Hemophagocytosis in adults
(Hemophagocytic Syndrome)

Brady Miller
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University of Washington
• Hemophagocytosis
  – Definition
    • Phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues
    – Unspecific phenomenon found in several conditions such as hemolytic anemia, malignant disease, infections, and hemophagocytic syndrome.

• Hemophagocytic Syndrome (aka Hemophagocytic lymphohistiocytosis (HLH))
  – Uncommon, life-threatening hyperinflammatory syndrome caused by severe hypercytokinemia due to a highly stimulated but ineffective immune process
Case

- **HPI:** 58 year old female with a history of fibromyalgia presenting with one month of progressive malaise, body aches, nausea, emesis, diarrhea, and dyspnea. She presented to an outside hospital with 2 days of jaundice and 24 hours of epigastric abdominal pain radiating to her flanks. No history of fevers, chills, night sweats, weight loss, new medications, or toxin exposure.
• **PMH:**
  – Fibromyalgia. Several grams of morphine daily. Titrating down dosage over last month.

• **Meds:** morphine

• **SH:** No ethanol, tobacco, IV drugs. No toxin exposures.

• **PE:**
  – Stable vitals and afebrile
  – Normal exam, no LAD or splenomegaly
• Admission labs at outside hospital:
  – **WBC 36.9**  (73%N, 7%bands, 12)L, 7%M, 1%E)
  – HCT 41.8  **PLA 46**
  – **AST 91**  **ALT 33**  **Alk 120**  **T.bili 5.7**  **D.bili 4.0**
  – Normal creatinine

• Outside hospital was initially concerned about cholecystitis. However, transferred here on HD #5 because of unclear etiology of abnormal labs, LAD on a CT scan, and abdominal pain.
• HD #5 (day of transfer) labs/imaging:
  – WBC 60.8 (48.6N, 9.95L, 4.1M, 0E, 0.6baso)
  – HCT 34  PLA 21
    • Smear: Left-shifted with toxic granulation and dohle bodies. No obvious abnormal cells were noted.
  – AST 65  ALT 21  Alk 189  T.bili 9.3  D.bili 6.1
  – LDH 313  Uric acid 2.8  Fibrinogen 402  Cre 0.9  INR 1.4
  – Abd u/s: Mild splenomegaly(13 cm)
  – Chest/abd/pelvic CT:
    • Mediastinal, hilar, pelvic, and retroperitoneal LAD. Two large necrotic LN at porta hepatitis(4.3cm and 3.7cm).
    • Mild splenomegaly(13 cm), which is heterogenous
    • No hepatomegaly
• Quickly detiorated:
  – HD #5
    • Intubated secondary to respiratory failure
  – HD #6
    • Pressors started
  – HD #7
    • Bone Marrow biopsy performed since not clinically stable to undergo LN biopsy
      – Population of atypical lymphocytes noted in flow cytometry of aspirate (reactive vs neoplasm).
      – No obvious hemophagocytosis
  • Febrile
  • Anemia
  • Repeat abd CT
    – Hepatomegaly. Stable LAD and mild **splenomegaly**. Diffuse colon wall thickening.
  • Liver and renal failure quickly progressing
  – HD #8
    • Liver biopsy
    • **TRY 284, Ferritin 19,500**, LDH increased to 1843, fibrinogen stable in upper 300’s
    • Empirically treated with high dose solumedrol
• HD #9
  – Peripheral flow cytometry
    • Abnormal CD30+ lymphocyte population identified (6.1% of total nucleated cells)
      – Abnormal expression of CD7 (high), CD30 (variable with subset very high), and CD43 with normal expression of CD45 without CD2, CD3, CD4, CD5, CD8, CD33, CD34 or CD56
  – Bone Marrow interpretation
    • Atypical lymphocyte population (7.5%) with flow markers identical to above peripheral flow and IHC positive for ALK-1
  – Liver bx interpretation
    • Involvement by atypical lymphocyte population
    • Hemophagocytosis identified
  – Dx: Anaplastic Large Cell Lymphoma with Hemophagocytic Syndrome
  – Pt with cardiac arrest and expired
Hemophagocytic lymphohistiocytosis (HLH)

- Not a single disease, but a clinical **syndrome** than can be associated with a variety of underlying conditions leading to the same characteristic hyperinflammatory phenotype with hypercytokinemia and excessive activation of lymphocytes and macrophages.

<table>
<thead>
<tr>
<th>Genetic HLH</th>
<th>chromosome location</th>
</tr>
</thead>
<tbody>
<tr>
<td>familial HLH</td>
<td></td>
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<tr>
<td>known gene defects</td>
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<tr>
<td><em>PFF1</em></td>
<td>10q21–22</td>
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</tr>
<tr>
<td>Chédiak-Higashi syndrome (<em>LYST</em>)</td>
<td>1q42.1–q42.2</td>
</tr>
<tr>
<td>Griscelli syndrome 2 (<em>RAB27A</em>)</td>
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</tr>
<tr>
<td>X-linked lymphoproliferative syndrome</td>
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<tr>
<td>1 (<em>SH2D1A</em>)</td>
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HLH Pathophysiology

– When immune system is triggered in a healthy person, histiocytes, Natural Killer (NK) cells, and cytotoxic T lymphocytes (CTL) are all activated which then mutually stimulate each other by receptor interaction as well as by secretion of inflammatory cytokines and chemokines.

• In healthy individuals this leads to killing of infected cells, removal of antigen, and then termination of the immune response.

• In HLH, there is an inherited or acquired defect of the NK and CTL cells, so they are unable to cope effectively with the infectious agent or antigen. This results in accumulation of activated T-lymphocytes and activated histiocytes with increasingly high levels of cytokines.

– Key cytokines found at extremely high levels in the plasma of patients with HLH include interferon gamma, tumor necrosis factor (TNF)-alpha, interleukins IL-6, IL-8, IL-10, IL-12, IL-18 and soluble IL-2 receptor (CD25)
HLH Pathophysiology (cont’d)

• Why are the activated NK cell and CTL cell defective?

• The killing function is mediated by a secretory pathway involving the activation, polarization, and release of cytoxic granules into the immunological synapse.

HLH Pathophysiology (cont’d)

- Why is the cytotoxic activity of the NK cell and CTL cell impaired?

- The killing function is mediated by a secretory pathway involving the activation, polarization, and release of cytotoxic granules into the immunological synapse

- This process is blocked in HLH

HLH Pathophysiology (cont’d)

- Why is the cytotoxic activity of the NK cell and CTL cell impaired?

- The killing function is mediated by a secretory pathway involving the activation, polarization, and release of cytoxic granules into the immunological synapse
- This process is blocked in HLH
- This results in accumulation of activated T-lymphocytes and activated histiocytes with increasingly high levels of cytokines

Hemophagocytic lymphohistiocytosis (HLH) underlying conditions

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Primary (genetic) vs. secondary (acquired) HLH

- No laboratory test or mode of presentation provides a means to distinguish between primary or secondary.
- Natural history are similar for both
  - If untreated, fatal with few exceptions. Usually this will be secondary to infection from prolonged neutropenia, multiorgan failure, or cerebral dysfunction due to inflammatory CNS lesions.
- Although there are rare exceptions, primary HLH is restricted to babies and young children (80% of time presents when < 1 year old).
- In children, approximately 25% of cases are primary, while in adults almost all cases are secondary.
Primary (genetic) HLH

• Restricted to babies and young children
• Incidence is 1.2/1,000,000 children per year
• Median survival < 2 months if untreated
• Most primary HLH episodes are triggered by an infection
• Familial vs immune deficiency syndromes
  – Both are genetic, however HLH is the only manifestation in fHLH.
Primary HLH (cont’d)

- Familial
  - All are autosomal recessive
  - Perforin (*PFR1*) gene mutation
    - FHLH-2
    - 20-40% of familial HLH (up to 50% in North America)
    - Stored in the secretory granules of cytotoxic cells and is a key effector molecule for the cytotoxic function of natural killer (NK) cells and CD8+ cytotoxic lymphocytes (CTLs)
  - *UNC13D* gene mutations
    - FHLH-3
    - 10-20% of familial HLH
    - Encodes protein Munc 13-4 which is crucial for cytolytic granule membrane fusion and exocytosis
  - Syntaxin 11 (*STX11*) gene mutations
    - FHLH-4
    - 10-20% of familial HLH
    - Thought to be involved in cytotoxic granule release or trafficking
  - FHLH-1
    - Unknown mutation. Accounts for 30-70% of familial HLH.

Primary HLH (cont’d)

- Immune deficiency syndromes
  - Chediak-Higashi syndrome (CHS-1)
    - Partial albinism, recurrent infections, bleeding tendency, enlarged lysosomes
    - Mutations in the lysosome trafficking regulator (LYST) gene which is involved in lysosome fusion/fission and results in ineffective release of cytotoxic granules
  - Griscelli syndrome 2 (GS-2)
    - Partial albinism, recurrent infections
    - Mutations in RAB27A, which is important for docking of cytotoxic granules to the cell membrane in activated T-cells.
      - Shown to interact with Munc 13-4 during cytotoxic granule fusion to the cell membrane.
  - X-linked lymphoproliferative syndrome (XLP)
    - Fulminant infections, lymphomas, dysgammaglobulinemia
    - Mutations in SLAM-associated protein (SAP), which is important for intracellular signaling and cytotoxicity of NK and CTL cells.

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Secondary (acquired) HLH

- Occurs in all age groups. No published data on incidence or age distribution.
- Underlying conditions include infections, autoimmune diseases, malignancies, and immune suppression/organ transplantation.
- As in primary HLH, the cytotoxic activity of the NK and CTLs are blocked. The mechanisms that lead to this in acquired HLH are not clear. Some hypotheses include:
  - Viruses may interfere with CTL function.
  - High levels of cytokines may impair NK cells and CTLs
  - Genetic polymorphisms for CD45, leukocyte common antigen, have been described in several HLH cases. Perhaps certain individuals are more likely to deliver a HLH response to certain underlying conditions
Secondary HLH (cont’d)

– Infections
  • Most episodes of familial HLH are triggered by an infection, so should screen for genetic causes in pediatric population.
  • Virus are the predominant pathogens
    – EBV, CMV, Measles, HHV-8, HIV.
      » EBV associated HLH with increased prevalence in Asia
    – Has been reported to occur shortly after initiation of HAART therapy.
  • Bacterial
    – TB, Brucella
  • Parasitic
    – Leishmaniasis
      » 12% of acquired cases in Germany
  • Fungus
Secondary HLH (cont’d)

– Autoimmune
  • Also known as Macrophage activation syndrome (MAS)
    – In pediatric population some authors consider this a form of acquired HLH, while some consider it a separate condition.
      » Presentation and underlying pathophysiology very similar to HLH
    – In adult population most authors do consider this a form of acquired HLH
  • Most frequently occurs in systemic-onset juvenile idiopathic arthritis (soJIA).
    – Approximately 7% of patients with mortality of 10-20%
  • Also has been reported to occur in lupus erythematosus, rheumatoid arthritis, Still's disease, polyarteritis nodosa, mixed connective tissue disease, pulmonary sarcoidosis, systemic sclerosis, dermatomyositis and Sjogren's syndrome
    – Can be triggered by infection or the autoimmune disease itself
Secondary HLH (cont’d)

- Malignancies
  - More common in adults
  - Usually lymphomas
  - HLH in adults should always prompt a malignancy workup.
  - Reported to occur on presentation and during treatment
  - Several small series that have reported very poor clinical outcomes when HLH is associated with hematological malignancies
    - A series of adult patients from 1997; all 5 patients expired (2 NHL, 1 MDS, 1 MM, 1 AML)
  - A more common type of lymphoid malignancy reported in adults is anaplastic large cell lymphoma.
Secondary HLH (cont’d)

• Anaplastic Large Cell Lymphoma (ALCL)
  – Brief overview
    • Uncommon aggressive T/null-cell lymphoma
    • Usually present with painless LAD and found to have widespread disease on staging (40-60% with extranodal disease)
  • Diagnosis
    – Based on clinical features, morphology, IHC patterns, and cell markers. Strongly positive for CD30 and negative for B-cell antigens.
  • Several subtypes
    – Cutaneous (almost always ALK negative)
    – Systemic ALK negative
      » 5 year OS of 37%
    – Systemic ALK positive
      » More than half of systemic ALCL fall into this category
      » 5 year OS of 77-93%
  • ALK is a receptor tyrosine kinase that plays role in proliferation, differentiation, and anti-apoptosis.
    – Usually fused to the NPM gene in ALCL via translocation t(2;5) (note that the presented patient presented had this translocation), although other translocation sites have been identified. These translocations all lead to expression and constitutive activation of ALK.
  • Treatment is usually with CHOP
Secondary HLH (cont’d)

• Association of anaplastic large cell lymphoma with HLH
  – ALCL thought to be derived from cytotoxic T-cells
    • Very intriguing since pathophysiology of HLH includes over-activated dysfunctional T-cells
  – Some anecdotal evidence that it may be related to cytokine release
    • A liver ALCL mass presented as a rheumatic syndrome with generalized arthralgias, fatigue, weight loss, and night sweats.
      – Resolved after tumor resection
      – Tumor was noted to produce large quantities of IL-6 and IL-8 (no TNF-alpha).
  • Elderly male presented with an ALCL ALK+ that was aggressive and widespread with fevers/neutrophilia. Noted to have increased GCSF and IL-6 levels serum.
  • An ALCL ALK+ cell line derived from a patient with HLH produced increased concentrations of several cytokines
Secondary HLH (cont’d)

– Immune suppression/organ transplantation
  • Post-chemotherapy
  • After organ transplantation
  • During immunosuppressive treatment
HLH Clinical findings

- Secondary to cytokines and infiltration by activated immune cells
- More common
  - Prolonged fever
    - Increased IL-1, TNF-alpha, and IL-16
  - Hepatosplenomegaly
    - Organ infiltration by activated immune cells
  - Cytopenias
    - Suppression by TNF-alpha and INF-gamma and consumption by hemophagocytosis.
    - Anemia and thrombocytopenia are more common
  - Neurologic
    - Organ infiltration by activated immune cells
    - Seizures, cranial nerve palsies
    - LP in more than half of patients with slightly elevated cell count and/or moderately increased protein
    - Imaging can include diffuse abnormalities, focal lesions, and parenchymal calcifications.
- Less common
  - Lymphadenopathy
  - Rash
  - Jaundice
HLH Laboratory values

• Characteristic laboratory values
  – Elevated ferritin
    • Likely secreted by activated macrophages
  – Elevated tryglycerides
    • Increased levels of TNF-alpha suppress activity of lipoprotein lipase
  – Elevated LDH
  – Depressed fibrinogen
    • Increased levels of plasminogen activator secreted by activated macrophages
  – Impaired NK cell activity
  – Elevated soluble IL-2 receptor (sCD25)
  – Transaminitis
Diagnosis criteria for HLH

1) Familial disease/known genetic defect
2) Clinical/laboratory criteria
   – Fever
   – Splenomegaly
   – Cytopenia (at least 2 cell lines)
     • HGB < 9
     • PLA < 100,000
     • ANC < 1000
   – Hypertryglyceridemia and/or hypofibrinogemia
     • Fasting TRY > 265 mg/dL
     • Fibrinogen < 150 mg/l
   – Hemophagocytosis in bone marrow, CSF, or lymph nodes
   – Decreased/absent NK cell activity *
   – Ferritin > 500 ug/l *
   – Soluble CD25 > 2400 U/ml *

* Added in 2004
- Fulfill 5 of 8 above clinical/laboratory criteria (do not need to fulfill this if have a family history or molecular diagnosis that is consistent with HLH). **Note that these current diagnostic criteria from the Histiocyte Society do not differentiate between “major” and “minor” criteria that are discussed in the UpToDate HLH article.**
- Other supportive evidence includes cerebral symptoms with moderate pleocytosis and/or elevated protein, transaminitis, hyperbilirubinemia, and elevated LDH.
- It is common that the first bone marrow examination does not reveal hemophagocytosis.
Clinical findings and diagnosis

- Elusive diagnosis (postmortem diagnosis is not unusual). Presentation is generally non-specific.

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Patients Initially</th>
<th>% Patients at Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>80</td>
<td>80</td>
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<tr>
<td>Bicytopenia</td>
<td>60</td>
<td>60</td>
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<tr>
<td>Fibrinogen &lt; 1.5 g/l</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Triglycerides =/&gt; 3 mmol/l</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Hemophagocytosis</td>
<td>20</td>
<td>20</td>
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<tr>
<td>NK cell activity negative or decreased</td>
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<td>10</td>
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<tr>
<td>sCD 25 =/&gt; 2400 U/ml</td>
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<tr>
<td>Ferritin =/&gt; 500 ng/ml</td>
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</tr>
<tr>
<td>LDH =/&gt; 500U/l</td>
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<td>ALT =/&gt; 100U/l</td>
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<td>AST =/&gt; 100U/l</td>
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<tr>
<td>Bilirubin =/&gt; 34μmol/l</td>
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<td>CSE cells =/&gt; 5/μl</td>
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<tr>
<td>CSE protein =/&gt; 0.5g/l</td>
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</table>

Ferritin

• Easy lab to send, get results same day
• Can increase over a range of several 10000 ug/L within several hours in HLH
• Mechanisms leading to hyperferritinemia in HLH are not entirely clear. Hypotheses include:
  – Passive release due to cell damage
  – Increased secretion by macrophages and/or release during erythrophagocytosis
    • In rat in vitro model, there was shown to be a massive release of ferritin in the supernatant after ingestion of erythrocytes by macrophages.
  – Increased ferritin gene expression by cytokine TNF-alpha
  – Decreased clearing due to lower glycosylation
• Sensitivity and specificity for ferritin > 500 in diagnosis of HLH
  • Sensitivity 82%, Specificity 42%
• Differential diagnosis when ferritin > 10,000 is rather limited
  – HLH, histiocytic malignancies, adult-onset Still’s disease
Ferritin (cont’d)

• Very nice recent publication by Allen et al.*
  – Performed chart review on all patients with a ferritin > 500 at Texas Children’s Hospital from January 10, 2003 through January 10, 2005.
    • 330 patients
      – 10 diagnosed with HLH

• Sensitivity and specificity for ferritin > 10,000 in diagnosis of HLH in this select population
  – Sensitivity 90%, Specificity 96%

Distribution of initial ferritin values from different disease categories

The unknown group includes 10 patients (only two were evaluated for HLH)

Distribution of peak ferritin values from different disease categories

### TABLE IV. Statistical Analysis of Ferritin Levels for HLH: Maximum Ferritin

<table>
<thead>
<tr>
<th>Maximum ferritin level (µg/L)</th>
<th>Other variable</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Number of patients a</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,000</td>
<td></td>
<td>90% (71–100)</td>
<td>77% (73–82)</td>
<td>11% (4–18)</td>
<td>99.6% (99–100)</td>
<td>330</td>
</tr>
<tr>
<td>6,000</td>
<td></td>
<td>90% (71–100)</td>
<td>90% (86–93)</td>
<td>21% (9–34)</td>
<td>99.7% (99–100)</td>
<td>330</td>
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<tr>
<td>10,000</td>
<td>LDH &gt; 4,000 µ/L</td>
<td>90% (71–100)</td>
<td>96% (94–98)</td>
<td>41% (20–61)</td>
<td>99.7% (99–100)</td>
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<tr>
<td>10,000</td>
<td>Fever</td>
<td>90% (71–100)</td>
<td>98% (94–100)</td>
<td>75% (45–100)</td>
<td>98.8% (96–100)</td>
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<tr>
<td>10,000</td>
<td>ALT &gt; 100 µ/L</td>
<td>90% (71–100)</td>
<td>98% (96–99)</td>
<td>56% (32–81)</td>
<td>99.7% (99–100)</td>
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<tr>
<td>10,000</td>
<td>AST &gt; 300 µ/L</td>
<td>70% (42–98)</td>
<td>97% (94–99)</td>
<td>47% (21–72)</td>
<td>98.7% (97–100)</td>
<td>241</td>
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<tr>
<td>10,000</td>
<td>Cytopenia (2 or 3 lines)</td>
<td>40% (10–70)</td>
<td>98% (97–100)</td>
<td>44% (12–77)</td>
<td>98.1% (97–100)</td>
<td>322</td>
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<tr>
<td>10,000</td>
<td>Splenomegaly</td>
<td>50% (19–81)</td>
<td>99% (98–100)</td>
<td>56% (23–88)</td>
<td>98.4% (97–100)</td>
<td>329</td>
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</tbody>
</table>

aNumber of patients for different combinations of labs varies based on availability of lab values. Labs indicated in “other variable” were only included in analysis if they were obtained within 24 hr of ferritin.

Impaired NK cell activity

- Lab specimen requires special handling and will take 1-2 weeks for results (send out lab).

- Functional assay that allows direct measurement of the NK cell defect (inherited or acquired), which is a central theme in HLH pathophysiology.
Soluble CD25

- Measurement of these levels takes 1-2 weeks (send out lab)
- Soluble IL-2 receptor
- Elevated levels of soluble CD25 are observed in patients with hematologic malignancies including hairy cell leukemia, anaplastic large cell lymphoma (ALK positive), solid tumors and a variety of autoimmune and infectious diseases.
- Known marker of disease in HLH, although role in the pathophysiology of disease is unclear.
- 1995 review of 74 HLH cases by Imashuku et al.
  - Majority were pediatric cases
  - Soluble CD25 ranged from 465 - 93,500 U/ml
  - Soluble CD25 > 10,000 U/ml was correlated with poorer prognosis
    - 5 year survival of 36% vs 78%
Hemophagocytosis

• Although it has been considered the gold standard for HLH, it is not required for diagnosis of HLH.
• Hemophagocytosis has also been documented without HLH
  – Blood transfusions
  – Incidental findings in LN biopsies
    • One study even reported hemophagocytosis in axillary LN biopsies after a breast biopsy
  – Study reported 64.5% of ICU patients with fatal sepsis had hemophagocytosis on autopsy
Prognosis of HLH

- Pediatric population
  - 3 year survival of 55%

- Adult population
  - Not nearly as clear as pediatric population because of lack of adult clinical trials
  - Analysis of 34 adult HLH cases in 1997 by Kaito et al.
    - 41% survived
    - Treatment was variable and included no treatment, steroids, chemotherapy with etoposide, and chemotherapy without etoposide
    - Underlying diseases and outcomes
      - 20 with unknown underlying disease (13 expired)
      - 14 with known underlying disease (7 expired)
        - 5 hematological malignancies (all expired)
          » 2 NHL
          » 1 MDS
          » 1 MM
          » 1 AML
        - 6 infections (1 expired)
          » 2 parainfluenza
          » 2 malaria
          » 2 EBV (1 expired)
        - 2 auto-immune (none expired)
          » 1 SLE
          » 1 Adult Still’s disease
        - 1 chronic renal failure (expired)
Prognosis of HLH

- Analysis of 34 adult HLH cases in 1997 by Kaito et al. (cont’d)
  - Risk factors associated with death

<table>
<thead>
<tr>
<th>Factors</th>
<th>On admission</th>
<th>During course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 30 yr</td>
<td>$p = 0.0002$</td>
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<tr>
<td>Absence of lymph-node swelling</td>
<td>$p = 0.0220$</td>
<td></td>
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<tr>
<td>Presence of underlying malignancy</td>
<td>$p = 0.0428$</td>
<td></td>
</tr>
<tr>
<td>Presence of hepatosplenomegaly</td>
<td>$p = 0.1600$</td>
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</tr>
<tr>
<td>Presence of underlying disease</td>
<td>$p = 0.3800$</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>$p = 0.4400$</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &lt; 2.0 (x 10⁹/l)</td>
<td>$p = 0.6422$</td>
<td>$p = 0.1885$</td>
</tr>
<tr>
<td>Hb &lt; 10.0 (g/dl)</td>
<td>$p = 0.0207$</td>
<td>$p = 0.0021$</td>
</tr>
<tr>
<td>Platelet &lt; 100.0 (x 10⁹/l)</td>
<td>$p = 0.0413$</td>
<td>$p = 0.0015$</td>
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<tr>
<td>AST &gt; 150 (IU/l)</td>
<td>$p = 0.2000$</td>
<td>$p = 0.9300$</td>
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<tr>
<td>ALT &lt; 200 (IU/l)</td>
<td>$p = 0.9316$</td>
<td>$p = 0.8964$</td>
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<tr>
<td>LDH &gt; 800 (IU/l)</td>
<td>$p = 0.0972$</td>
<td>$p = 0.6455$</td>
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<tr>
<td>Alp &gt; 740 (IU/l)</td>
<td>$p = 0.1873$</td>
<td>$p = 0.0058$</td>
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<tr>
<td>T.bil &gt; 1.3 (mg/dl)</td>
<td>$p = 0.1229$</td>
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<tr>
<td>FDP &gt; 10 (µg/ml)</td>
<td>$p = 0.0080$</td>
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<tr>
<td>Ferritin &gt; 500 (ng/ml)</td>
<td>$p = 0.0080$</td>
<td></td>
</tr>
<tr>
<td>β₂-MG &gt; 3.0 (µg/ml)</td>
<td>$p = 0.0323$</td>
<td></td>
</tr>
</tbody>
</table>

HLH Treatment

• **Immediate goals**
  – Suppress the severe hyperinflammation
    • Steroids
      – Dexamethasone since it crosses blood-brain barrier
    • Cyclosporine A
      – Inhibits T-cell activation
  – Kill the over-stimulated antigen-presenting cells (macrophages)
    • Etoposide
      – Highly effective in other monocytic and histiocytic diseases
  – Treat the triggering agent, if exist (infection, neoplasm, etc.)
    • It is usually not sufficient to only treat the triggering agent

• **Longer term goals**
  – If genetic, replace the defective immune system via allogenic SCT
HLH Treatment (cont’d)

• Dexamethasone
  – Cornerstone of HLH treatment.
  – Dexamethasone or methylprednisone are used (both penetrate blood-brain barrier)
  – Included in HLH-2004 protocol
• Cyclosporine A
  – Targets T-cells and macrophages
    • Inhibits early steps of T-cell activation
    • Decreases expression of IL-6, IL-1, and TNF-alpha by macrophages
  – Included in HLH-2004 protocol
• Etoposide
  – Shown to be very active in treatment of EBV associated HLH in pediatric population
  – Included in HLH-2004 protocol
• Allogenic SCT
  – First success published in 1986
  – Integrated into HLH-2004 protocol
• ATG
• Rituximab
  – EBV associated HLH
• IVIG
  – Two series of adult patients
    • Response rates
      – Overall - 59%
      – Infection related – 78%
      – Remaining – 39%
  – Several reports showing to be ineffective in lymphoma associated HLH in adult population
  – A report showing limited efficacy in EBV associated HLH in pediatric population
• Plasma exchange
  – Cytokine removal?
  – Case reports
  – There’s even case report showing HLH to develop in a patient undergoing plasmapheresis for TTP
HLH Treatment (cont’d)

- HLH-94 and HLH-2004 protocols
  - Dexamethasone/etoposide/cyclosporine
  - IT therapy for patients with persistent active CNS disease
  - 8 weeks of therapy for secondary non-genetic disease. For genetic disease continue therapy after week 8 until SCT.
  - Major difference between protocols is that cyclosporine is started at onset of therapy in HLH-2004 (In HLH-94 started at week 9, so only patients that continue therapy will receive cyclosporine)
  - HLH-94
    - Compared to historical controls, this protocol dramatically improved outcomes of children with HLH.
    - 3 year overall survival of 55%
    - 20% did not respond to treatment
    - 3 year overall survival for the patients that underwent SCT
      - Overall - 64%
      - Matched related - 71%
      - Matched unrelated – 70%
      - Family haploidentical – 50%
      - Mismatched unrelated – 54%
    - High transplant related mortality of 30%
HLH-2004 protocol

- IT(MTX and corticosteroid) therapy is recommended for patients with signs of persistent active CNS disease.
- HSCT/continuation therapy is for patients with family history of HLH or a genetic defect.
Algorithm for treatment of HLH and MAS

* Test for genetic defects. If positive for genetic defect, then HCT.
Presented Case

• Fulfilled diagnostic criteria for HLH on HD #8
  – Splenomegaly HD #5
  – Two lineage cytopenia HD #7
  – Fever HD #7
  – Elevated TRY HD #8
  – Elevated ferritin HD #8
  – Documented hemophagocytosis HD #9

• By day of HLH diagnosis, pt with multi-organ failure

• Treatment
  – Empiric high dose solumedrol
  – Expired before further therapy

• Learning points
  – HLH in adults is bad
  – HLH associated with a hematologic malignancy in adults is even worse
  – Ferritin levels are very useful
  – Aggressively pursue tissue diagnosis
### HLH Summary

- Rare, life-threatening hyperinflammatory syndrome caused by severe hypercytokinemia due to a highly stimulated but ineffective immune process

### Diagnosis

1. Familial disease/known genetic defect
2. Clinical/laboratory criteria
   - Fever
   - Splenomegaly
   - Cytopenia (at least 2 cell lines)
     - HGB < 9
     - PLA < 100,000
     - ANC < 1000
   - Hypertryglyceridemia and/or hypofibrinogemia
     - Fasting TRY > 265 mg/dL
     - Fibrinogen < 150 mg/l
   - Hemophagocytosis in bone marrow, CSF, or lymph nodes
   - Decreased/absent NK cell activity *
   - Ferritin > 500 ug/l *
   - sCD 25 > 2400 U/ml *

* Added to diagnostic criteria in 2004

- Fulfill 5 of 8 above clinical/laboratory criteria (do not need to fulfill this if have a family history or molecular diagnosis that is consistent with HLH).
- Other supportive evidence includes cerebral symptoms with moderate pleocytosis and/or elevated protein, transaminitis, hyperbilirubinemia, and elevated LDH.
- It is common that the first bone marrow examination does not reveal hemophagocytosis.

### Treatment

- Suppress severe hyperinflammation
  - Consider HLH-2004 protocol
- Treat triggering agent
References