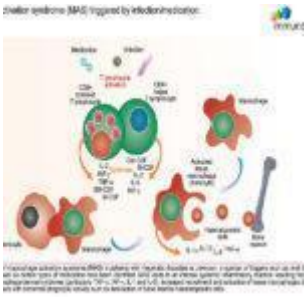
A case of decreased joint function, fever and rash



Patient Presentation

A 7 year old girl presented to her local hospital for the second time in 3 months with arthralgia, a migratory skin rash and fever for 5 days. She was admitted and within 2 days developed a depressed level of consciousness, epistaxis and seizures.

Acknowledgement

This case study was kindly provided by Dr Monika Esser MMed Paed, Head of Division of Immunology, N.H.L.S Coastal Branch, Tygerberg Hospital.

History

Patient was diagnosed one year earlier with pulmonary TB (PTB) on positive cultures obtained from gastric washings. Her PTB infection was accompanied with symptoms of fever and torticollis. She was started on TB treatment but only completed 2 months of treatment.

Six months later she had not resumed TB treatment and was diagnosed with mitral regurgitation on echocardiography, with an elevated antistreptolysin O titre (ASOT) and an elevated anti-dnase test. She was admitted to hospital and treated for acute rheumatic fever (ARF) with benzyl penicillin. The mitral regurgitation normalised on echo and she was discharged.

Over the course of the following 3 months she developed progressive arthritis, progressive loss of joint function and a chronic remitting fever and rash.

Differential Diagnosis

- Post streptococcal arthritis
- Pulmonary TB
- Systemic Lupus Erythematosus
- Acute rheumatic fever
- Juvenile rheumatoid arthritis

Examination

An admission child appears miserable and toxic:

- Height and weight < 3rd centile
- Pyrexial – 38°C
- Pale
- Generalised lymphadenopathy
- Urticarial rash
- 2cm hepatosplenomegaly

- Tender and bilaterally limited range of motion in the wrists, knees, ankles and proximal and distal interphalangeal joints of the fingers

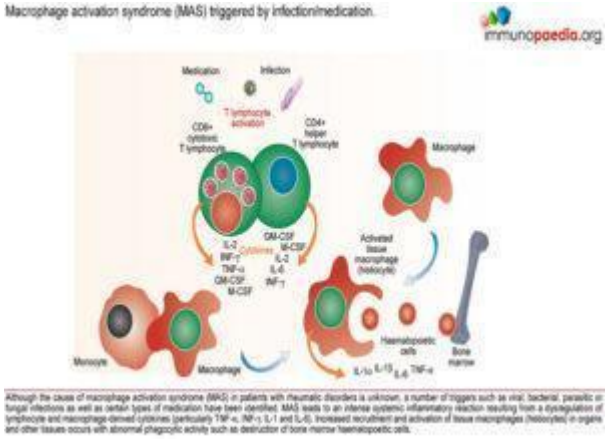
2 days later:

- Depressed level of consciousness
- Epistaxis
- Seizures
- Pyrexia ranging from 38-40°C
- Severe hepatosplenomegaly
- Consolidation of right upper lobe of the lung with bronchial breathing

Investigations

On admission		
WCC	9.26 x10^9/L	(4,5-10 x10^9/L)
HB	11.2 g/L	(12.1 to 15.1 g/L)
Platelets	338 /mm^3	(150 to 400 x10^9/L)
HCT	0.36	(0.36 -0.44)
ESR	110 mm/hr	(3 to 13 mm/hr)
ALT	39U/L	(5-40 U/L)
C3	2.12	(75-135 mg/dl)
C4	0.33	(13 to 75 mg/dL)
Rheumatoid factor	negative	
Anti nuclear factor	negative	
ASOT	483 units/mL	(positive >200 units/mL)
anti-dnase	1630 units/mL	(positive > 170 Todd units/mL)
Mantoux skin test	(positive >10mm)	12mm
Chest X-ray	normal	
Day 4		
WCC	36.9 x10^9/L	(4,5-10 x10^9/L)
HB	2.6 g/L	(12.1 to 15.1 g/L)
HCT	0.31	(0.36 -0.44)
MCV	72 fL	(80 to 100 fL)
Platelets	45/mm^3	(150 to 400 x10^9/L)
INR	1.47	(0.8-1.2)
PTT	49.9	(25-39s)
AST	2861U/L	(5-40 U/L)
ALT	661U/L	(5-40 U/L)
GGT	390 U/L	(11-51 U/L)
LDH	8130 U/L	(70-250 U/L)
Ferritin	89210 µg/L	(12-200 µg/L)
Day 6		
WCC	0.38 x10^9/L	(4,5-10 x10^9/L)
Bone marrow aspirate showed activated macrophages		

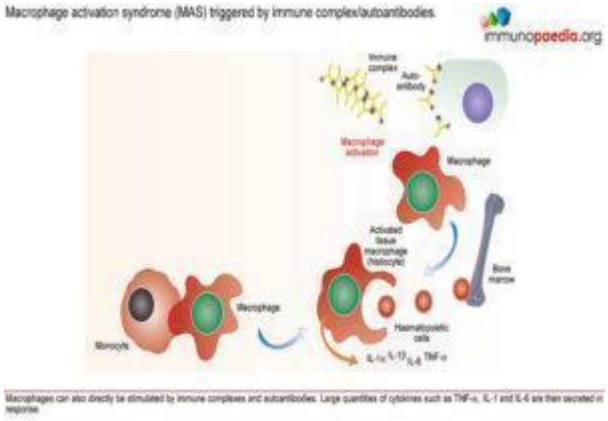
Discussion



Based on the clinical presentation and investigations the differential diagnosis must now include Macrophage activation syndrome (MAS).

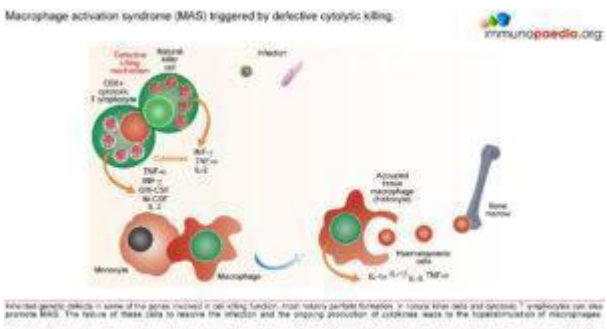
Cause*:*

- Unknown but a number of triggers such as infection (EBV, bacterial, parasitic and fungal) and certain types of medication have been identified.Excessive activation and proliferation of T lymphocytes and tissue macrophages (histiocytes) with massive cytokinaemia, including high levels of: TNF-a, INF-g, IL-1 and IL-6
- This produces an overwhelming, potentially fatal, inflammatory reaction. With increased recruitment and activation of tissue macrophages in organs and other tissues with abnormal phagocytic activity such as destruction of bone marrow haematopoeitic cells
- Defective functioning of perforin (perforin is a protein involved in the cytolytic processes and control of lymphocyte proliferation).



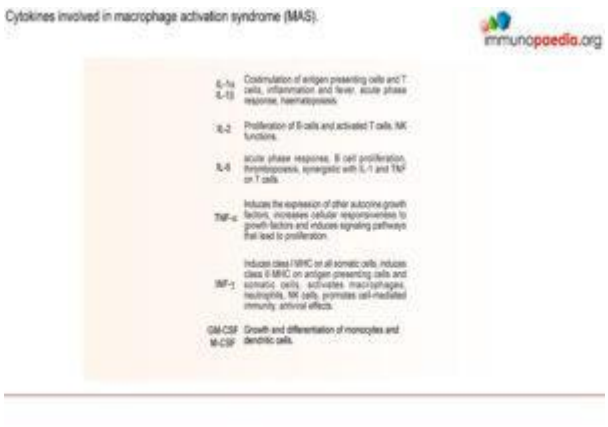
Sign and symptoms

- Non-remitting high fever
- Hepatosplenomegaly
- Lymphadenopathy
- Pancytopenia,
- Liver insufficiency,
- Coagulopathy
- Haemorrhages
- Neurological symptoms



Laboratory features

- Cytopenia
- Abnormal liver function tests
- Coagulopathy
- Decreased erythrocyte sedimentation rate
- Hypertriglyceridaemia
- Hyponatremia
- Hypoalbuminemia
- Hyperferritinemia
- Histopathological features
- Macrophage haemo phagocytosis in the bone marrow



Epidemiology

- Incidence is unknown
- Rare complication
- Most commonly affects children with systemic juvenile inflammatory arthritis (JIA) but has been observed in different subtypes of JIA or in other systemic diseases such as systemic lupus erythematosus (SLE)
- Generally develops in the earlier phases of the underlying disease and may occasionally be the presenting manifestation, but occurrence as late as 14 years after diagnosis has been reported
- In most patients, the primary disease is clinically active at the onset of MAS, but the syndrome may also develop during quiescent phases
- Triggered by flare-up of the underlying disease, aspirin or other nonsteroidal anti-inflammatory drug toxicity, viral infections, a second injection of gold salts, and sulfasalazine therapy.

Pathogenesis*:*

May be the result of a mutation in the perforin gene leading to decreased expression of perforin:

- Perforin – is a protein that is expressed in lymphocytes, macrophages, and other bone marrow precursors. Its main role in the cytolytic process is to form pores in the cell membrane, leading to osmotic lysis of the target cells.

- May also control lymphocyte proliferation

Diagnostic Guidelines:

Variables that showed the highest (0.75) sensitivity and specificity for MAS:

- elevated ferritin (above 10,000 ng/mL),
- elevated triglycerides (above 160 mg/dL),
- elevated aspartate aminotransferase (above 59 IU/mL),
- elevated fibrinogen (above 250 mg/dL),
- elevated alanine aminotransferase (above 40 IU/mL),
- elevated glutamyl transferase (above 40 IU/mL),
- low platelet count (below 262 x109/L),
- bone marrow aspirate showing hemophagocytosis

(b) Variables that did not prove sufficiently sensitive and specific:

- fever (38°C),
- lymphoadenopathy,
- neurologic manifestations
- arthritis,
- rash
- hemorrhages,
- decreased leukocyte count (below 4,00 x109/L),
- elevated erythrocyte sedimentation rate (above 50 mm/h),
- elevted lactate dehydrogenase (above 900 IU/mL)
- decreased serum sodium (below 130 mEq/L).

Management: Treatment strategies for MAS

MAS is a potentially life threatening complication. It is therefore important to have a high threshold of suspicion in order to make an early diagnosis and start prompt treatment:

- Parenteral administration of high doses of corticosteroids.
- Cyclosporin A – treating severe or corticosteroid-resistant MA
- It causes a “switch-off” effect on the disease process,

leading to resolution of fever and improvement of laboratory abnormalities

- Suppression of the early steps in T-cell activation
- Affects macrophage production of IL-6, IL-1, and TNF
- Inhibits the expression of inducible nitric oxide synthetase and cyclooxygenase-2 in macrophages.
- High-dose intravenous immunoglobulins
- Etanercept might be an effective adjunctive therapeutic agent in MAS.

Diagnostic Rule:

The diagnosis of MAS requires the presence of any 2 or more laboratory criteria or of any 2 or more clinical and/or laboratory criteria. A bone marrow aspirate for the demonstration of haemo phagocytosis may be required only in doubtful cases.

Laboratory criteria:

1. Decreased platelet count (≤262 x 109/L)
2. Elevated levels of AST (> 59 U/L)
3. Decreased white blood cell count (≤ 4.0 x 109/L)
4. Hypofibrinogenemia (≤2.5 g/L)

Clinical criteria:

1. Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
2. Haemorrhages (purpura, easy bruising, mucosal bleeding)
3. Hepatomegaly (≥ 3cm below the costal arch)

Histopathological criterion:

Evidence of macrophage haemophagocytosis in the bone marrow aspirate

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Treatment

- The patient was treated with IVIG and repeated intravenous methylprednisolone pulsing.
  Methotrexate was started with normalisation of liver functions.
- She required repeat blood transfusions and was kept on broad spectrum antibiotic cover but all cultures remained negative.

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Final Outcome

- The patient proceeded to make a rapid and complete recovery and is currently maintained on low dose Methotrexate.
- A full course of TB treatment was completed with normalisation of liver functions.

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Evaluation – Questions & answers

What is the diagnosis?

Macrophage activation syndrome (MAS) also known as haemophagocytic lymphohistiocytosis is a macrophage-related disorder of the immune system characterised by excessive activation of tissue macrophages (histiocytes). It is thought that increased levels of lymphocyte and macrophage derived cytokines, particularly TNF-a, INF-g, IL-1 and IL-6 lead to the excessive activation of macrophages and systemic inflammation. Increased recruitment and activation of tissue macrophages in organs and other tissues occurs with abnormal phagocytic activity such as destruction of bone marrow haematopoeitic cells.

What is the cause of Macrophage activation syndrome (MAS)?

The cause is unknown but a number of triggers such as infection and certain types of medication have been identified.

What is the effect of increased levels of T-cell and macrophage derived cytokines, particularly TNF-a, INF-y, IL-1 and IL-6?

An overwhelming systemic inflammatory reaction, which is potentially fatal.

What is perforin?

Perforin is primarily expressed in CD8+ T cells and NK cells. Its role in the cytolytic process is to form pores in the membrane, leading to osmotic lysis of the target cells. There is evidence that perforin expression is important in preventing both humoral and cellular autoimmunity. Perforin deficient CD8+ and Natural Killer (NK) cells may perpetuate a chronic proinflammatory response. Perforin deficiency may therefore increase macrophage activation due to increased production of IFN-γ and granulocyte macrophage colony

stimulator factor (GM-CSF) associated with persistent lymphocyte activation. It is possible that it therefore plays a role in the predisposition to or occurrence of MAS. Most patients with a low perforin expression have had a history of previous MAS episodes.

What is the mechanism of macrophage activation syndrome (MAS)?

Again this is unclear, however a possible explanation is that patients with MAS have decreased natural killer (NK) function which may be responsible for a diminished ability to kill infected cells and remove the source of antigenic stimulation. This persistent antigen stimulation would lead to persistent antigen driven T-cell activation and proliferation associated with an increased production of cytokines such as IFN-γ and GM-CSF which stimulate macrophages. This sustained macrophage activation causes tissue infiltration with resulting clinical symptoms and tissue damage.

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