‘Down the rabbit hole’ – a case that gets curiouser and curiouser …

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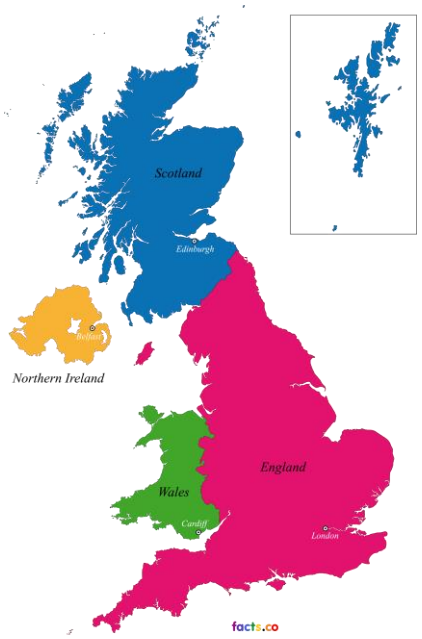

Case presentation

- 36 year old gentleman

- presented to his GP 14 days ago with sore throat, fever, fatigue and swollen glands

- presented with 48 hours of bloody diarrhoea, abdominal pain and jaundice

Past medical history – Crohn's disease

Current mediation – Azathioprine

Key examination findings:

→ clinically dehydrated, tachycardic (129bpm), pyrexic (38.9°C)

→ Icteric sclera, generalised abdominal tenderness (not peritonitic)

Admission blood results

- Full blood count:

  → pancytopenia

  haemaglobin11.8 g/dL *(13.5-18)*
  white cell count 1.1 x10^9/L *(4-11)*
  platelets 6x10^9/L *(150-400)*

- Renal function: normal

- Liver function tests: normal except

  → hyperbilirubinaemia 37 umol/L (0-17)

- EBV IgM +ve, IgG –ve & heterophile +ve antibody

WHAT IS THE DIAGNOSIS & WHAT NEXT?

Differential of pancytopenia

1. Infectious
2. Bone marrow failure
3. Inflammatory / immune
4. Toxic
5. Malignant

Clinical impression:

- Pancytopenia - myelosuppression 2˚ azathioprine
- ↑ bilirubin - attributed to EBV infection

Treated as an infective exacerbation of crohn's colitis

→ *Piperacillin/tazobactam, metronidazole*
→ *Intravenous fluids*
→ *Hydrocortisone*

- <u>48hrs following admission:</u>

  - increasing oxygen requirements

    PaO2 9.8kPa, PaCO2 3.12kPa on FiO2 0.6

  - hypotension requiring multiple fluid boluses to maintain systolic blood pressure >90mmHg

  - deranged acid base

    pH 7.1kPa, HCO_3 12mmol/L, BE -8.1, lactate 4

  - increased transfusion requirements to match colonic losses

  - urgent bloods: ↓haemoglobin, platelets, fibrinogen & ↑INR

WHAT IS THE CAUSE FOR HIS DETERIORATION?

Blood gas reference ranges: pH 7.35-7.45, PaO_2 9.3-13.3kPA, $PaCO_2$ 4.7-6kPA

Septic shock & DIC

- **Sepsis:** life-threatening organ dysfunction caused by a dysregulated host response to infection[1]

- **Septic shock:** vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia[1].

- **Disseminated Intravascular Coagulation (DIC)**
  = widespread activation of coagulation cascade resulting in

i. formation of clots in small blood vessels → multiple organ damage

ii. Consumptive coagulopathy → severe bleeding[2]

Severity is scored using the ISTH DIC scoring system[3]

→ Admitted to the High dependency unit for inotropic support

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-810.

Transfusion requirements

Day 1	6 x concentrated red cells (CRC)
Day 2	4 x CRC, 4 x cryoprecipitate (cryo), 4 x fresh frozen plasma (FFP), 1 x platelets
Day 3	25 x CRC, 4 x cryo, 12 x FFP, 6 x platelets, 1 x 1g fibrinogen
Day 4	9 x CRC, 2 x cryo, 12 x FFP, 12 x platelets, 6 x 1g fibrinogen

TOTAL: **44 units of Concentrated Red Cells**
10 cryoprecipitate
28 Fresh Frozen Plasma
19 pools of platelets
7 x 1g fibrinogen

Haematology input sought:

- massive transfusion protocol activated
- advised to exclude: *Haemophagocytic Lymphohistiocytosis* (HLH)

Massive transfusion[4]

- 100% of total blood volume lost within 24hrs

Parameter	Value	Blood product to be given
Haematocrit	<0.3	Red Blood Cells
Platelets	<75 x 10^9/L	Platelets
Fibrinogen	<1.0g/L	Cryoprecipitate
PT ± APTT ratio*	>1.5 x control	Fresh Frozen Plasma

- Complications:
  1. hypothermia
  2. hypocalcaemia coagulopathy
  3. hyperkalaemia
  4. lactic acidosis
  5. dilutional
  6. ARDS

4. Provan D, Singer C, Baglin T, Dokal I. Chapter 13: Haematological emergencies. Oxford Handbook of Clinical Haematology. 3rd Edition 2009; 652-653

* PT = prothrombin time; APTT = activated partial thromboplastin time

Further Investigations:

- EBV PCR → positive
- Ferritin & triglycerides → increased

  (ferritin 8250ng/mL, triglyc 6.1mmol/L)

- Computer Tomography → hepatosplenomegaly
- Bone marrow

→ hypercellular, prominent macrophage phagocytic activity

Characteristic of EBV associated Haemophgocytic Lymphohistiocytosis (HLH)

Treatment

- Supportive treatment according to sepsis & DIC protocols
- Started on cyclosporin A, dexamethasone & iv immunoglobulins

  → Once stabilised planned induction with etoposide

Haemophagocytic Lymphohistiocytosis (HLH)

- Diagnostic criteria (need to meet 5/8)[5,6]

1. Fever
2. Splenomegaly
3. Bicytopenia
4. Haemophagocytosis
5. Hyperferritinaemia
6. Hypertryglyceridaemia ± hypofibrinogenaemia
7. Low/absent NK cell activity
8. High soluble IL-2 receptor levels

- Profound cytopenias are a prominent feature[7]

- Hepatomegaly, jaundice, maculopapular rashes & neurological involvement are seen in up to 74%[7]

5. Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Seminars in Oncology. 1991 Feb;18(1):29-33.

6. Henter JI, Horne A, Aricó M et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007 Feb;48(2):124-31.

7. Fisman DN. Hemophagocytic syndromes and infection. Emerging Infectious Diseases 2000; Vol

- **HLH poor prognostic markers[7]:**
  1. DIC → haemorrhage, 2° bacterial infection & MOD
  2. ↑ serum ferritin & β2 microglobulin levels
  3. Presence of anaemia, thombocytopenia & jaundice
  4. age > 30yrs

- **HLH treatment[6]:**

- Steroids
- Immunoglobulins
- Cyclosporin A (targets T-lymphocytes)
- Etoposide chemotherapy (toxic to macrophages)
- Allogeneic bone marrow transplant

6. Henter JI, Horne A, Aricó M et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007 Feb;48(2):124-31.

7. Kaito K, Kobayashi M, Katayama T, Otsubo H et al. Prognostic factors in hemophagocytic syndrome in adults: analysis of 34 cases. Eur J Haematol 1997;59:247-53

Summary – top tips of when to consider HLH for the Internist

- A rare condition that can masquerade as sepsis

- Consider HLH in patient presenting as sepsis with a known trigger

  + fever & hepatosplenomegaly

  + pancytopenia, ↓ fibinogen, ↑bilirubin, ↑ trigycerides

- HLH should always be considered in those who develop DIC & pancytopenia