Pan Arab Rheumatology 2014
14-17 January 2014, Dubai - UAE
Macrophage Activation Syndrome in Children with Systemic Juvenile Rheumatoid Arthritis

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Consultant Pediatric Immunologist and Rheumatologist
QRCH-KHMC-JORDAN
A 7 year male patient
Diagnosis of systemic onset JIA was made 3 years ago
Controlled on:
  - Prednisolone 5 mg/day,
  - Methotrexate 20 mg/week,
  - Etanercept 20 mg/week
12 months ago, admitted with unremitting fever, petechial rash, nasal epistaxis, hepatosplenomegaly
Patient’s data as follow
Extensive work up for infection was inconclusive
Diagnosis: Macrophage Activation Syndrome

Clinical and laboratory improvement were observed during with corticosteroid and cyclosporine therapy
Hemophagocytic Syndrome in Children: An Important Diagnostic Consideration in Fever of Unknown Origin

Debra L. Palazzi, Kenneth L. McClain, and Sheldon L. Kaplan
Table II. Clinical and laboratoristic features of macrophage activation syndrome.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>100</td>
<td>100</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>Skin rash</td>
<td>44.4</td>
<td>4.2</td>
<td>45</td>
<td>65</td>
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<tr>
<td>Hepatomegaly</td>
<td>88.9</td>
<td>58</td>
<td>44</td>
<td>88</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>88.9</td>
<td>100</td>
<td>61</td>
<td>59</td>
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<tr>
<td>Lymphoadenopathy</td>
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<td>64</td>
<td>41</td>
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<tr>
<td>Hemorrhages</td>
<td>11.1</td>
<td>16.6</td>
<td>–</td>
<td>23</td>
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<tr>
<td>Liver dysfunction</td>
<td>88.8</td>
<td>98</td>
<td>89</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>33.3</td>
<td>50</td>
<td>44</td>
<td>–</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>33.3</td>
<td>16</td>
<td>62</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>–</td>
<td>42</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neurological dysfunction</td>
<td>22.2</td>
<td>50</td>
<td>–</td>
<td>–</td>
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</table>
Table II. Clinical and laboratoristic features of macrophage activation syndrome.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Anemia</td>
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<td>–</td>
<td>70</td>
<td>82</td>
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<tr>
<td>Leukopenia</td>
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<td>28*</td>
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<td>Thrombocytopenia</td>
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<td>95.8</td>
<td>47</td>
<td>88</td>
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<tr>
<td>Coagulopathy</td>
<td>66.6</td>
<td>83.3</td>
<td>62</td>
<td>–</td>
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<tr>
<td>Reduced erythro-sedimentation rate</td>
<td>33.3</td>
<td>12</td>
<td>–</td>
<td>60</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>88.8</td>
<td>98</td>
<td>–</td>
<td>94</td>
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<tr>
<td>Elevated bilirubine</td>
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<td>–</td>
<td>46</td>
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<tr>
<td>Elevated lactate dehydrogenase</td>
<td>–</td>
<td>–</td>
<td>82</td>
<td>87</td>
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<tr>
<td>Hypoalbuminemia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>15</td>
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<td>Hypofibrinogenemia</td>
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<tr>
<td>Hypertriglyceridemia</td>
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<tr>
<td>Low sodium levels</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>58.3</td>
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<tr>
<td>Hyperferritinemia</td>
<td>–</td>
<td>–</td>
<td>97</td>
<td>100</td>
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<tr>
<td><strong>Histopathological marker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophagocytosis in bone marrow</td>
<td>44.4</td>
<td>58.3</td>
<td>80</td>
<td>83.3</td>
</tr>
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</table>
Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis (Behrens EM et al. J Rheumatol 2007;34:1133-8)

Retrospective review of 15 patients with syst JIA who underwent BM aspiration within initial diagnostic workup

Eight of 15 (53%) patients had BM aspirate suggestive of MAS

Two patients were diagnosed clinically with MAS

Three patients had frank hemophagocytosis, only 1 of whom was diagnosed with MAS clinically

**Suggestion**: MAS may be an integral part of the spectrum of syst JIA, ranging from its most severe, life-threatening form to its mild, occult form manifest only by biochemical abnormalities and BM hemophagocytosis
Preliminary diagnostic guidelines for MAS complicating systemic JIA

**Laboratory criteria**
- Decreased PLT ($\leq 262 \times 10^9$)
- Elevated GOT/AST ($> 59$ mU/L)
- Hypofibrinogenemia ($\leq 2.5$ g/L)
- Decreased WBC ($\leq 4.0 \times 10^9$/L)

**Histopathologic criterion**
- Hemophagocytosis in the bone marrow

**Clinical criteria**
- Hemorrhages (purpura, easy bruising, mucosal bleeding)
- CNS dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
- Hepatomegaly ($\geq 3$ cm below the costal arch)

**Diagnostic rule:** The diagnosis of macrophage activation syndrome requires the presence of any 2 or more of the following laboratory criteria or 2 or more of the following clinical criteria: A BM aspirate for the demonstration of macrophage hemophagocytosis may be required only in doubtful cases.

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**Table:**

<table>
<thead>
<tr>
<th>Laboratory discriminators</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhages</td>
<td>67</td>
</tr>
<tr>
<td>Central nervous system dysfunction</td>
<td>63</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>1092</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>247</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>70</td>
</tr>
<tr>
<td>Hypofibrinogenemia</td>
<td>165</td>
</tr>
</tbody>
</table>

The best separation between patients and control subjects occurred when any 2 or more laboratory criteria were simultaneously present.

The second best performance was provided by the presence of any 2, 3, or more clinical and/or laboratory criteria.

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:

1. A molecular diagnosis consistent with HLH is made.
2. Diagnostic criteria for HLH are fulfilled (5 of the 8 criteria below):
   * Fever
   * Splenomegaly
   * Cytophenia: application of the HLH-2004 protocol to MAS/HLH secondary to sJIA may be imperfect.
     * hemoglobin < 100 g/L, platelets < 100 × 10⁹/L, neutrophils < 1.0 × 10⁹/L
   * Hypertriglycerideridemia and/or hypofibrinogenemia: fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 265 mg/dL), fibrinogen ≤ 1.5 g/L
   * Hemophagocytosis in BM, spleen, or lymph nodes
   * Low or absent NK-cell activity (according to local laboratory reference)
   * Ferritin ≥ 500 µg/L
   * Soluble CD25 (i.e., sIL2r) ≥ 2400 U/mL†
1. Incidence and prevalence unknown, Probably more common than previously though (7 of 103 diagnosed with sJRA developed MAS at some point in their illness.)
2. Approximately 100 cases reported in the literature
3. Most commonly an early complication of active disease
TRIGGERS OF mas IN AVALAIBE CASE REPORTS

NUMBER OF PATIENTS

TRIGGERS

- total cases
- infection
- NO
- ONSET
- BMT
- MEDICATIONS
- INFLIXIMAB
- ETANERCEPT
- SAZ
- MTX
- GCSF
In 20 cases HLH might have been triggered by immunosuppressive treatment of the rheumatic condition, including adalimumab/, infliximab, etanercept, leflunomide, sulfasalazine, azathioprine, methotrexate.

It is possible that immunosuppression induced by anti-TNF-α treatment may favor the occurrence of serious infections leading, in turn, to HLH.

Pathogenesis

• **Central question:** is there an underlying abnormality of the immune response that contributes to lack of control of an exaggerated immune response?

• **Starting point:** strong clinical similarities with hemophagocytic lymphohistiocytosis (HLH)

• **Familial HLH:** decreased NK and cytotoxic cell function often secondary to *mutations in the gene encoding perforin (PRF1)*, a protein that mediates cytotoxic activity of NK and T cells. The number of NK cells is usually normal

• **Virus-associated HLH:** very low or absent cytolitic NK cell activity related to *profoundly decreased number of NK cells* rather than impaired perforin expression. NK function may completely recover after resolution of acute phase
Role of Perforin in the Cytotoxic Response

Pathogenesis of Hemophagocytic Syndromes

Decreased Perforin Expression + / - Trigger (Drug or infection)

Excessive Macrophage Activation

Hypercytokinemia

End organ damage
Fig. 1 Serum cytokine concentrations in different patient groups. Serum concentrations of (A) IL-1β, (B) neopterin, (C) IL-6, (D) sTNF-RI and (E) sTNF-RII from the different patient groups are shown. Bars represent median values. Statistically significant differences between each patient group are shown as *P < 0.05, **P < 0.01 and ***P < 0.001.
15/24 MAS patients improved within 5-15 days of steroid initiation.

**IVIG:** Occasional anecdotal responses, Rarely used in isolation

**CYCLOSPORIN-A:** 5 cases of successful treatment with CsA alone

**VP 16 (Etoposide):** Used in unresponsive or very severe patients with MAS, Evidence in MAS is anecdotal
Macrophage activation syndrome: a frequent but under-diagnosed complication associated with rheumatic diseases. Tristano AG

Treatment of MAS in patients with rheumatic diseases has not been standardized yet, but it commonly includes a variety of agents such as high-dose corticosteroids, cyclosporine, cyclophosphamide, etoposide, and intravenous immunoglobulin (IVIG).


HLH-2004 chemo-immunotherapy includes etoposide, dexamethasone, cyclosporine A upfront and, in selected patients, intrathecal therapy with methotrexate and corticosteroids. Subsequent hematopoietic stem cell transplantation (HSCT) is recommended for patients with familial disease or molecular diagnosis, and patients with severe and persistent, or reactivated, disease.
Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Stéphan JL

immediate withdrawal of potentially triggering medications, anti-infective therapy when relevant, and urgent immunosuppressive treatment, measures that are very often effective. Cyclosporin A may be the drug of choice.

Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile arthritis: report of five cases. Mouy R,

These observations underline the usefulness of cyclosporine A in this complication. The use of this drug may circumvent the need for increased doses of corticosteroids in some patients. The mechanism of action of cyclosporine A remains speculative, but these results indicate indirectly that T-helper lymphocytes may play a role in the pathogenesis of MAS.
A macrophage activation syndrome, possibly related to methotrexate toxicity, developed in a boy with systemic juvenile rheumatoid arthritis. Corticosteroid administration was ineffective, whereas a prompt response to cyclosporine was observed. Two months later, Pneumocystis carinii pneumonia developed.
In 18 cases biologicals were used for HLH treatment including infliximab in three cases etanercept in 13 cases, and Anakinra in two cases.

Anakinra & MAS

– Lurati A et al. MAS during anakinra therapy in a child with systemic JIA. Pediatr Rheumatol Oline J 2005


– On day 13 of treatment 2 patients presented laboratory features consistent with MAS

– Both patients discontinued anakinra and were treated with oral corticosteroids and Cyclosporin A, with rapid control of MAS

– Six months later, one patient was re-treated with anakinra for a relapse of his underlying disease and no signs of MAS were observed after 6 mo of follow-up
**Table 1** Baseline patient characteristics, selected laboratory results pre- and post-anakinra and eventual outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Eventual rheumatic diagnosis</th>
<th>ICU</th>
<th>Prior medications for MAS</th>
<th>Ferritin** -2 days</th>
<th>Ferritin** +14 days</th>
<th>CRP** -2 days</th>
<th>CRP** +5 days</th>
<th>MAS resolution, days</th>
<th>CS stopped after anakinra, days</th>
<th>Follow-up, months</th>
<th>Outcome, resolution of MAS</th>
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<tbody>
<tr>
<td>1</td>
<td>13.5</td>
<td>M</td>
<td>ARF</td>
<td></td>
<td>Mpred, IVIG, Csp</td>
<td>8900</td>
<td>438</td>
<td>ND</td>
<td>8.9</td>
<td>15</td>
<td>48</td>
<td>13</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>M</td>
<td>sJIA</td>
<td></td>
<td>Mpred, IVIG, Csp</td>
<td>4787</td>
<td>201</td>
<td>121</td>
<td>8.7</td>
<td>15</td>
<td>51</td>
<td>11</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>F</td>
<td>sJIA** b, c</td>
<td></td>
<td>Mpred, IVIG, Csp</td>
<td>2279</td>
<td>393</td>
<td>125</td>
<td>11.8</td>
<td>12</td>
<td>5</td>
<td>23</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>M</td>
<td>sJIA** b, c</td>
<td></td>
<td>Mpred, IVIG, Csp, etanercept</td>
<td>3141</td>
<td>125</td>
<td>263</td>
<td>9.1</td>
<td>8</td>
<td>30</td>
<td>40</td>
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<tr>
<td>5</td>
<td>0.5</td>
<td>M</td>
<td>ANCA + vasculitis</td>
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<td>Mpred, IVIG</td>
<td>500</td>
<td>276</td>
<td>78</td>
<td>0.1</td>
<td>19</td>
<td>35</td>
<td>19</td>
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<tr>
<td>6</td>
<td>8</td>
<td>F</td>
<td>sJIA</td>
<td></td>
<td>Mpred, IVIG, Csp</td>
<td>423</td>
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<td>89</td>
<td>5.8</td>
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<td>7</td>
<td>1.5</td>
<td>F</td>
<td>sJIA** b, e</td>
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<td>Mpred, IVIG, Csp</td>
<td>438</td>
<td>19</td>
<td>102</td>
<td>0.3</td>
<td>17</td>
<td>105</td>
<td>15</td>
<td>+</td>
</tr>
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<td>8</td>
<td>6</td>
<td>F</td>
<td>Churg-Strauss vasculitis</td>
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<td>9</td>
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<td>M</td>
<td>sJIA</td>
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<td>Mpred, IVIG, Csp</td>
<td>1265</td>
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<td>169</td>
<td>7.2</td>
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<td>43</td>
<td>33</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>M</td>
<td>KD**</td>
<td></td>
<td>Mpred, Csp, Eto</td>
<td>&gt;10000</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>10</td>
<td>NA†</td>
<td>24</td>
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<tr>
<td>12</td>
<td>8</td>
<td>F</td>
<td>sJIA** b</td>
<td></td>
<td>Mpred, Csp, Eto</td>
<td>&gt;10000</td>
<td>430</td>
<td>ND</td>
<td>ND</td>
<td>10</td>
<td>NA†</td>
<td>5</td>
<td>+</td>
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</tbody>
</table>

**Rheumatology key message**

- Early use of anakinra, in conjunction with standard immunosuppression, is effective in severe MAS.
 MAS mortality estimated 8-22%
Hematopoietic stem cell transplantation as a curative treatment for primary Hemophagocytic Lymphohistiocytosis in children: Immunology group at Queen Rania Children’s Hospital Experience:

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Fulfill criteria of HLH</th>
<th>Initial treatment</th>
<th>Engraftment and chimerism</th>
<th>Immunreconstitution</th>
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<tbody>
<tr>
<td>Chediak Higashi Syndrome</td>
<td>COMPLETE</td>
<td>HLH-2004</td>
<td>100% DONOR</td>
<td>CURED/FULL</td>
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<tr>
<td>Chediak Higashi Syndrome</td>
<td>COMPLETE</td>
<td>HLH-2004</td>
<td>100% DONOR</td>
<td>CURED/FULL</td>
</tr>
<tr>
<td>Chediak Higashi Syndrome</td>
<td>COMPLETE</td>
<td>HLH-2004</td>
<td>100% DONOR</td>
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<td>Griscelli Syndrome type II</td>
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<td>HLH-2004</td>
<td>100% DONOR</td>
<td>CURED/FULL</td>
</tr>
<tr>
<td>Griscelli Syndrome type II</td>
<td>COMPLETE</td>
<td>HLH-2004</td>
<td>100% DONOR</td>
<td>CURED/FULL</td>
</tr>
</tbody>
</table>
Key messages
1. MAS is a rare complication of childhood rheumatic disease
2. It is a potentially fulminant disorder, which may occur as part of the initial presentation of the rheumatic disease
3. An infective trigger may herald the onset of this complication in predisposed patients
4. Differentiation from a disease flare may be difficult, but is critical to ensure optimal outcome
5. An early and dramatic fall in platelet count is characteristic, with changes in WBC and haemoglobin being more variable early and common
6. Elevation in transaminases and coagulation abnormalities may not be present at onset of MAS
7. Bone marrow examination is supportive, but false negative reports occur as a result of sampling errors or the subtle nature of the disease
8. Multisystem involvement is a poor prognostic sign
Call for Abstract

Participants are invited to submit an abstract of 250-300 words for oral or poster presentation by March 15, 2014 to the following email addresses:-

Dr. Adel Al-Wahadneh
Chief of the Scientific Committee
Email: adelwahadneh@yahoo.com

Or to the Organizing Company:
Email: medical@jordan-valley.com

* English is the official language of the congress.

CME:
This congress will be accredited by The Jordanian Medical Council for CME

Registration Fees
- International Participants US $ 200
- Jordanian Society of Allergy & Immunology Members JD. 30
- Jordanian Medical Association Members JD. 40
- Residents, Medical Technologies, and Scientists JD. 20
- Medical Students JD. 10

General Information
Weather: Average temperature in May 25-28 degrees C
Currency: One Jordanian Dinar is equivalent to 1.4 US Dollar.

The 5th International Jordanian Congress of Allergy & Immunology

In collaboration with
- The European Academy of Allergy and Clinical Immunology (EAACI)
- The World Allergy Organization (WAO)
- American College of Allergy, Asthma and Immunology (ACAAI)
- Paediatric Rheumatology European Society (PRES)

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Holiday Inn Hotel, Amman

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