Hyperferritinaemia and hyperinflammation

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February 2019
Plan of the talk

• What is Hyperinflammation/HLH?
• When should you suspect it?
• How could/should we treat it?
• Three illustrative cases
Innate immunity and autoinflammation

- Macrophages activated to phagocytose pathogens
- (haemo) Phagocytose and destroy antigen
- NK cells and CTL shut down response: induce apoptosis of macrophages
- Activate other macrophages by releasing IL-1
Inappropriate, pathological autoinflammation (hyperinflammation)

defect in shut down mechanism due to immune dyregulation

NK cell
Or CTL

→ cytokine release.....
...hyperinflammation
.......cytokine storm

HLH
What is HLH?

- Immune dysregulation leading to hyperinflammation and tissue destruction
  - Haemophagocytic lymphohistiocytosis (HLH) or Macrophage activation syndrome (MAS)
  - [Haemophagocytic syndrome, Malignant histiocytosis, hyperinflammatory lymphohistiocytosis]

- High mortality (58-75%)
  - Multi-organ failure
  - Haemorrhage
  - Sepsis

- Defining characteristics
  - Fever (cytokine storm)
  - Haemophagocytosis by macrophages
HLH as a final common pathway

- Primary genetic
- Haematological/malignancy
- Infection
- Rheumatological
How to change outcome

1. Recognize the signs
2. Start treatment promptly
3. Try not to kill the patient with the drugs
Clinical features

- Unremitting fever
  - Masked by paracetamol
- Hepatomegaly
- Splenomegaly
- Lymphadenopathy
- Bleeding
- Confusion, fitting

Blood results

- High ferritin
- Pancytopaenia
  - Falling platelets often first sign
- Transaminitis
- High CRP, falling ESR
- Coagulopathy
- High LDH
- High triglycerides
- Low fibrinogen
- Soluble CD25 (Il-2 receptor α), marker of T cell activation

Bone marrow showing haemophagocytosis by macrophages: can be absent
Loss of immune regulation

Uncontrolled activation of T cells and macrophages

Hypersecretion of inflammatory cytokines

Indolent HLH

Cytokine storm
The H Score

http://saintantoine.aphp.fr/score/

### Score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
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<tr>
<td>Known underlying immunodepression</td>
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<tr>
<td>Maximal Temperature (°C)</td>
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<tr>
<td>Hepatomegaly</td>
<td>Select</td>
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<tr>
<td>Splenomegaly</td>
<td>Select</td>
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<tr>
<td>Lower Hemoglobin level</td>
<td>Select</td>
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<tr>
<td>Lower Leucocytes count</td>
<td>Select</td>
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<tr>
<td>Lower Platelets count</td>
<td>Select</td>
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<tr>
<td>Higher Fibrin level (ng/mL)</td>
<td>Select</td>
</tr>
<tr>
<td>Higher Triglyceride level (mmol/L)</td>
<td>Select</td>
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<tr>
<td>Lower Fibrinogen level (g/L)</td>
<td>Select</td>
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<tr>
<td>Higher SGOT/ASAT level (UI/L)</td>
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<tr>
<td>Hemophagocytosis features on bone marrow aspirate</td>
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**HScore**

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**Probability of having HS (%)**

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Could it be HLH/MAS? What is the evidence of hyperinflammation?

Soft signs
- Lymphadenopathy, hepatosplenomegaly
- (pan)cytopaenia
- Transaminitis
- Clotting dysregulation, hypofibrinogenaemia
- Falling/inappropriately low ESR/CRP
- Hypertriglyceridaemia
- (Haemophagocytosis in bone marrow)

Hard Signs
- Hyperferritinaemia
- Persistent fever
- Low platelets
- CNS dysfunction
- CRP/ESR too ‘good’ for state of patient
- Underlying illness eg SLE being treated, patient worsening
Fig. 3 Diagnostic algorithm for MAS/sHLH in adults

Adult with Pyrexia of Unknown Origin in “At-risk” Population

Check serum ferritin

- <500 µg/L: MAS unlikely
- 500 - 10 000 µg/L: MAS possible
- >10 000 µg/L: MAS probable

- a
  - Check serial FBC, ferritin, fibrinogen, triglycerides, AST, LDH
  - Perform HScore

- a
  - Confirm Consistency with fibrinogen, triglycerides, AST, LDH, HScore and start immediate treatment

Where underlying cause is not known, investigative approach includes imaging/bone marrow biopsy for malignancy, thorough infectious screen and targeted viral serology dependent on epidemiological risk for exposure to various pathogens (EBV serology and EBV DNA is recommended in all patients). MAS: macrophage activation syndrome; sHLH: secondary haemophagocytic lymphocytosis; FBC: full blood count; AST: aspartate transaminase; LDH: lactate dehydrogenase.
Fig. 4 Recommended treatment protocol for adults with MAS/sHLH

Immediate Treatment
IV methylprednisolone 1g daily for 3-5 days
Plus
IVIG 1g/Kg daily for 2 days (repeat in 14 days)

Second-line Treatment
Established MAS/sHLH\(^a\)/clinical deterioration despite immediate treatment:
Anakinra starting at 1-2mg/kg, increasing to maximum 8mg/Kg/day

Third-line/refractory Treatment
Discuss with haematologist
Etoposide150mg/m\(^2\) twice weekly for two weeks, then Etoposide150mg/m\(^2\) once weekly for 6 weeks

Parallel treatment considerations
EBV identification and treatment – consider rituximab
Targeted antibiotics to treat infectious triggers
Investigation for malignant triggers and consideration for cancer targeted chemotherapy
Ciclosporin can be considered as second line treatment for early MAS/sHLH at 2-7mg/kg/day and has a role to prevent recurrent episodes
IVIG half-life is 14-21 days therefore consider repeat administration at 14 days

Absolute cytopenia
Coagulopathy
Neurological dysfunction
Haemophagocytosis
Organ dysfunction

MAS: macrophage activation syndrome; sHLH: secondary haemophagocytic lymphocytosis.
Anti-cytokine therapies

• The anakinra story
  – Case series in MAS
  – Generally accepted as safe

• Other options
  – Canakinumab (anti IL1)
  – Tocilizumab (anti IL6)

• Non-rheumatomatological cases
  – Little experience
Case 1

- 25 year old man
- 3 day history
  - Chest pain and shortness of breath
  - Fever
  - Sore throat
  - Arthralgia
  - Myalgia
  - Rash
Results/Differential

- CRP 235
- Neutrophilia (17)
- Normal renal/liver function
- Troponin moderately raised
- Non-specific T wave changes
- ECHO showing EF 40%

- Acute rheumatic fever
- Viral infection
  - Acute HIV sero-conversion
- Bacterial sepsis

Day 3: Ferritin 15,624, diagnosed AOSD, pulsed steroid
From indolent HLH to cytokine storm

<table>
<thead>
<tr>
<th></th>
<th>Ferritin</th>
<th>Fibrinogen</th>
<th>Triglycerides</th>
<th>ALT</th>
<th>Platelets</th>
<th>ESR</th>
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<td>1</td>
<td>22663</td>
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- Pulsed methyprednisolone (1g x 3)
- Rapid resolution of fever, CRP and symptoms
- Ciclosporin started
- BMA = haemophagocytosis
Key points from case 1

1. HLH is relatively common in adult onset Still’s disease

2. Indolent HLH versus cytokine storm
   – Early intervention limits need for toxic drugs
Case 2

• 74 yr old male
• Self caring and very active
• 10 day history
  – Fatigue
  – Lethargy
  – Cough
  – Fever
  – Intermittent confusion

• Clammy and unwell
• Temperature 38.1 °C
• No localising signs of infection
• Saturations 98% on air
• Respiratory rate 21
• Pulse rate 100
• Confused
Initial investigations and management

- Raised CRP (87)
  - Other bloods largely normal
- Started tazocin
- Septic screen negative
- Immunology negative
- Confused and febrile
- No response to Abx x3

- No diagnosis
- Patient worsening
- Transferred to ITU
Email to rheumatologist with interest in HLH

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<th>WBC</th>
<th>Platelets</th>
<th>HB</th>
<th>ALT</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>3.1</td>
<td>190</td>
<td>146</td>
<td>42</td>
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<td>Day 6</td>
<td>2.5</td>
<td>72</td>
<td>97</td>
<td>202</td>
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“I'm on for ITU today. I was wondering if you were interested in this patient with possible HLH despite no known rheumatological or haematological disorder...........

his ferritin is 16000 and I have calculated an H-score today giving a probability of 95% for HLH....”
Rheumatology review

- History from wife
  - “he’s not been right since he had shingles 3 weeks ago”

- Diagnosis
  - Acquired HLH secondary to shingles

- Treatment
  - 1g IV methylprednisolone
  - Add IVIG 2g/kg over 48 hours
  - Source anakinra in case needed

- Extubated by day 13
- Discharged home, well
Key points from case 2

1. Consider hyperinflammation in ‘sepsis plus’
   – Sometimes called MASL

2. Benefits of multidisciplinary HLH MDTs/learning
Case 3

- 69 Y/O gentleman
- TB treatment in 2013
  - culture negative, presumptive 6m treatment
- Type 2 diabetes
- Ischaemic heart disease
- Hypertension
- CKD

- 3 month history of weight loss and fatigue
- Seen in TB clinic
  - Fever, confusion
  - Admitted
Investigations

• Early evidence of HLH
  – Ferritin 1536, slightly elevated triglycerides, normal fibrinogen
  – Mild anaemia
  – Mild thrombocytopenia
  – BM: marked haemophagocytosis

• Cause of HLH unclear
  – Investigated for lymphoma
    • PET diffuse uptake in spleen, very non-specific
    • No obvious malignancy
  – Investigated for TB
    • Lumbar puncture: high protein, monocytosis, PCR negative
    • MRI Head: pachymeningeal thickening and enhancement
Treatment and progress

• Treated for presumed TB
  – But culture/PCR negative

• Treated for HLH
  – Methylprednisolone
  – Anakinra

• Initial good response
  – Resolution of fever
  – Fall in ferritin

Progressive confusion
Transferred to ITU
Further treatment

- Anakinra doubled
- Treated for sepsis
- Survived one cardiac arrest
- About to start another round of investigations
- Second cardiac arrest

Died 4 months after initial presentation

Post mortem: intravascular large B cell lymphoma
Key points from case 3

1. Lymphoma is most common cause of HLH in adults
   - Biopsy, biopsy, biopsy
   - Lymphoma can be masked by steroids

2. Outcome in lymphoma associated HLH remains very poor
The future of HLH

1. Early recognition
   - In the context of inflammation
     • Falling/normal platelets/ESR
     • Rising ALT
   - Low threshold for checking ferritin

2. Early treatment
   - Minimizing drug toxicity

3. Involve multiple specialities and share learning