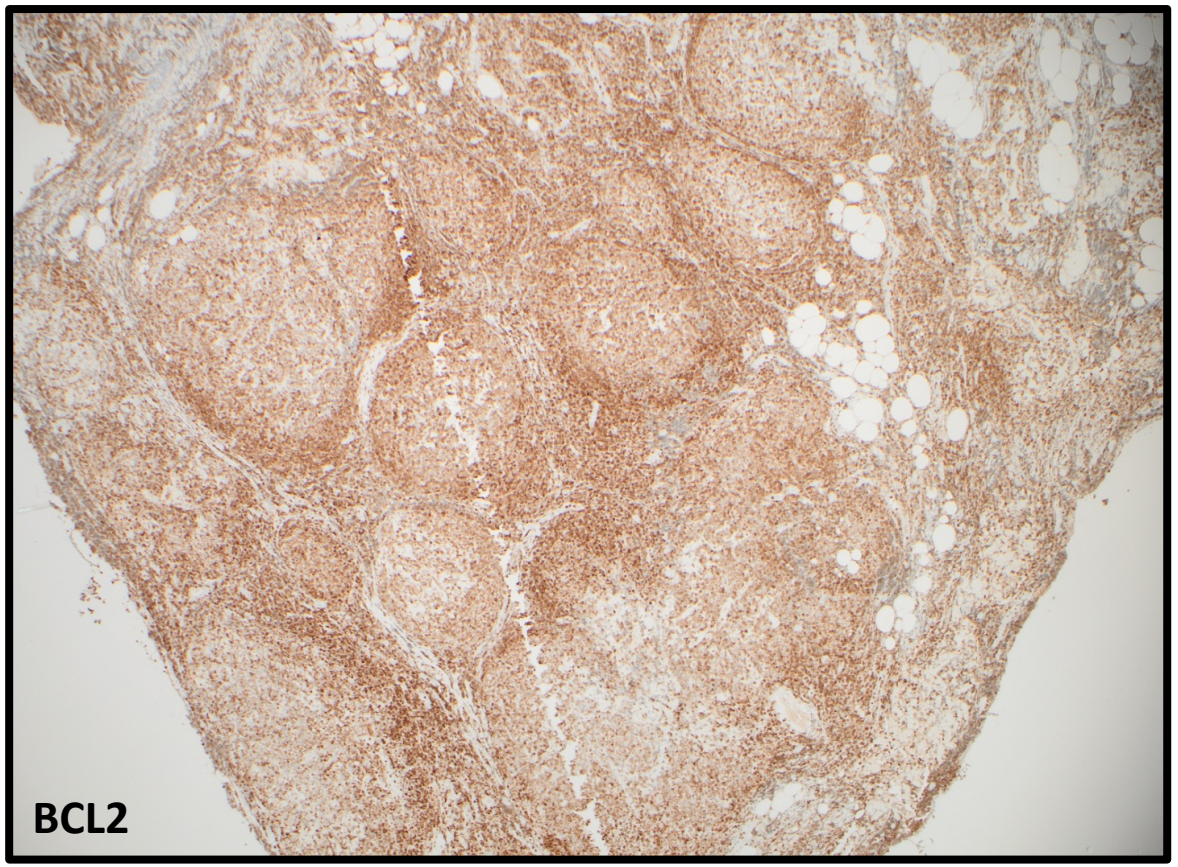

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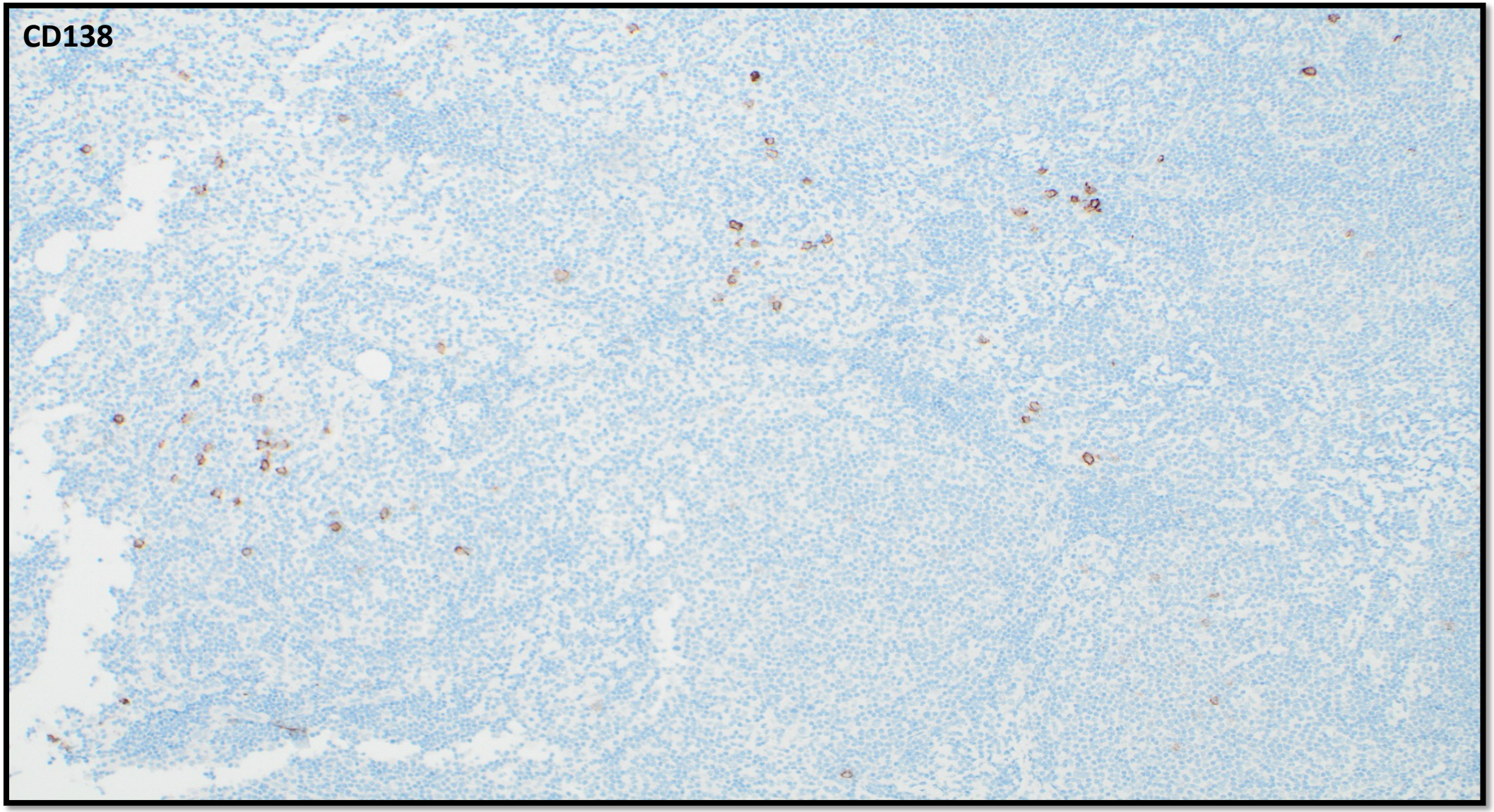

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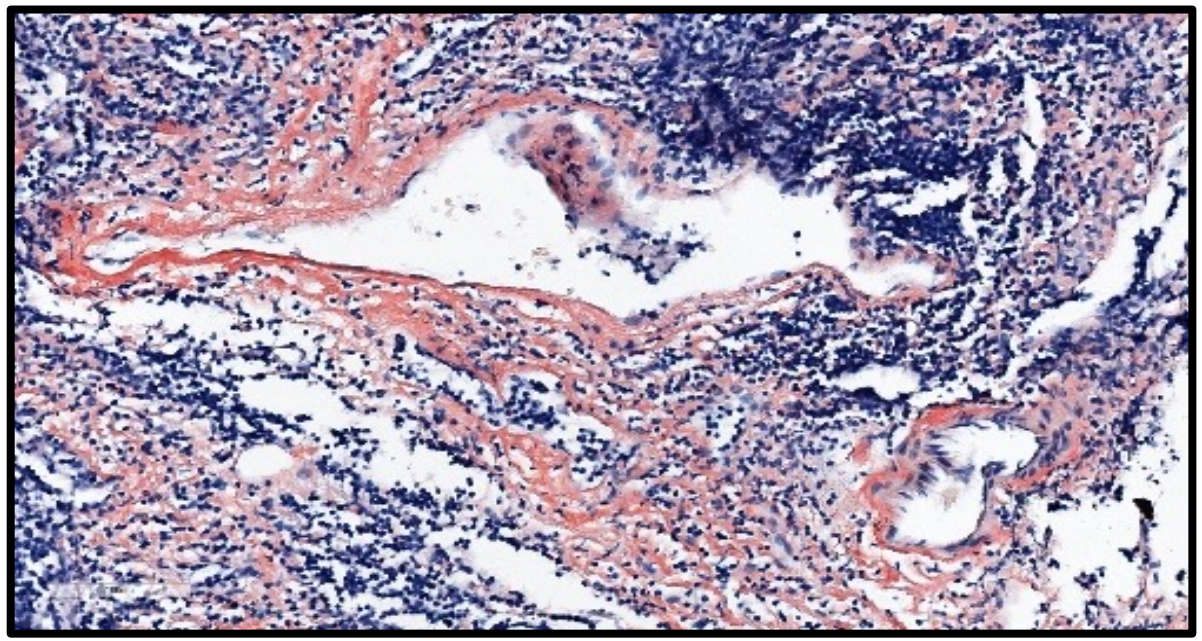

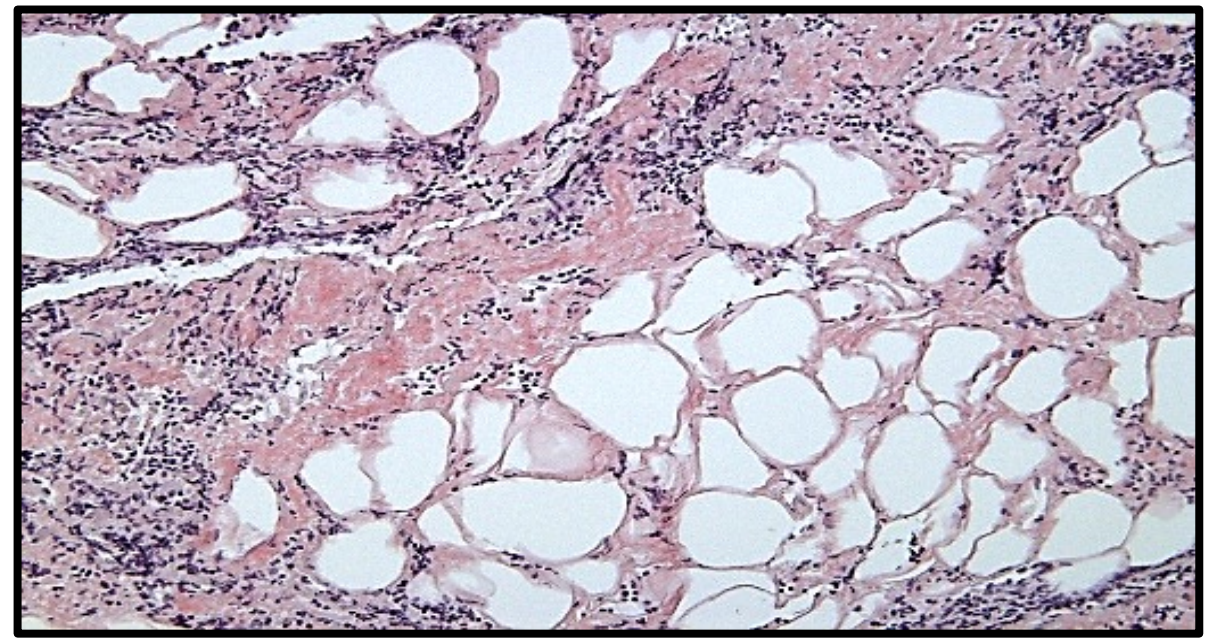

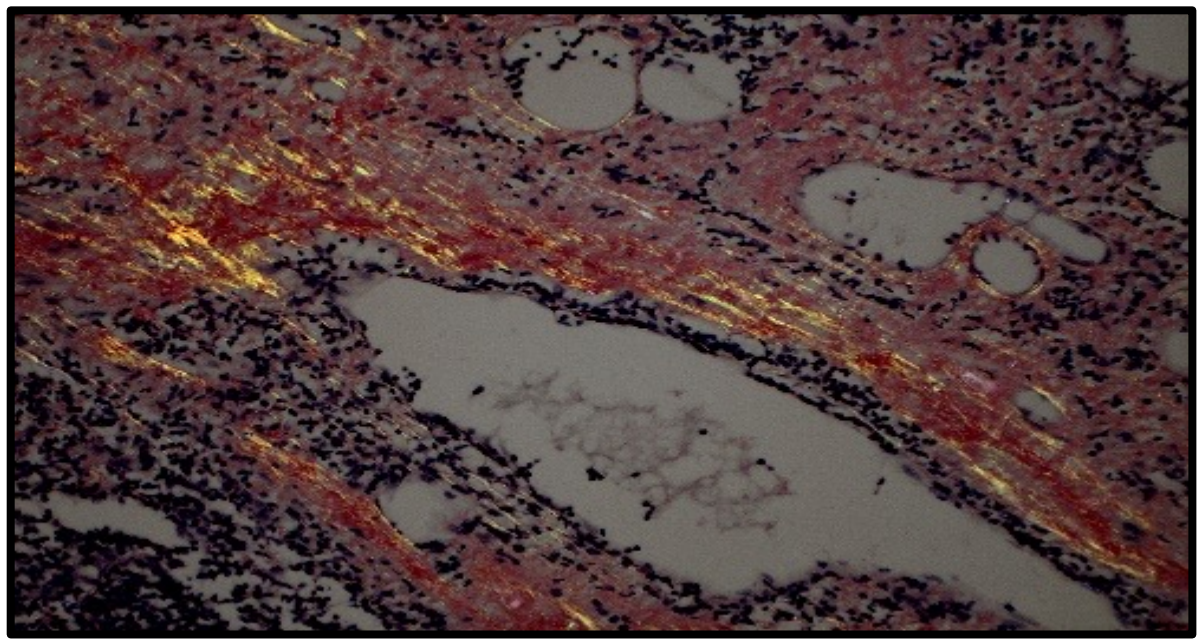

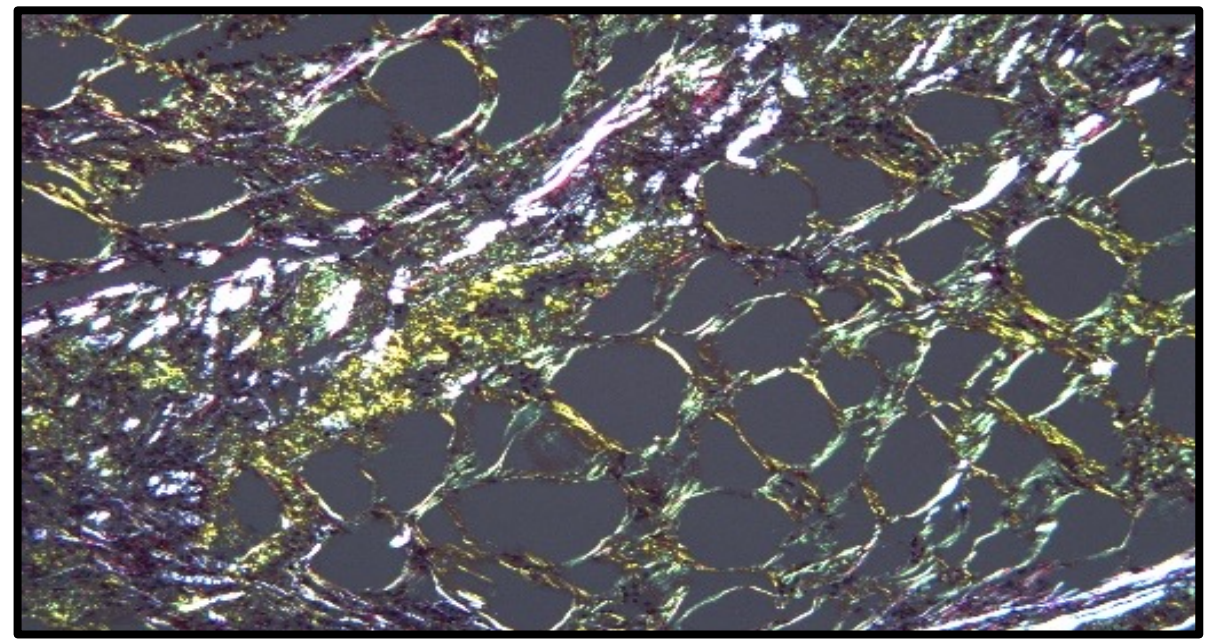

Ancillary tests

- **Molecular:** t(14:18) *IGH::BCL2* translocation was detected by multiplex PCR

- National Amyloidosis Centre, London confirmed AL Amyloidosis, lambda subtype

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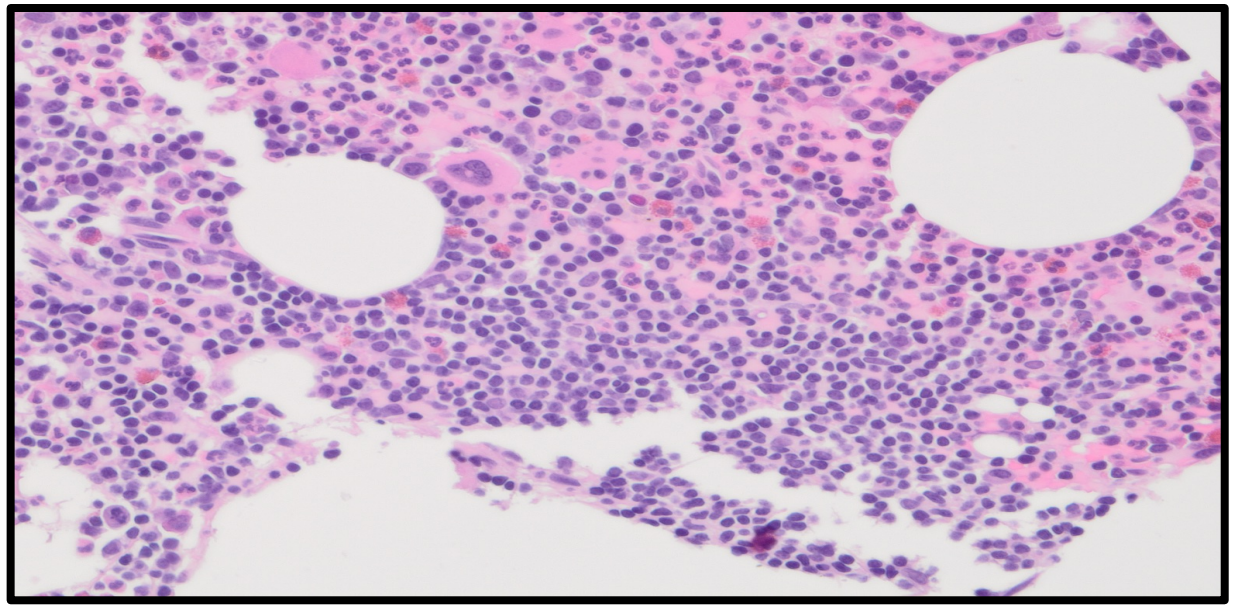
Bone Marrow Findings

- Bone marrow aspirate demonstrated normal trilineage hematopoiesis
- Flow Cytometry
  - Lambda restricted B Cell clonal population
- Trephine Biopsy:



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Diagnosis

- Follicular lymphoma with associated AL Amyloidosis

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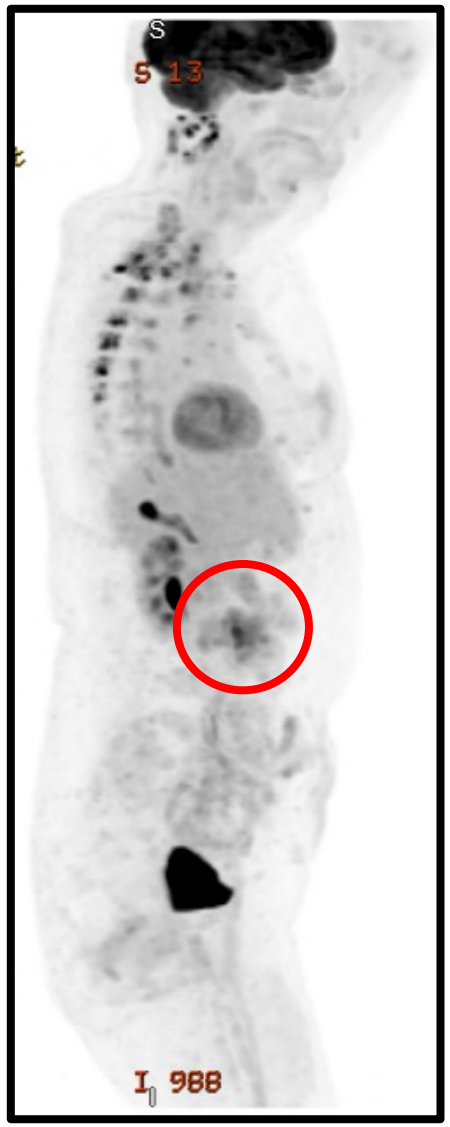
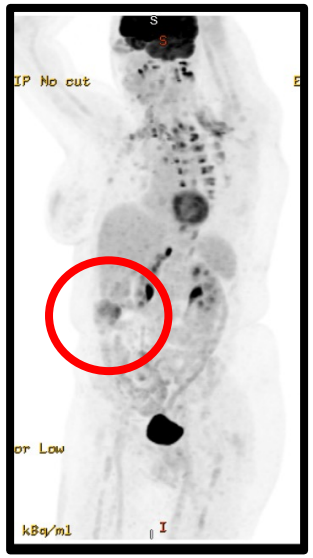
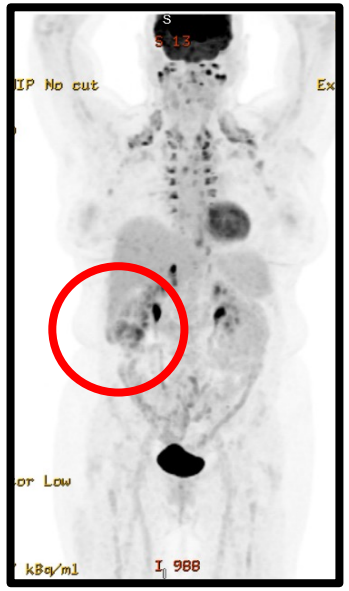
Staging PET-CT

- Mild uptake within mesenteric nodules and nodes, max SUV 4.1, ?low-grade lymphoma
- Low grade uptake in 1x1cm para-aortic node SUV 2.9, ?reactive vs lymphomatous involvement







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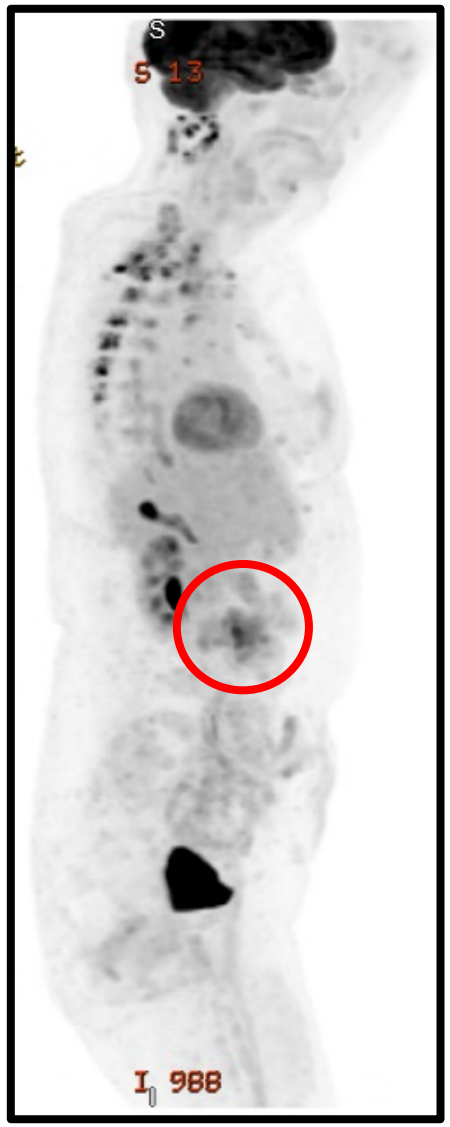
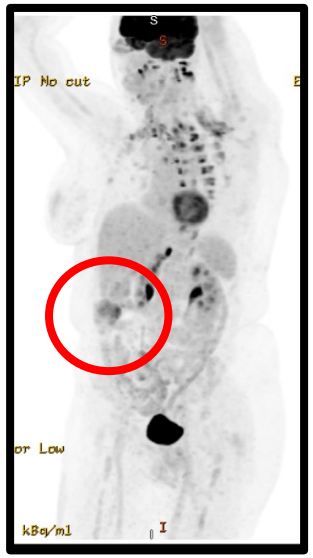
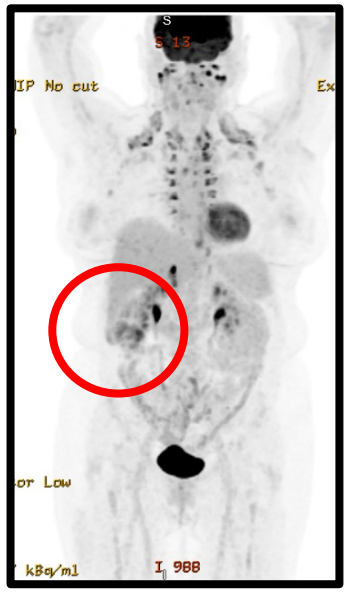
Treatment

- Commenced O-CVP - symptomatic
- FLIPI = 2
  - Stage IV FL
  - Age >60







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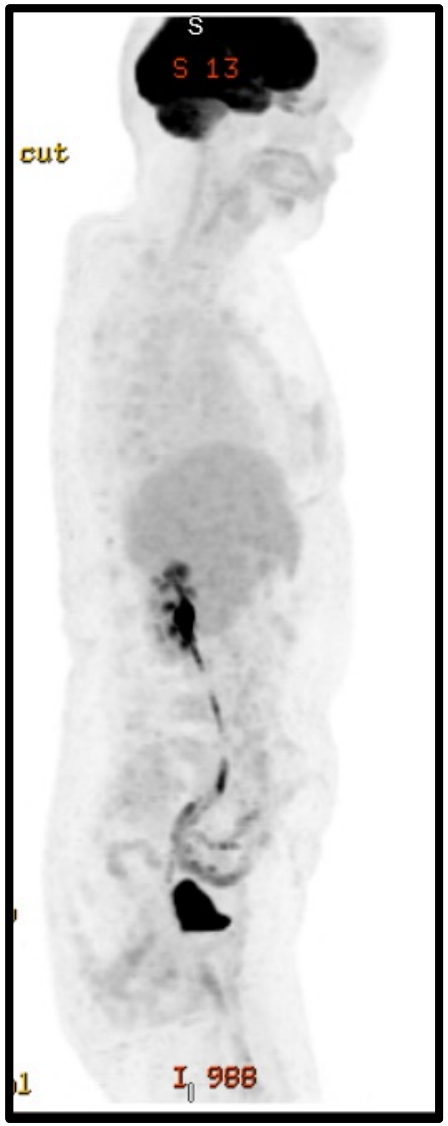
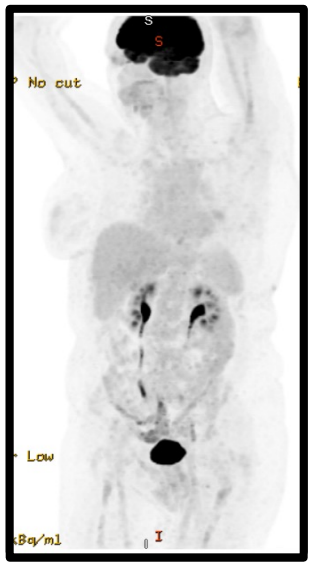
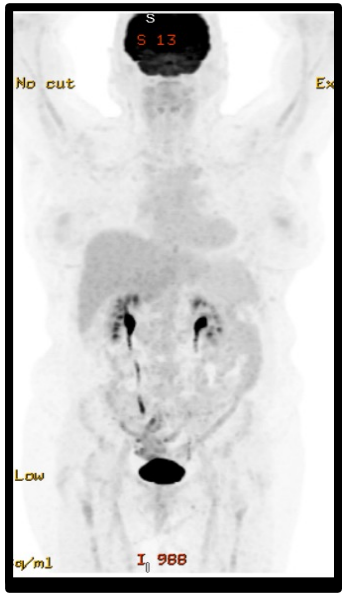
PET-CT Post-C4

- PET-CT showed complete metabolic response (Deauville Score 2), with interval decrease in size and avidity of nodes.

- Completed six cycles of OCVP with maintenance Obinutuzumab commenced thereafter







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Follicular Lymphoma

- Median age in the 6th decade of life
- Can be asymptomatic and have widespread disease at presentation
- Low grade neoplasm - transformation rate to DLBCL of around 2% per year (Wagner-Jonston et al)
- Primarily involves lymph nodes but can also involve spleen, bone marrow, peripheral blood and tonsillar tissue
- Genetically characterised by t(14:18)(q32:q21) which leads to translocation of BCL2 and IGH genes leading to overexpression of BCL2 and prolonged survival of B lymphocytes

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Follicular Lymphoma Classification

WHO 4Th edition	WHO 5Th edition
FL grade 1, 2 and 3A	Classical FL (cFL)
FL grade 3B	Follicular large B cell lymphoma (FLBCL)

- Follicular lymphoma with uncommon features (uFL)
  →Basaloid (large centrocytes)
  →diffuse type

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Unusual morphologic patterns of FL

- FL with Castleman-like changes
- FL with plasmacytic differentiation with or without IgG4 positive plasma cells
- FL with marginal zone differentiation, typically involving MALT sites
- FL negative for CD10, positive for MUM1 with *BCL6* abnormalities
- EBV positive FL
- Floral variant of FL

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Amyloidosis

- Heterogeneous acquired or hereditary disease that results from the abnormal deposition of beta-sheet fibrillar protein aggregates in various tissues.

- Localised or systemic

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Amyloidosis Types

Amyloid Type	AL Amyloidosis	AA Amyloidosis	ATTR Amyloidosis	Aβ2M Amyloidosis	B-Amyloid	ALECT2 Amyloidosis
Precursor Protein	Ig Light Chains	Serum Amyloid A	Transthyretin	β2M	Amyloid precursor protein	Leukocyte cell-derived chemotaxin-2 protein
Associations	Lymphoplasma-cytic lymphoma (WM)/Myeloma/ Non-Hodgkins Lymphoma	Chronic inflammation	Familial amyloid polyneuropathy and senile systemic amyloidosis	Haemodialysis-associated Amyloidosis	Alzheimers	Often found in those with kidney disease

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Amyloidosis

- AL Amyloidosis is typically associated with plasma cell disorders
  - 2-4% of cases associated with B-NHL (Telio et al, 2010)

- Localised peritumoral AL Amyloidosis significantly prognosis than systemic amyloidosis (Basset et al 2018)
  - Low to undetectable M-protein
  - Most remain asymptomatic or minimally affected with stable disease on prolonged follow up.

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Studies

- Case series in AJH 2010
    - **10 patients** from 1997–2008 in Vancouver, Canada
    - 5 MZL
    - 3 LPL
    - 2 small B Cell lymphoma with plasmacytic differentiation
    - Described two distinct entities of localised and systemic amyloidosis.
- Retrospective analysis in ASH 2018
    - **34 patients** from Italian database from 2004-2018
    - LPL-associated AL-Amyloidosis excluded from study.
    - 17 MZL
    - 7 LG BCL
    - **1 FL**
    - 1 HCL
    - 1 HL

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Studies

- Retrospective analysis published in CLML 2021
    - **35 patients** from a Canadian database
    - 12 LPL
    - 11 MZL
    - 2 low grade BCL
- Case report IJH Japan 2020
    - **FL** with plasmacytic differentiation and localised amyloidosis located in ileum
- Retrospective analysis in HemaSphere 2022
    - **14 patients** from Czech Republic
    - 10 MZL
    - 4 LPL

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Discussion

- Widespread AL amyloidosis with systemic organ involvement is the most predominant form.
- Amyloid deposition from light chains
- Velcade/Cyclophosphamide/Dexamethasone +/- Daratumumab

- AL Amyloidosis subtype → secretes IgM paraprotein, similar to WM, has some overlap features between plasma cell and lymphoid neoplasm
- Responds well to Bendamustine/Rituximab

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Discussion

- FL with associated localized peritumoral AL amyloidosis, distinct entity.

- Immunoglobulin gene could not be determined.
- IgM and IgG both stained positive on IHC.
- No M Protein detectable on immunofixation.

- Amyloidosis is not expected to have a significant impact on prognosis in this case

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Summary

- A rare case of *Follicular Lymphoma* (FL) associated with localised *AL Amyloidosis*.
  - Genetic hallmark: *IGH::BCL2* translocation.
  - Localised amyloidosis has a significantly better prognosis compared to systemic amyloidosis.
- Amyloidosis occurring in patients with follicular lymphoma may not always be primary, a secondary cause should be clinically excluded.
  - Typing of the amyloid essential!
- Future research should focus on elucidating the mechanisms underlying the relationship of follicular lymphoma and AL amyloidosis and optimizing treatment protocols for affected patients.

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