# Clinicopathological Case Conference of Haematological Medicine

## Episodes 7: Angioimmunoblastic T cell Lymphoma and autoimmune associations

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# 70 years old gentleman

- Admitted to hospital via AE
- with progressive decline for 4-6 weeks
- Increased lethargy
- Tiredness and SOB
- Night sweats for 6 weeks
- Noticed lumps for last 2 weeks In the cervical and axillary area.
- Skin tightness , painful fingers and toes

# PMH

- OSA on CPAP
- HTN

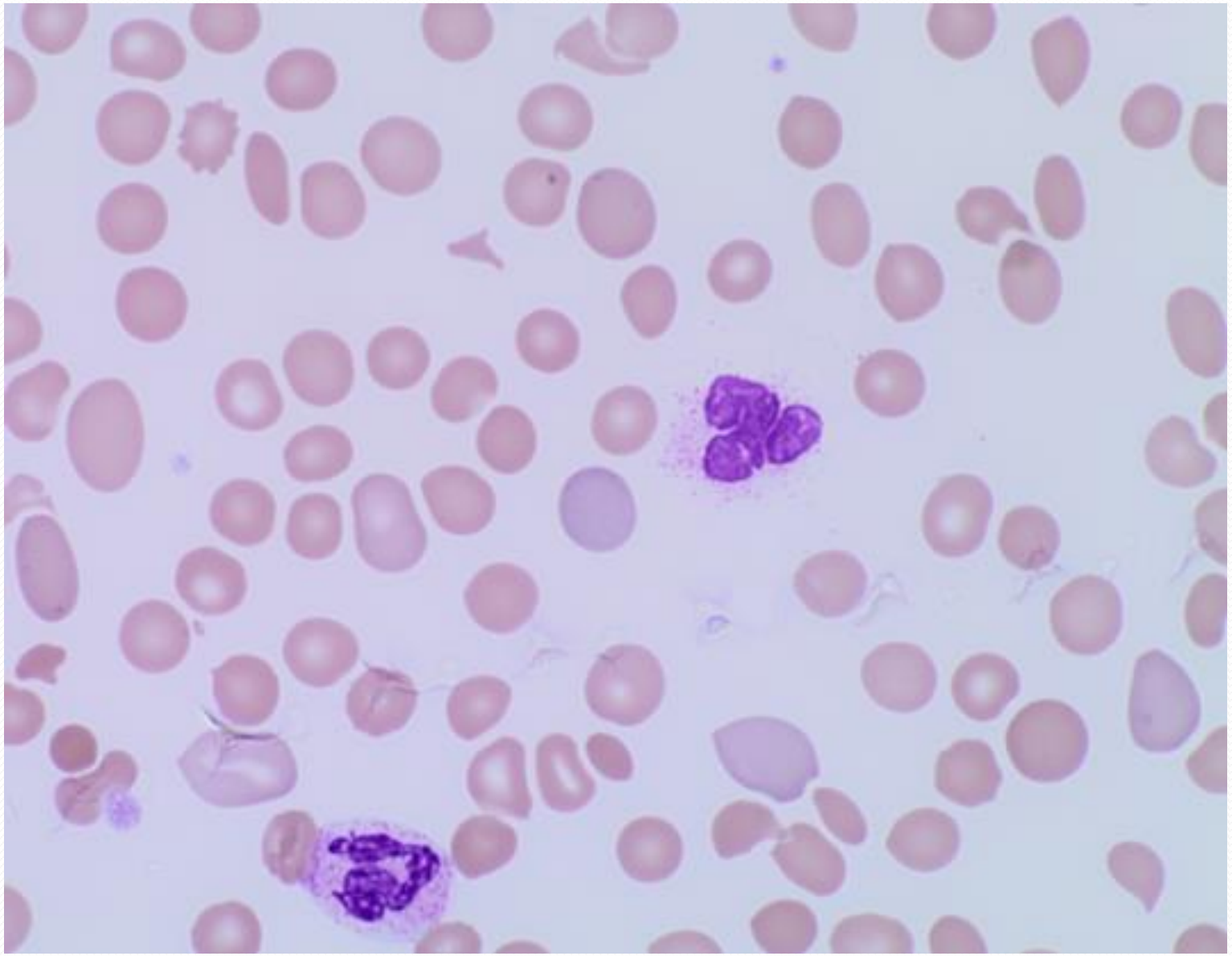
Medication

- Perindopril
- Indapamide
- No drugs allergy

# Bloods in AE

- HB 69, MCV 120
- WCC 7.2, lymphocytes 1.79, neutrophils 6.26, PLT 332
- LFTS: bilirubin 23, rest normal
- Creatinine 132,  CRP 12
- Bones profile : Normal, Calcium 2.63
- Full clotting screen : Normal
- B12 , Folate, Ferritin: All normal

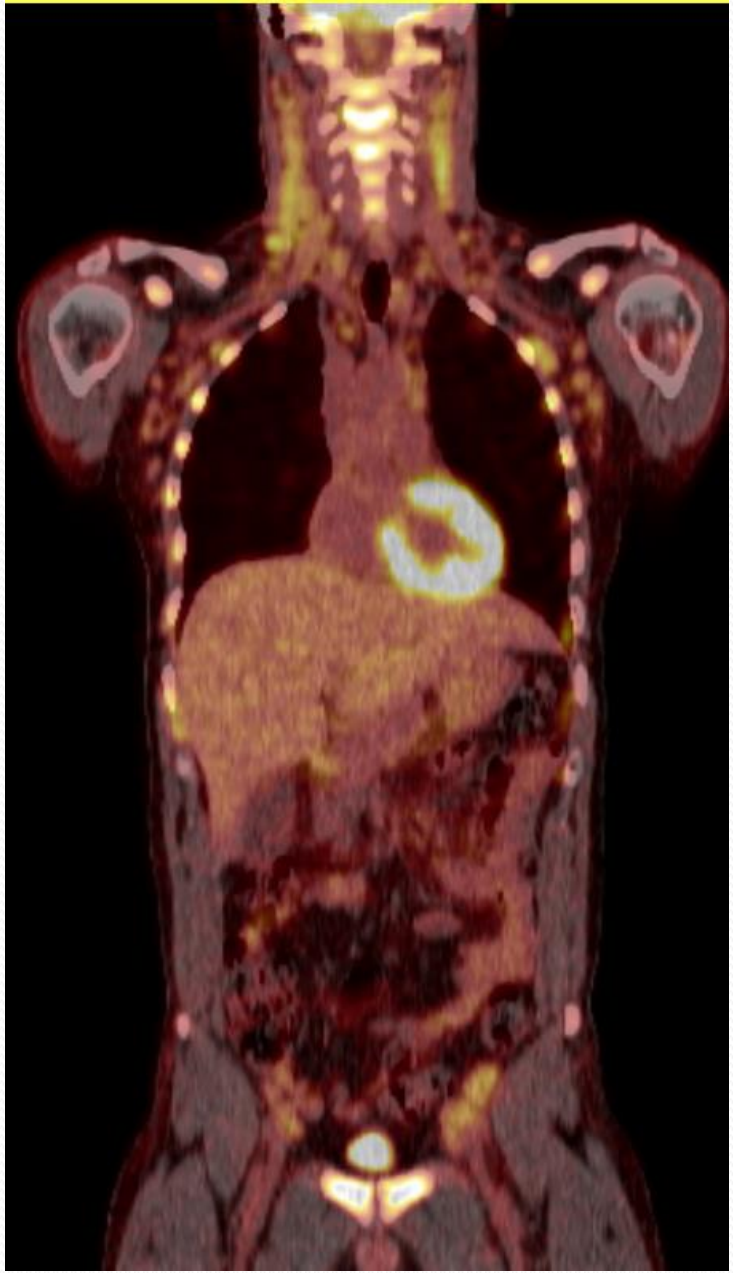
# Blood film



# Haematology review and Further blood tests

- LDH 1200: High
- DAT : Positive IgG 4+, AntiC3d 3+
- Reticulocytes 6.3%: High
- Haptoglobulin 0.3 :Low
- Viral serology : Sent
- PET-CT : Requested
- BMAT: Arranged
- SPE: IgM pp 7 gm/l kappa
- Serum free light: Slightly raised K/L ratios:

# PET-CT a similar patient from ref



- What tests or investigations would you do before starting treatment for AIHA in his case?

# LYMPH NODE BIOPSY: left axillae sent

- Every effort should be taken to do PET-CT or CT CNAP and biopsy taken before commencement of steroids if LPD is suspected unless in Emergency
- BIOPSY must BE UNDERTAKEN AS SOON Practical TO GET PRECISE DIAGNOSIS
- NOTE: Post steroid biopsy can be very confusing and may not be possible at all

# Initial treatments commenced

- Blood transfusion  in AE
- Needs to check compatibility
- Elution study at NBS
- Emergency: least incompatible bloods can be given or O blood be given
- Folic acid indefinitely
- Corticosteroid 1 mg/kg daily with PPI after biopsy
- Blood sugar  monitoring daily as on high dose steroids

# Further test

- Viral serology negative
- HIV negative
- ANA : negative
- ECHO: EF 60% normal

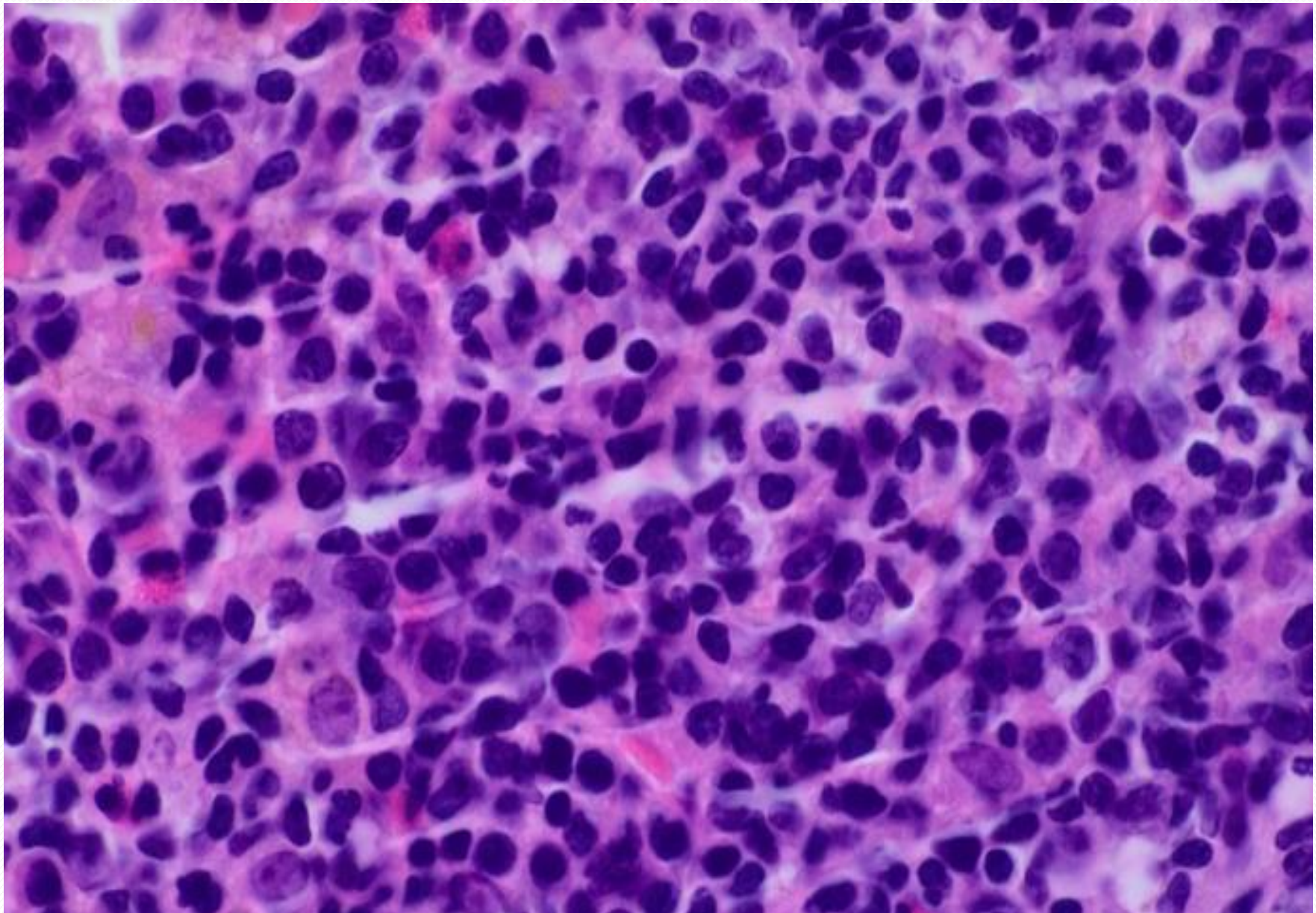
# Bone marrow test

- Bone marrow aspirate
- Haemodiluted but cellular
- 15 % of morphologically lymphoplasmocytoid cells
- 5% plasma cells are noted
- Aw trephine

# Immunophenotying on BMA

- MDT Summary: Low-level CD5-/CD10- B-NHL by flow.
  Unable to specify further.
  3% of WBCs (14% of lymphocytes) are CD19+, CD30+, CD5-,CD10-,CD23-, CD160-, CD200+/-, CD38+ Kappa restricted B-cells.

# Bone marrow trephine HE stain



- What would you do next?

# BMT HE and IHC

- Heavy infiltrations with small to medium seized lymphoid cells
- CD38+, CD138+, CD20 moderately positive, CD3 +, CD7+, CD30+, CD19 positive
- Kappa restricted B cell
- Lymphoplasmocytic Lymphoma with reactive T cell infiltrations suggested
- Aw T cell Clonality study

# Bone marrow diagnosis

- Lymphoplasmocytic Lymphoma with reactive T cell infiltrations? Awaits T cell Clonality study

# Lymph node biopsy results

**Microscopic Description:**

Needle cores shows a lymphoid lesion with a diffuse polymorphous infiltrate composed of a mix of small, medium and large sized lymphoid cells and eosinophils. Medium and large sized lymphoid cells show atypia. Large cells have prominent nucleoli. Classical RS cells are not seen.

Larger cells express CD45, CD20 (variable intensity), CD30, MUM1 and PAX5, and are negative for CD15 and EBER. They show kappa light chain restriction. Small and medium sized cells are T cells expressing CD2, CD3, CD5 and CD7, with a CD4:CD8 ratio of 2:1, and these include cells with atypia. A proportion of these cells express CD10 and PD1. CD21 and CD23 identify irregular aggregates of FDC meshworks. There are scattered EBER+ small lymphoid cells. Cyclin D1 is negative. Ki67 expression is 60-70%.

**Final Diagnosis:**

Needle core biopsy, left axillary lymph node: Features are suggestive of angioimmunoblastic T cell lymphoma with an evolving light chain restricted large B cell population interpreted as diffuse large B cell lymphoma (refer to comments).

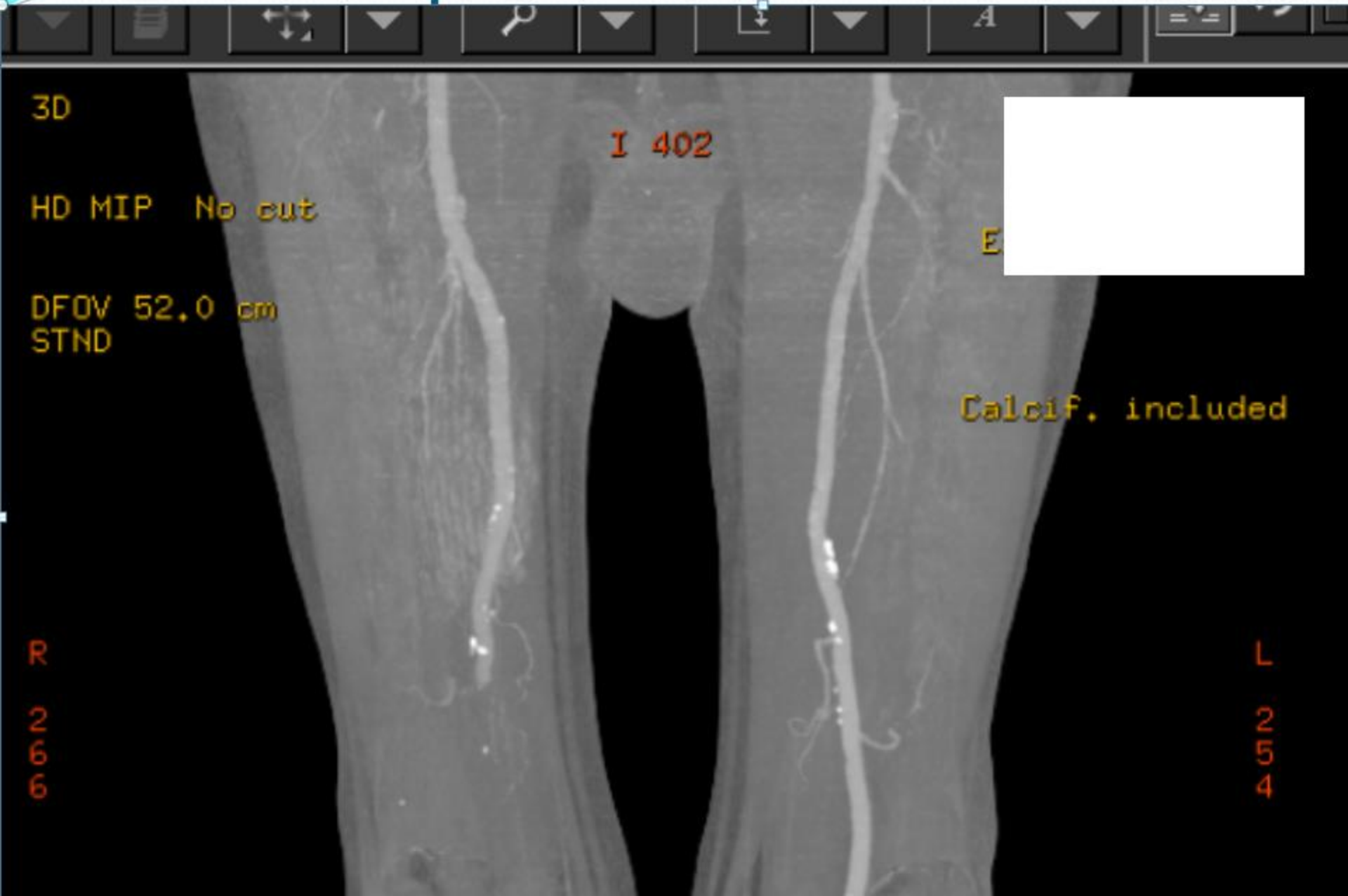
# MDT recommendation

- AITL with High grade B cell transformation and associated AIHA
- BMT: LPC with T cell proliferations?
- Treat with R-CHOP
- No Etoposide as elderly for now
- Total 6 courses advised followed by ASCT in 1st CR
- Consider PET after 2 cycles to assess response
- Hb improved to 112 on tapering dose prednisolone
- Discharged home and plan for readmission for R-CHOP

# Patient admitted for R-CHOP

- On admission right foot noted to be cold, blue  pulse couldn't be palpated –
- vascular team involved.

# A similar patient from the ref



# CT Angio

- CT Angiogram showed small right CIA aneurysm with some mural thrombus. Occlusion of the right SFA.
- Run off is seen into anterior tibial artery and peroneal artery occlusion of the right SFA.
- Thromboembolectomy (Right CFA) and calf fasciotomy
- IV Heparin post op started

# Complicated with

- Further Right leg ischemia - operated and several embolectomy  done
- subsequent  below knee amputation
- Complicated with stump infection and further ischemia
- Underwent above knee amputation unfortunately

- Anti cardiolipin antibodies negative
- Thrombophilia test ; NAD

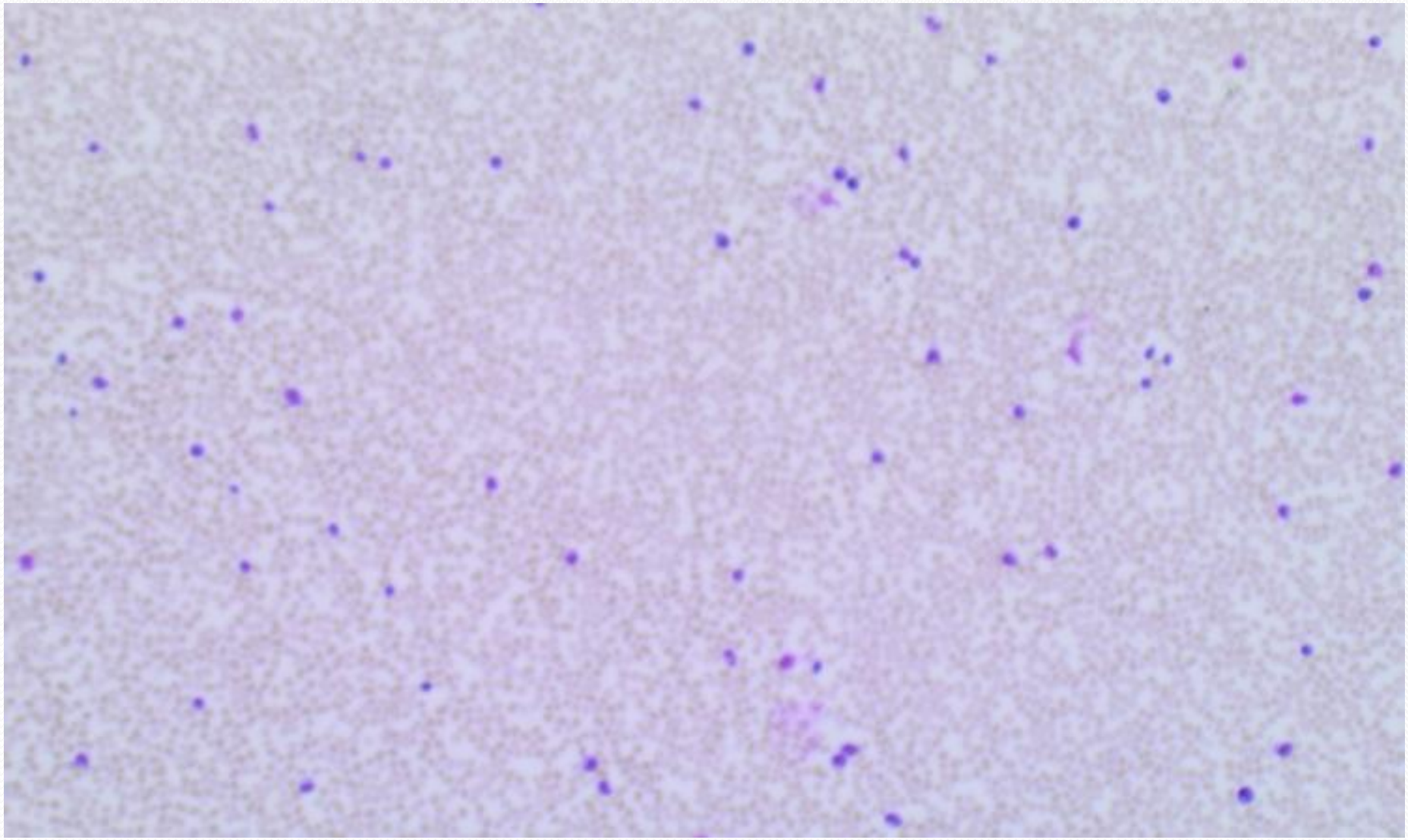
# RECEIVED 1 ST CYCLES OF CHEMO as R-CVP ( modified)

- 8 WEEKS AFTER THE DIAGNOSIS
- DELAY DUE TO SURGERY AND INFECTION
- WAS STILL ON PREDNISOLONES TAPERRING DOSE

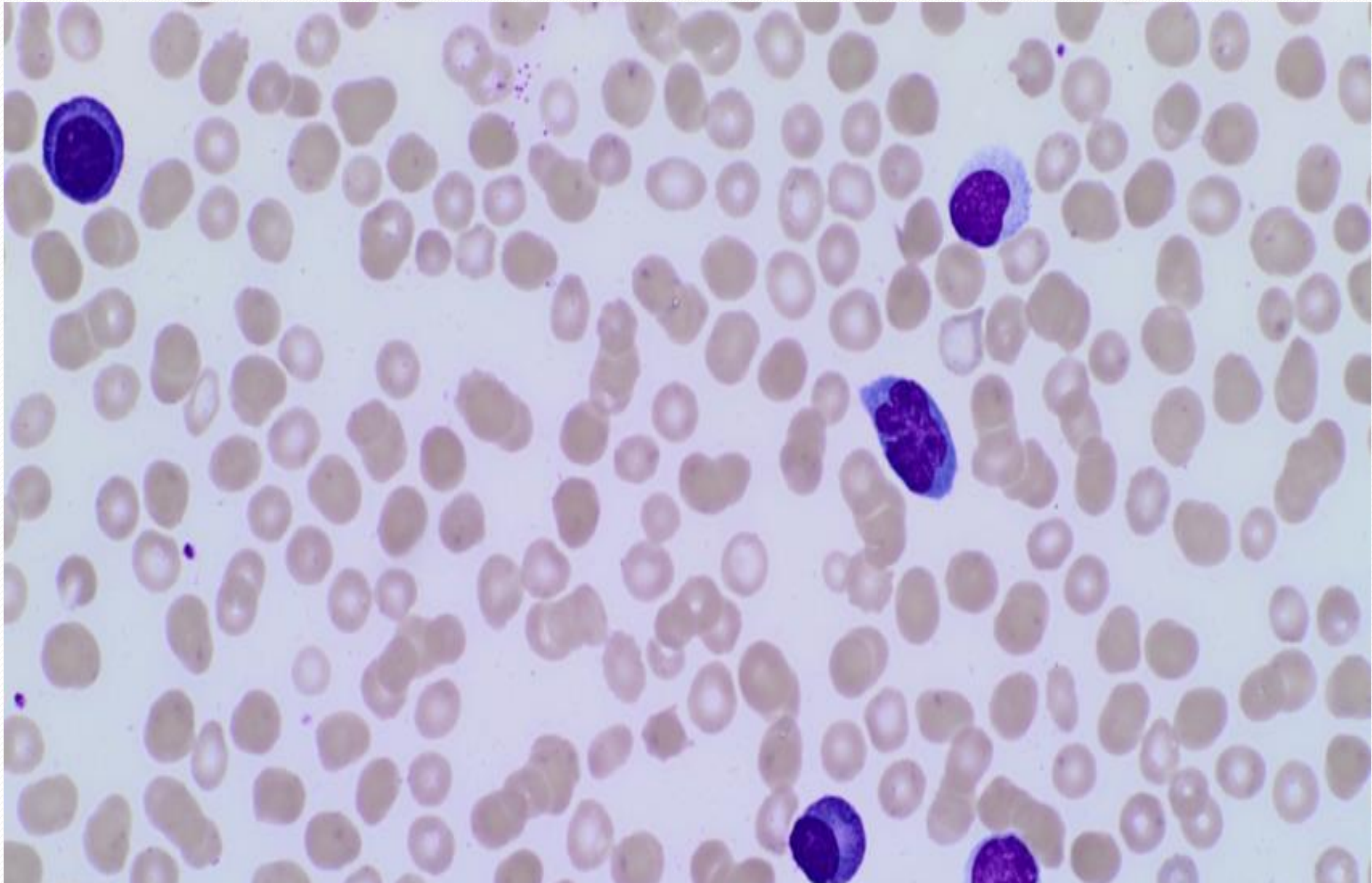
# Readmitted 10 days post chemo

- With fever and cough.
- Had a periarrest in A and E.
- CXR showed right sided consolidation.
- HB 111 WCC 12, neutrophils  3.5, PLT 270, CRP 75
- Treated with Tazocin and clarithromycin.
- Improved clinically

# Film: WCC rising -not on GCSF



# Film high power



# What test next?

# Flow cytometry

- 8% of WBCs are CD138+ CD38+ CD19+ CD56- , cD117- Cyto kappa restricted plasma cells .

  3% of lymphoid cells have a dual CD4/CD8 ratio ? incidental

- Noted previous B.M. sample reported as having a smallCD19+ CD5-, CD23- CD38+ B cell clone.

(Flow report: always underestimate due to cell death on transit)

# Conclusion from flow and Film

- The peripheral blood film showed 40 % plasma cells

Together with peripheral blood flow cytometry consistent with

A diagnosis of plasma cell leukaemia/LPC

- prognosis is very poor
- started on steroids and Lenalidomide being transformed from AITL

# MDT

- MDT: also approved Single agent IBRUTINIB if no response with LEN/Dex
- NOT for more aggressive Salvage due to Frailty and poor PS
- Very uncommon presentation and rapid progression
- Transformed B cell Lymphoma from AITCL and now plasma cell leukaemia
- As of today Continuing LEN/Dex with good clinical response

# Learning points

Point Against myeloma

- CD19 +, CD 56-, CD117 –
- IgM paraprotein
- EBER + on histology
- No real lytic bone lesion on scans and x rays
- CD 19 almost always negative in myeloma
- CD56 + 70-80% Myeloma,
- CD117 20% myeloma
- CD20 + 5-10% myeloma aberrant expression

# The final possible diagnosis

- Transformed B Cell Lymphoma from AITL and rapidly progressing plasma cell leukaemia/ lymphoma

# AITL

- Angioimmunoblastic T-cell lymphoma (AITL)
- an uncommon subtype of mature peripheral T-cell lymphoma (PTCL).
- The history of AITL is much longer and deeper than the literature would suggest given the many names that has preceded it.
- Advanced stage disease is common with uncharacteristic laboratory and autoimmune findings that often slow or mask the diagnosis.
- Significant strides in the immunohistochemical and molecular signature of AITL have brought increased ability to diagnose this uncommon type of PTCL.

- The 2016 World Health Organization (WHO) classification of lymphoid neoplasms recently acknowledged the complexity of this diagnosis with the addition of other AITL-like subsets.
- AITL now resides under the umbrella of nodal T-cell lymphomas with T Follicular helper phenotype.

# AITL associations

- Autoimmune phenomena common
- Very prothrombotic condition
- Profound T cell Dysregulation
- Prone to have viral infection/reactivations
- Needs checking CMV/EBV/Adeno virus status
- variable Skin manifestations
- Fingers and toes scleroderma types of features are common

# A Typical Histology and IHC of AITCL

Lymph nodes showing effacement by a lymphoid lesion showing a diffuse and vaguely nodular architecture. The lesion extends into adjacent fat. Lymph node appears to show vascular proliferation with arborising high endothelial ventures. The infiltrate appears heterogenous and is composed of medium sized lymphoid cells showing irregular, mildly pleomorphic nuclei and prominent nucleoli. Small lymphocytes, plasma cells and occasional eosinophils are also seen.

On immunohistochemistry, the atypical cells are T cell positive for CD3 (weak and partial loss), CD5, CD4, CD2, PD1 (weak), BCL2 (weak), BCL6 (weak and focal) and CD7 (strong focally to moderate with partial loss), CD30 is positive in a significant proportion of atypical cells. They appear negative for ALK1, CD8, and CD25. CD10 highlights few lymphoid cells and EBER ISH is positive in many lymphoid cells ranging from small lymphocytes to large cells. Lymphoid cells appear negative for cyclin D1. CD20 highlights few B cells seen in loose aggregates and few large, nucleolated cells seen singly. CD23 highlights focal irregular and expanded FDC meshworks. The Ki67 proliferation fraction is 60%. Plasma cells appear polytypic on light chain analysis.

Final Diagnosis:
Right inguinal lymph node:
- Features are of T cell lymphoma interpreted as Angioimmunoblastic T cell lymphoma: see comment.

Note:
Material will be submitted for clonality analysis

Addendum:
Abnormal T cells are positive for ICOS and negative for CXCL 13.

# AITL standard of care in the UK

- Various regime used worldwide
- Typically in the UK

CHOEP X6 followed by ASCT in 1st CR

- Relapsed /Refractory disease is troublesome
- Consider intensive salvage to Allogeneic stem cell transplantation in second remission if feasible

Investigational

- Brentuximab vedoitin where cells are CD30 positive with CHOEP
- Single agent Brentuximab vedoitin when relapsed

# prognosis

- 3 years progression-free survival rates remain disappointing, ranging from 40% to 50%

In refractory /relapsed cases and unsuitable for salvage chemo

- Single agent Lenalidomide has variable success rate
- Several Case reports of more than 24 months survival with Lenalidomide has been observed

# RomiCar trial on going in the UK


**Phase I/II study to determine the maximum tolerated dose and activity of the combination of romidepsin and carfilzomib in relapsed or refractory peripheral T-cell lymphoma**

# Relapsed /refractory

Journal of Oncology Practice > List of Issues > Volume 15, Issue 3 >

CLINICAL REVIEWS

Practical Treatment Approach for Angioimmunoblastic T-Cell Lymphoma



Alison J. Moskowitz, MD[1]

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## RELAPSED/REFRACTORY AITL

Choose

Owing to the possibility of development of EBV-related diffuse large B-cell lymphoma either concurrently with AITL or at relapse, repeated biopsy is essential to confirm the etiology of relapsed or refractory disease. The approach to treatment of patients with relapsed/refractory AITL (as well as the other nodal PTCLs) depends on the whether the goal of therapy is cure or palliative.[34] There are multiple regimens that can induce disease control and possibly remission in AITL; however, the choice of therapy and how to sequence treatment depends heavily on whether consolidation with an alloSCT is being considered.

### What Is the Consolidation Plan: ASCT, alloSCT, or Neither?

Although ASCT is routinely used in the relapsed/refractory setting for B-cell lymphomas, results from several series (Table 2) demonstrated disappointing outcomes when ASCT was used for relapsed/refractory PTCL.[35,36] In particular, data from the Cleveland Clinic and from MSKCC show relapse rates greater than 80% when ASCT is used for relapsed/refractory PTCL.[35,36] In contrast, Center for International Blood and Marrow Transplant Research registry data suggest more promising results with ASCT for relapsed PTCL; however, this series is heavily represented by patients with anaplastic large-cell lymphoma, which may explain the more favorable outcomes observed. Therefore, with the exception of anaplastic large-cell lymphoma, ASCT is unlikely to lead to long-term remission for patients with relapsed/refractory AITL and other PTCLs.[37] More promising outcomes are observed with alloSCT, which is associated with a 2- to 5-year PFS of 45% to 53% for nodal PTCLs and as high as 81% for AITL.[38-41] Therefore, for appropriate patients, consolidation with alloSCT is strongly considered provided disease control can be obtained.

# Good read

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CLINICAL REVIEWS

## Practical Treatment Approach for Angioimmunoblastic T-Cell Lymphoma



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