Case 8

Presented by
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NHS
The Leeds Teaching Hospitals
NHS Trust

HMDS
Haematological Malignancy Diagnostic Service

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Case

- 31 year old male investigated for incidental microcytic, hypochromic anaemia.
- Bilateral ankle pain, weight loss and night sweats
- PMH: Congenital talipes
- FHx: Treated Pulmonary Tuberculosis
- He previously declined investigation of his anaemia

Case

- BP 105/65 mmHg, HR 82bpm, temp 37.5^{o}C,
- RR 18, Sats 98% on air
- HS: I+II with a mild ESM
- Icteric sclera
- Bibasal reduced air entry on chest auscultation
- Mild abdominal distension, palpable splenomegaly
- Bilateral ankle oedema
- Rt sided talipes

Investigations 1

On admission	
Hb	**65g/L**
Retic	178 x10^9/L
MCV	**64fl**
WBC	3.08 x10^9/L
Plts	246 x10^9/L
Neuts	2.62 x10^9/L
Lymphs	**0.08 x10^9/L**
TBili	**79 umol/L**
ALP	**648 U/L**
Alb	**20 g/L**
ALT	**100 U/L**
CRP	**138.8 mg/L**
Ferritin	**3421 ug/L**

- CXR: Bibasal blunted costophrenic ankles, rt peri-hilar patchy opacification
- Abdominal US: Small hypoechoic liver lesions, splenomegaly

Case

- Treated for Sepsis of unknown origin
- Continued deterioration with high swinging fevers >39^{o}C and hypotension
- Increased peripheral oedema
- Transferred to ICU for inotropic support

Interactive question 1

Based on the information presented thus far what single screening investigation would you request next?

a) CT Neck, Chest, Abdomen Pelvis
b) Haemoglobin HPLC
c) Autoantibody screen
d) Septic screen/Virology
e) Lactate Dehydrogenase
f) Serum Lipid Profile
g) Coagulation Screen

Investigations 2

After 1 week	
Hb	**56g/L**
WBC	3.79 x10^9/L
Plts	**53x10^9/L**
Neuts	2.62 x10^9/L
TBili	**116 umol/L**
ALP	**807 U/L**
AST	**302 U/L**
ALT	**76 U/L**
LDH	**678 U/L**
Ferritin	**25547 ug/L**
Triglycerides	**2.77 mmol/L**
Clauss Fg	**1.9g/L**
EBV PCR	**58011 U/mL**

CT NCAP:

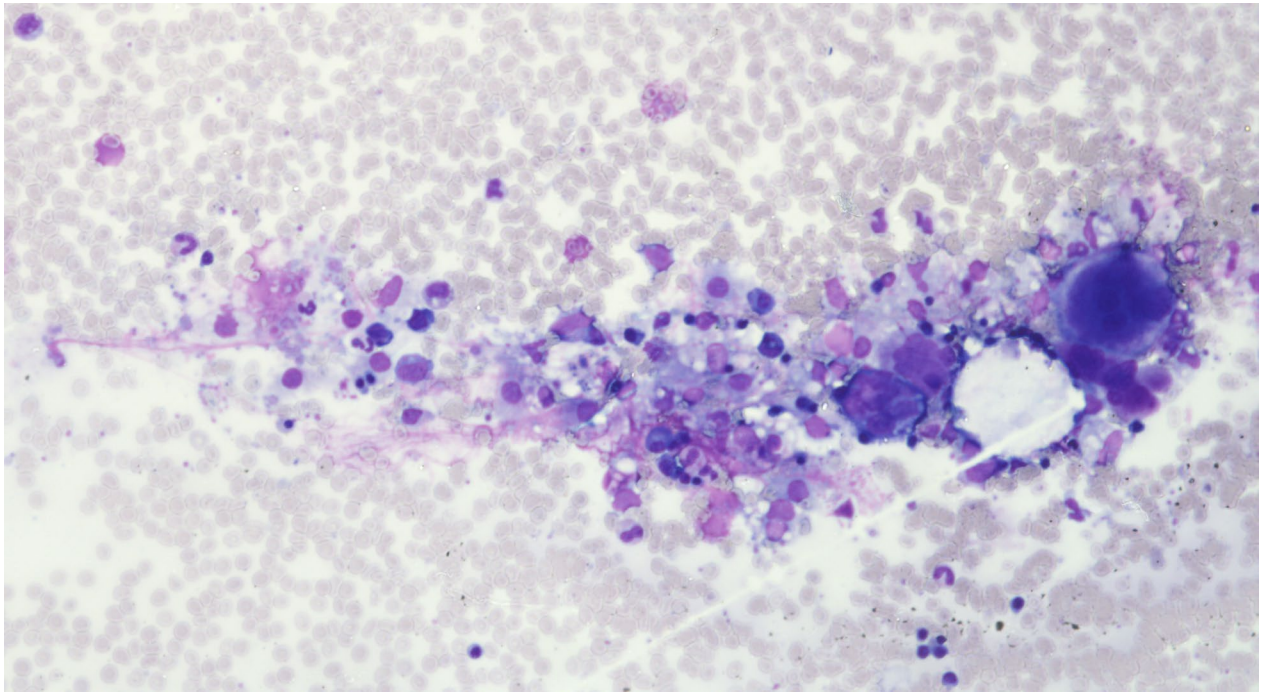
- Small bilateral pleural effusion
- 18cm splenomegaly
- Multiple splenic and hepatic hypoattenuating lesions
- Moderate vol. retroperitoneal and left pelvic lymphadenopathy
- Moderate vol. ascites

Interactive question 2

What test to identify the most likley cause for the clinical presentation would you request next?

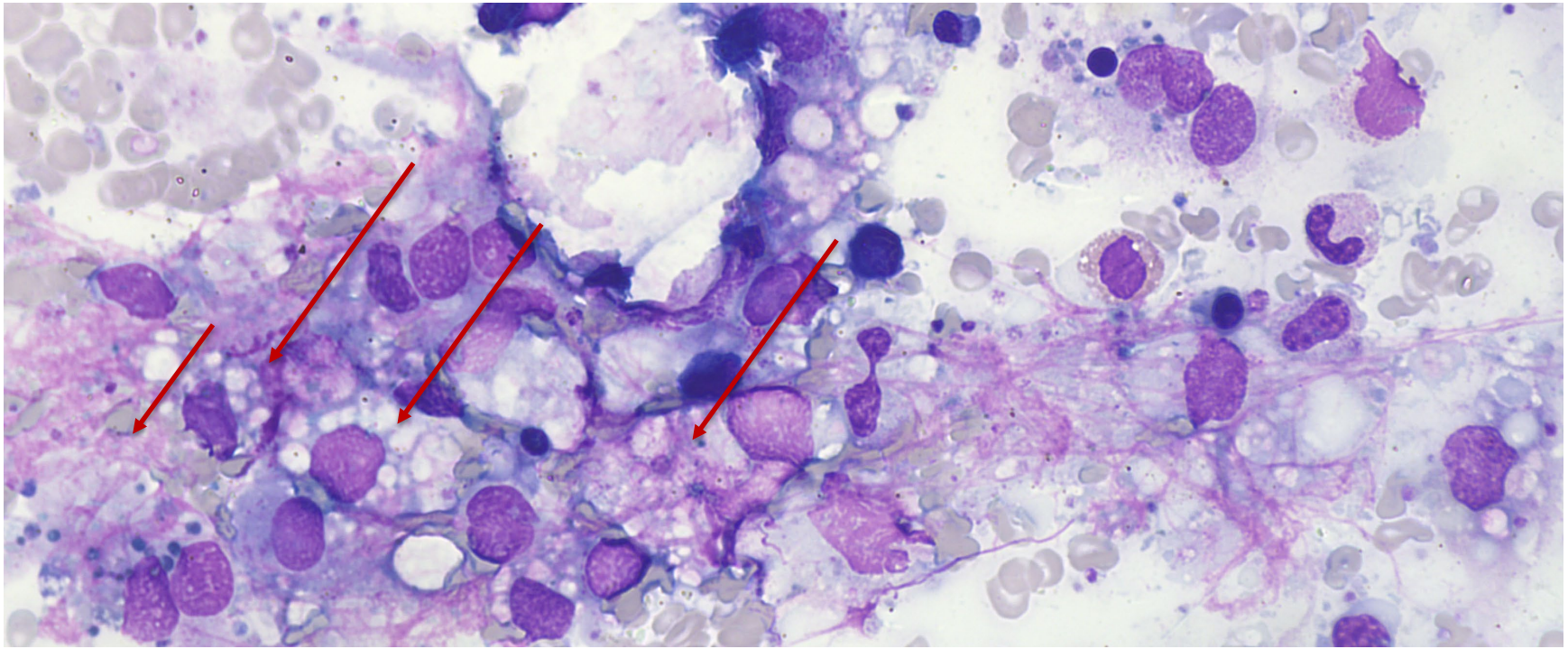
a) Soluble CD25
b) Splenic biopsy
c) Perforin and Granule Release Assay
d) T cell subsets
e) Bone marrow
f) XIAP, SAP, CD27, CD70 expression/levels

Bone marrow aspirate x 20



- Oligoparticulate
- Clotted
- Cellular evidence of trilineage haematopoiesis
- Increased macrophage activity

Bone marrow aspirate x 40 - Haemophagocytosis



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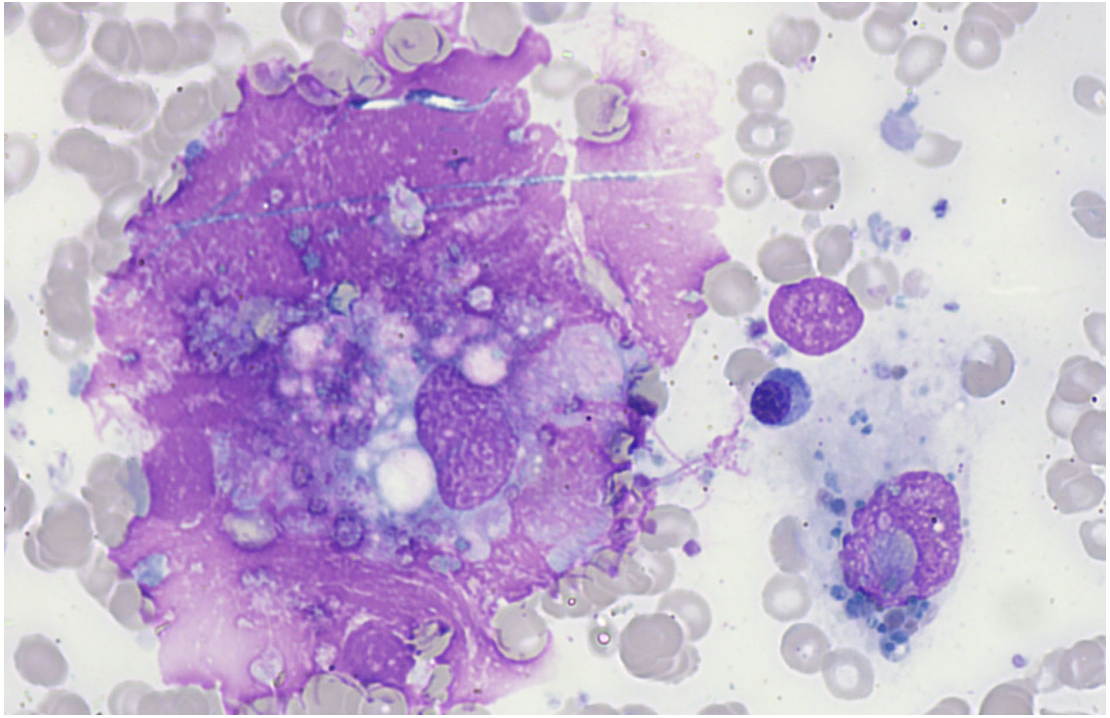
Bone marrow aspirate x 60



- Increased macrophage activity
- Haemophagocytosis

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Flow Cytometry

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CD34+ = 0.73% of leucocytes of which 87% are CD117+ and <5% are CD19+. CD34-117+ = 5.8% of leucocytes.
CD64+ Monocytes = 7% of leucocytes of which 78% are CD14+.

Plasma cells = 0.65% of leucocytes with a normal phenotype.

CD3+ T–cells = 2.1% of leucocytes, of which 30% are CD4+ helper T–cells and 58% are CD8+ cytotoxic T–cells. NK–cells = 0.99% of leucocytes.

B-cells = 0.02% of leucocytes. Kappa:Lambda ratio = 1.8:1 (normal).

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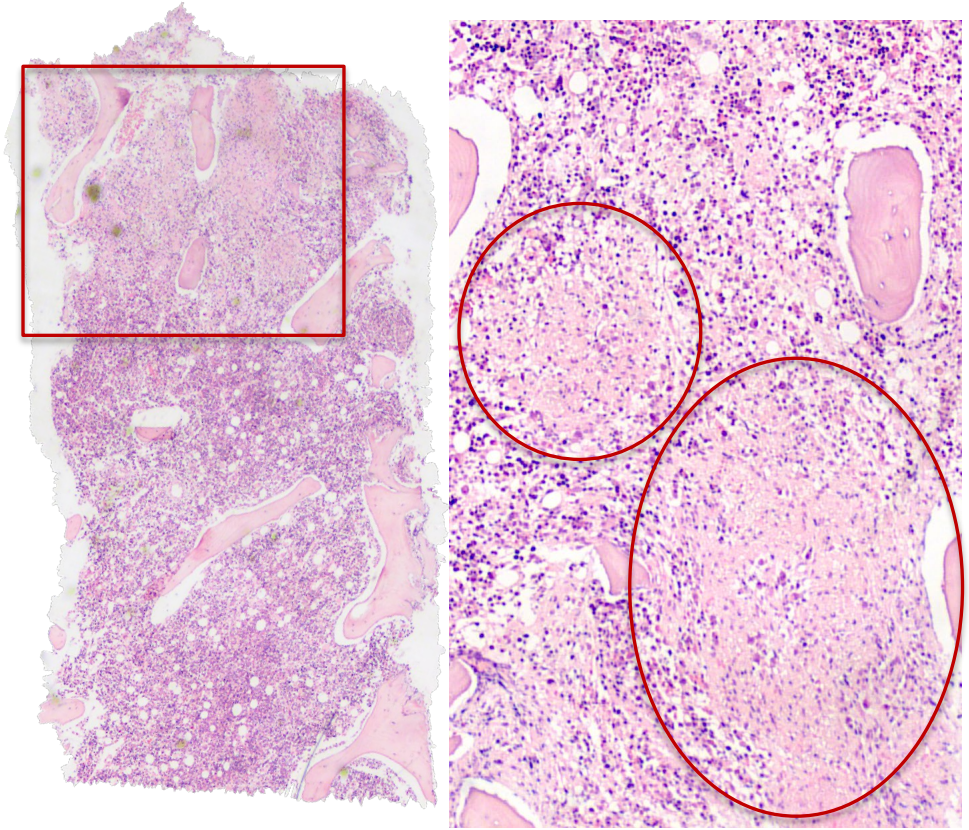
Interactive question 3

What is the suspected diagnosis?

a) Intravascular Large B Cell Lymphoma with Haemophagocytic lymphohistiocytosis
b) Adult-Onset Still's Disease
c) X-Linked Lymphoproliferative Syndrome Type 1
d) EBV- driven Haemophagocytic Lymphohistiocytosis
e) Hodgkin Lymphoma with Haemophagocytic lymphohistiocytosis
f) Metastatic Carcinoma
g) Insufficient information to make a diagnosis

Trephine



- Hypercellular
- Distorted architecture
- Multifocal patchy infiltrate
- Numerous large atypical binucleate and multinucleate cells
- Reactive background with histiocytes and eosinophils
- Florid macrophage activity
- Interspersed preserved by reactive haematopoiesis

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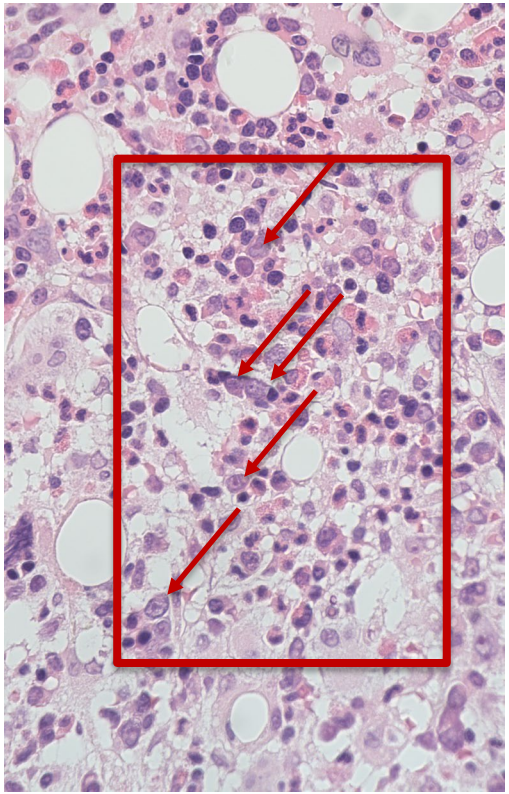
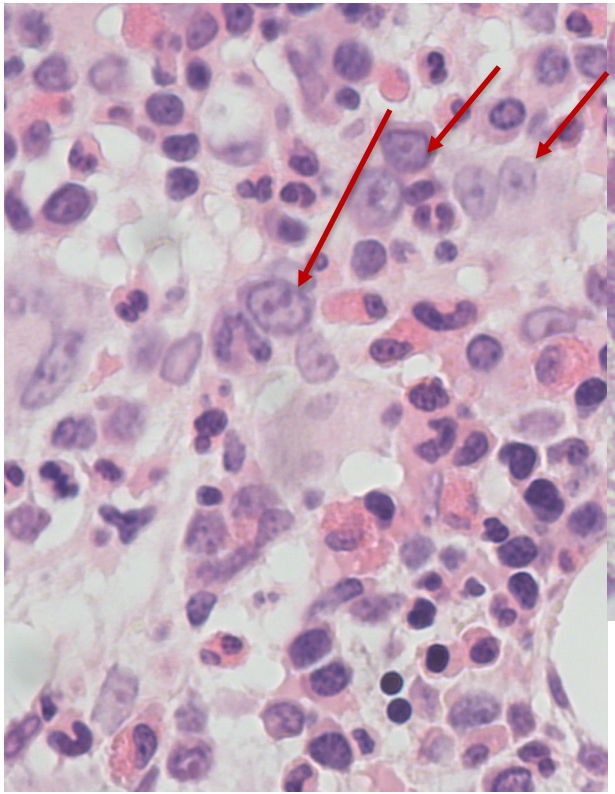
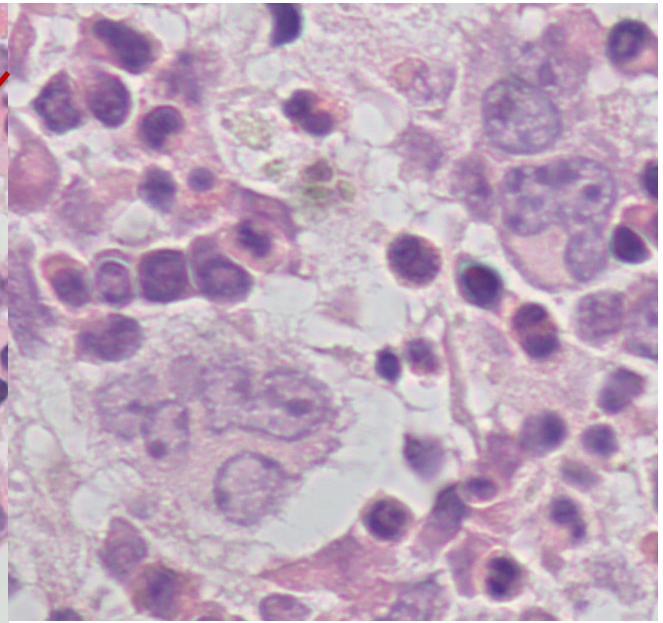
Trephine







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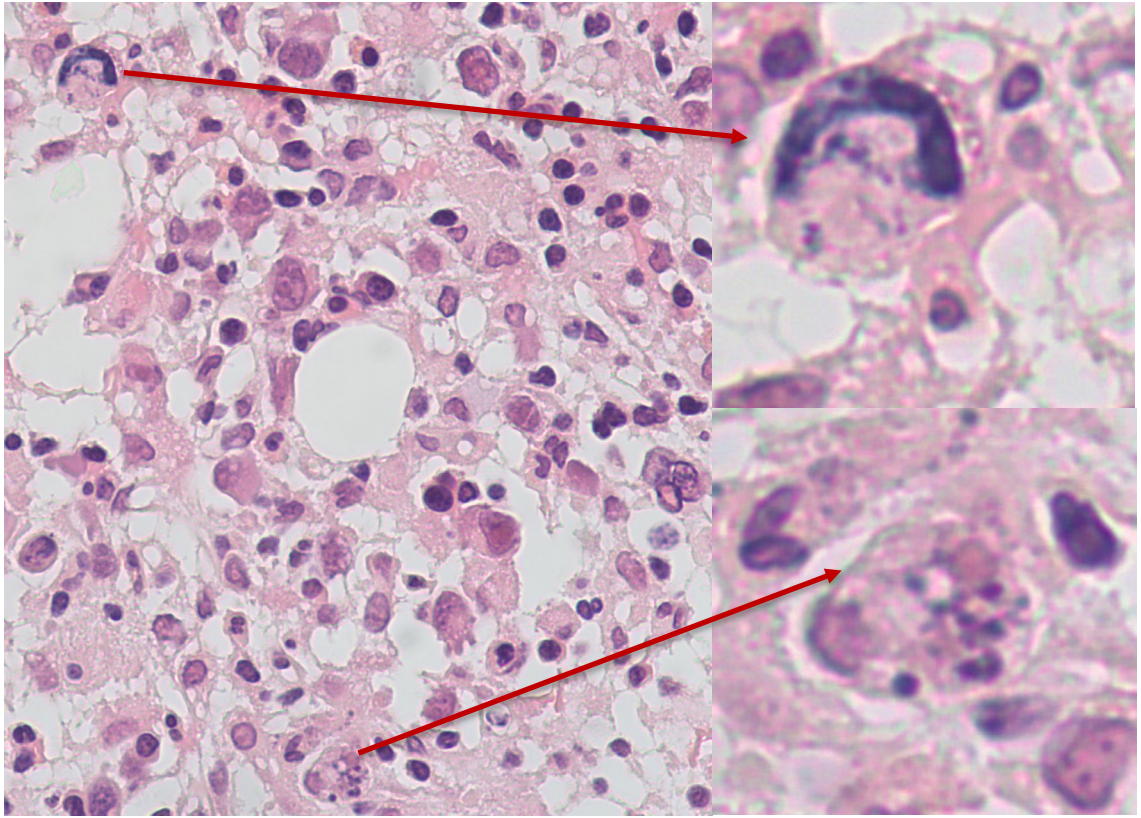
Trephine



- Florid macrophage activity
- Numerous atypical multi-nucleate cells
- Reactive background
- Haemophagocytosis

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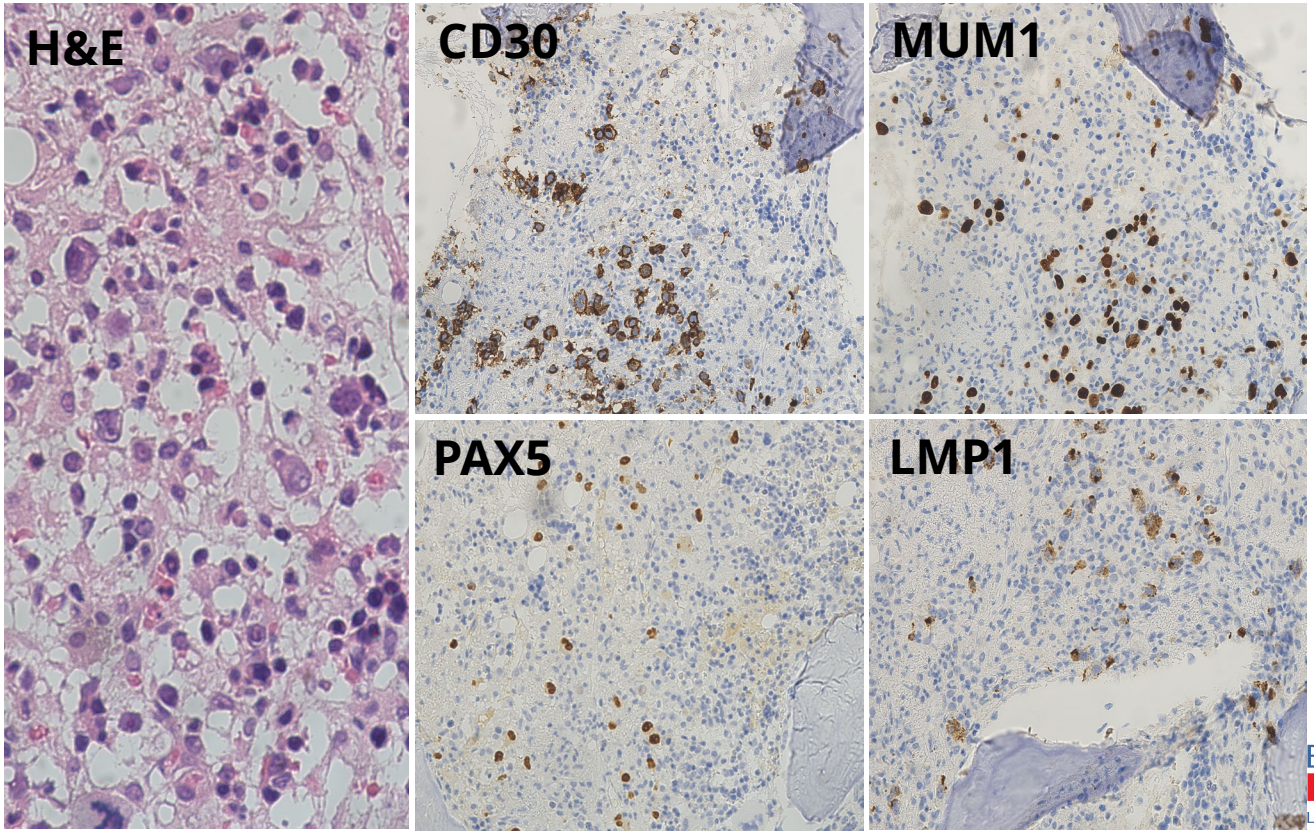
Immunohistochemistry



- Numerous atypical multi-nucleate cells
- Reed-Sternberg phenotype with latent EBV expression

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Interactive question 4

What is the final diagnosis?

a) Intravascular Large B Cell Lymphoma with Haemophagocytic lymphohistiocytosis
b) Adult-Onset Still's Disease
c) X-Linked Lymphoproliferative Syndrome Type 1
d) EBV- driven Haemophagocytic Lymphohistiocytosis
e) Hodgkin Lymphoma with Haemophagocytic lymphohistiocytosis
f) Metastatic Carcinoma

Diagnosis

f) EBV associated Hodgkin Lymphoma with Haemophagocytic lymphohistiocytosis

Management and Outcome

- Initially managed for HLH with methylprednisolone and Anakinra
- Commenced ABVD switched to EBVD in view of low LVEF (<30%)
- Stormy course, multiple episodes of melaena, due pangastritis
- Good recovery, with normalisation of blood counts
- Discharged from hospital
- Patient declined further treatment as an outpatient and died shortly after

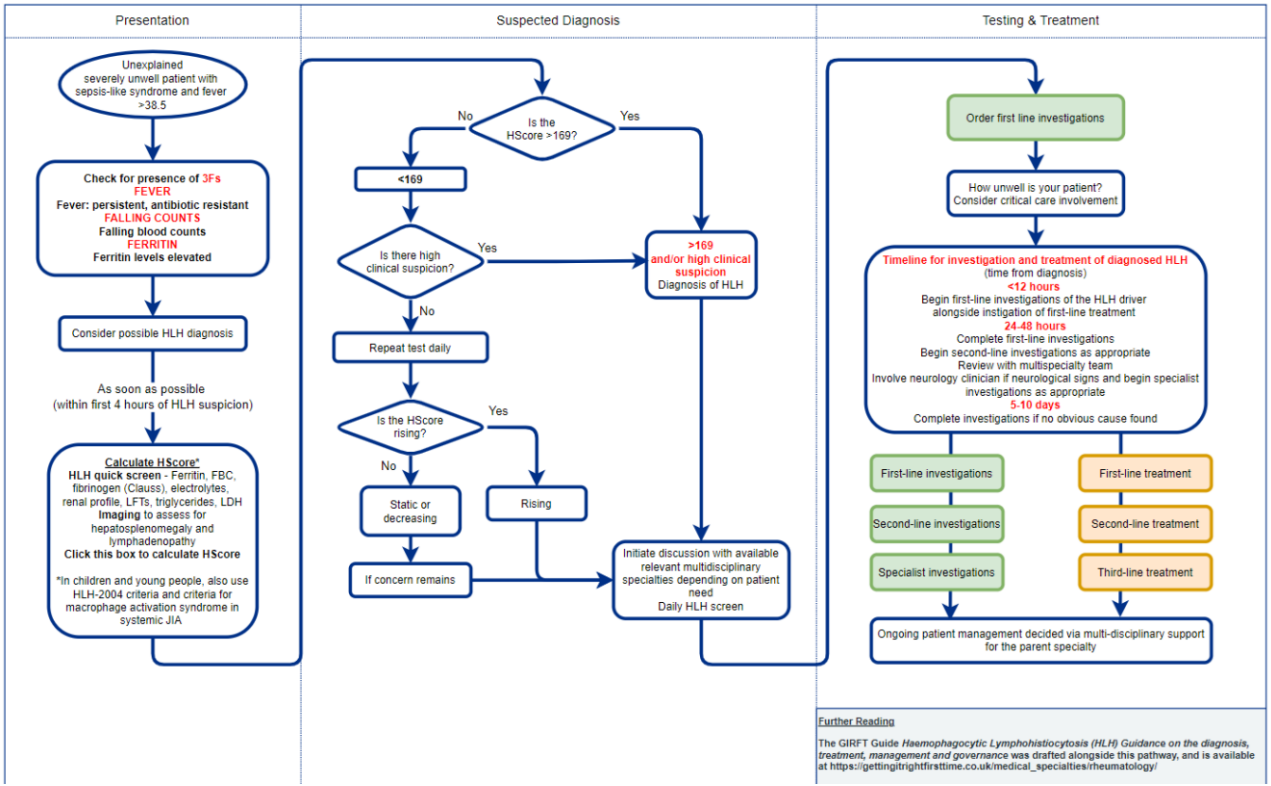
Summary

- 30 year old male presenting with non-specific and evolving signs and symptoms
- 3 Fs (Fever, Falling Counts, high Ferritin)
- High pretest probability of HLH
- High Hscore 203/337 (clinical, biological and morphological factors)
- Initial management for hyperinflammation
- Identification and treatment of underlying EBV associated Hodgkin Lymphoma
- High mortality with delayed identification and management

Take home message

- HLH severe uncontrolled hyperinflammatory syndrome
- Primary, pHLH, due to mutations affecting lymphocyte cytotoxicity and immune regulation (children and young adults)
- Secondary, sHLH triggered by infection, malignancy, auto-immune disorders
- High mortality, particularly those associated with haematological malignancy
- Prompt identification, based on a constellation of signs and symptoms and laboratory biomarkers
- Calculate Hscore in adults and the HLH-2004 score in children in those with high pretest probability
- Involve local/regional/national expert MDT to promptly identify and treat the underlying trigger
- Reduce morbidity and mortality.

GIRFT HLH Pathway Overview



https://gettingitrightfirsttime.co.uk/wp-content/uploads/2024/07/HLH-Pathway-FINAL-V1-July-2024.html

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Acknowledgments

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Andy Rawstron
Ruth DeTute
Richard Leach
Sharon Barrans
Polly Talley
Jane Shingles
Rachel Bradbury
Anne Clarke
Phillip Thompson

NHS
The Leeds Teaching Hospitals
NHS Trust

HMDS
Haematological Malignancy Diagnostic Service

Catherine Cargo
Cathy Burton
Alesia Khan
Roger Owen
Reuben Tooze
Hiba Ali

NHS
Lancashire Teaching Hospitals
NHS Foundation Trust

Mohiuddin Sharief
Vanessa Ambrose Fistus

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