Macrophage activation syndrome (MAS)

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- دختر ۴ساله ای را به علت تب بالا و خواب آلودگی ازروز گذشته، به اورژانس آورده اند. کودک از شش ماه قبل با تشخیص systemic JIA تحت درمان است. در معاینه سفتی گردن ندارد، پتشی پورپورا در تمام بدن و هپاتواسپلنومگالی دارد.در آزمایشات

- WBC= ۳۰۰۰/ mm, PLT=۱۶۵۰۰۰/ mm, Hb= ۸ mg/dl ,ESR=۱۰mm/h, Ferritn= ۱۲۰۰ng/ml,

- اقدامات تشخیصی و درمانی مناسب؟

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اقدامات تشخیصی و درمانی مناسب؟

- Macrophage activation syndrome (MAS) is a life-threatening complication of rheumatic diseases.
- more frequently in individuals with systemic juvenile idiopathic arthritis (SJIA) and in those with adult-onset Still disease.
- MAS appears most often as a complication of JIA, systemic lupus erythematosus, Kawasaki disease, sarcoidosis, dermatomyositis, Still's disease, Sjogren's disease) , infection (fungal, parasitic, viral, bacterial, zoonotic) or secondary of cancers .

- There have been reports of cases of MAS following treatment with various drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), gold salts, sulfasalazine or methotrexate, adalimumab , tocilizumab and etoposide .

Triggers of MAS

Trigger	Specific agents
Viral infections	Cytomegalovirus, herpes simplex virus, Epstein-Barr virus, Varicella-zoster virus, adenovirus, influenza virus, Dengue virus, Parvovirus B١٩, Coxsackie-virus
Bacterial infections	*Enterobacteriaceae, Salmonella, Haemophilus, Pneumococcus, Mycobacteria, Mycoplasma*, *Brucella, Staphylococcus*
Fungal infections	*Candida, Histoplasma, Cryptococcus*
Parasitic infestations	*Leishmania, Pneumocystis carinii*
Drugs	Sulphasalazine, aspirin, indomethacin, NSAIDs, penicillamine, methotrexate, gold salts, etanercept, phenytoin, intravenous soluble lipids

MAS pathophysiology

- Primary MAS is triggered by the excessive proliferation of LiTH١ which is caused by the decrease/lack of NK cell cytotoxicity, a decrease due to a mutation in the gene that encodes perforin (a protein that plays a role in the cytotoxicity of NK cells and CD٨$^{+}$ cytotoxic T lymphocytes).

- Perforin is involved in the apoptosis of tumor or viral infected cells and controls cell proliferation. Due to the decrease in perforin levels and the lack of NK cell activity, lymphocytes are persistently activated and secrete two major macrophage activators: INF-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Cytokines in HLH ,MAS and their potential roles

Cytokine/chemokine	Related features of HLH
TNF	Fever, cachexia, neurological symptoms, depression of hematopoiesis, elevated transaminases, hypoalbuminemia, hypofibrinogenemia, hypertriglyceridemia, disseminated intravascular coagulopathy (DIC), suppression of natural killer (NK) cell activity
IL-١	Fever, depression of hematopoiesis, coagulopathy due to plasminogen activation, hyperferritinemia, acute phase proteins, T-cell activation
IFN-γ	Fever, hemophagocytosis, depression of hematopoiesis, DIC, hypoalbuminemia, liver damage, hypertriglyceridemia, macrophage activation, stimulation of antigen presentation, stimulation of CD٤ T-helper ١ (Th١) response
IL-١٨	Liver pathology, prolonged exposure suppression of NK cell activity
IL-١٠	Suppression of T-cell activation, inhibition of Th١ cytokine production, regulation of hemophagocytosis, modulation of immune-mediating pathology
IL-٦	Fever, anemia, acute phase proteins, renal impairment, T-cell activation and infiltration, suppression of NK cell activity

Classification and underlying conditions of HLH

Genetic HLH

- Familial HLH (Farquhar disease[a])
- Known gene defects (perforin, munc ۱۳-۴, syntaxin ۱۱)
- Unknown gene defects
- Immune deficiency syndrome ,
- Chédiak-Higashi syndrome (CHS)
- Griscelli syndrome (GS) X-linked lymphoproliferative syndrome (XLP)

Acquired HLH

- Exogenous agents (infectious organisms, toxins)
- Infection-associated hemophagocytic syndrome (IAHS)

Rheumatic diseases, Macrophage activation syndrome (MAS)
Malignant diseases

Signs and symptoms

- MAS is characterized by pancytopenia, liver insufficiency, coagulopathy, and neurologic symptoms and is thought to be caused by the activation and uncontrolled proliferation of T lymphocytes and well-differentiated macrophages, leading to widespread hemophagocytosis and cytokine overproduction

- Typically, patients with macrophage activation syndrome become acutely ill with the sudden onset of nonremitting high fever, profound depression in all ٣ blood cell lines ,hepatosplenomegaly, lymphadenopathy, and elevated serum liver enzyme levels. High levels of triglycerides and lactic dehydrogenase and low sodium levels . prolongation of prothrombin time (PT) and partial thromboplastin time (aPTT), hypofibrinogenemia.

Differential Diagnoses

- Flare of underlying disease : SJIA, SLE
- Infection , Sepsis
- Side effects of medications
- In children with SJIA , the clinical picture may mimic sepsis or an exacerbation of the underlying disease:
- The pattern of fever is different from the remitting high-spiking fever seen in SJIA
- Signs and symptoms of arthritis and a precipitous fall in the erythrocyte sedimentation rate.
- Hypofibrinogenemia secondary to fibrinogen consumption and liver dysfunction.

MAS , HLH

- The recognition that MAS is clinically similar to HLH has led many clinicians to use the diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH) in the diagnosis of MAS.

- The use of HLH criteria in patients with MAS is associated with several problems; the chief problem is the requirement for tissue confirmation. A ٢٠١٤ retrospective analysis concluded that HLH-٢٠٠٤ guidelines are likely not appropriate for identification of MAS in children with SJIA, and that preliminary MAS guidelines showed the strongest ability to identify MAS in SJIA.

HLH-۲۰۰۴ diagnostic

a. **Molecular diagnosis**

b. **Diagnostic criteria**

- **Fever**
- **Splenomegaly**
- **Cytopenia (at least two of three lineages:**
- **Hemoglobin <۹۰ gm/l,**
- **Platelets <۱۰۰ × $۱۰^{۹}$/l,**
- **Neutrophils <۱٫۰ × $۱۰^{۹}$/l**
- **Hypertriglyceridemia and/or**
- **Hypofibrinogenemia (triglycerides ≥۲۶۵ mg/dl, fibrinogen ≤۱٫۵ gm/l)**
- **Hemophagocytosis BM, spleen, or lymph nodes**
- **Low or absent NK cell activity**

۲۰۰۵ preliminary diagnostic guidelines for MAS complicating sJIA

a**Laboratory criteria**

- **Decreased platelet count (≤۲۶۲ × $۱۰^{۹}$/l)**
- **Elevated levels of AST (>۵۹ U/l)**
- **Decreased WBC count (≤۴٫۰ × $۱۰^{۹}$/l)**
- **Hypofibrinogenemia (≤۲٫۵ g/l)**

b. **Clinical criteria**

- **Central nervous system dysfunction**
- **Hemorrhages**
- **Hepatomegaly (≥۳ cm below the costal arch)**

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۲۰۱۶ classification criteria for MAS complicating sJIA

A febrile patient with known or suspected sJIA is classified as having MAS if the following criteria are met:

Ferritin >۶۸۴ ng/ml and any two of the following:

- **Platelet count ≤۱۸۱ × $۱۰^{۹}$/l**
- **AST >۴۸ U/l**
- **Triglycerides >۱۵۶ mg/dl**
- **Fibrinogen ≤۳۶۰ mg/dl**

Medical Care

- The treatment of MAS is traditionally based on the parenteral administration of high doses of corticosteroids. The administration of high-dose intravenous immunoglobulins, cyclophosphamide, plasma exchange, and etoposide has provided conflicting results.

- The use of cyclosporin A (CyA) was considered based on its proven benefit in the management of familial hemophagocytic lymphohistiocytosis (FHLH). CyA was found to be effective in severe or corticosteroid-resistant MAS.

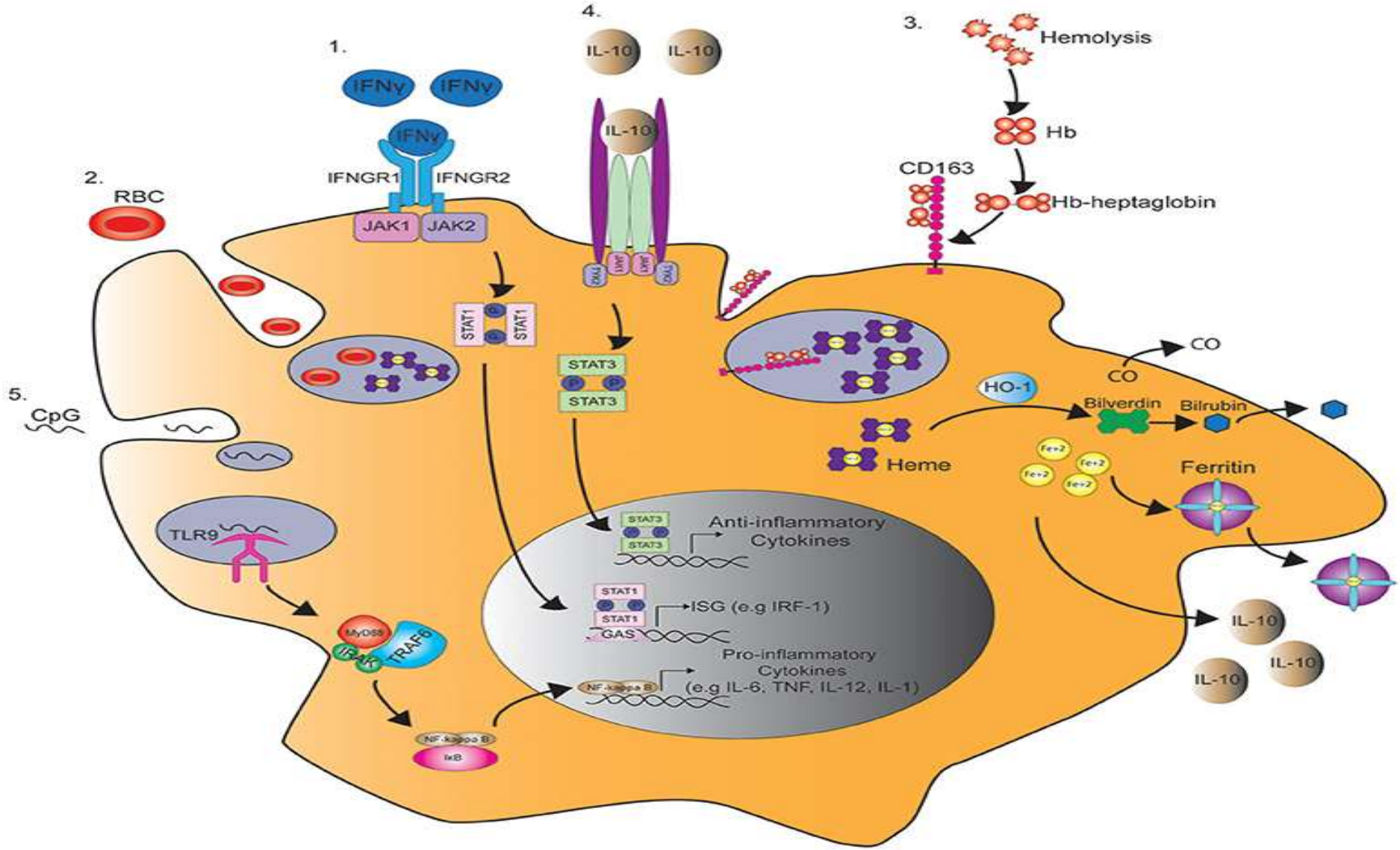
Medical Care

- Increased production of tumor necrosis factor (TNF) in the acute phase of macrophage activation syndrome has suggested the use of TNF-α inhibitors as potential therapeutic agents.

- Recombinant interleukin (IL)-١ receptor–antagonist anakinra.

Medical Care

- Etoposide has been shown to improve prognosis for Epstein-Barr virus (EBV)–related HLH; its effectiveness may be explained by inhibition of synthesis of EBV nuclear antigen. Whether HLH therapeutic protocols are suitable for use in children with MAS associated with rheumatic diseases is unclear.
- IVIG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IFNγ
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IFNγ
IFNGR1
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JAK2
2.
RBC
4.
IL-10
IL-10
IL-10
3.
Hemolysis
Hb
CD163
Hb-heptaglobin
STAT1
STAT1
STAT3
STAT3
5.
CpG
TLR9
MyD88
IRAK
TRAF6
IκB
NF-κB
STAT3
STAT3
Anti-inflammatory
Cytokines
STAT1
STAT1
ISG (e.g IRF-1)
GAS
Pro-inflammatory
Cytokines
(e.g IL-6, TNF, IL-12, IL-1)
HO-1
CO
CO
Bilverdin
Bilrubin
Heme
Fe+2
Fe+2
Fe+2
Fe+2
Ferritin
IL-10
IL-10
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Thank you