CASE REPORT

An important complication of a child with juvenile idiopathic arthritis: macrophage activation syndrome

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SUMMARY

A 4-year-old girl, a known case of juvenile idiopathic arthritis for 2 years presented to us with high-grade fever and abdominal distension for 2 months. On examination, her temperature was 104°F and she was found to be pale with bilateral cervical lymphadenopathy of up to 3×3 cm in size. Her liver was enlarged with a firm consistency and a span of 12 cm. Her spleen was enlarged up to 3 cm along its long axis. The rest of her systemic examination was normal. Laboratory investigations revealed leucocytosis, anaemia and thrombocytopenia with a mildly elevated erythrocyte sedimentation rate. Serum ferritin was 16 500 ng/dL and lactate dehydrogenase was 2311 U/L. A bone marrow aspirate showed macrophages showing ingested nuclei. She was diagnosed as having macrophage activation syndrome and was initiated on intravenous methylprednisolone 300 mg daily for 3 days and was switched over to oral prednisolone 2 mg/kg/day. She is currently doing well on follow-up.

BACKGROUND

Macrophage activation syndrome (MAS) is a rare but potentially fatal complication of juvenile rheumatic disorders especially systemic onset juvenile idiopathic arthritis (SoJIA)^{1 2} that usually presents as high-grade fever, lymphadenopathy, hepatosplenomegaly, cytopenia and at times, disseminated intravascular coagulation and central nervous system dysfunction.^{3 4}

We report a child with juvenile idiopathic arthritis who presented to us with fever, hepatosplenomegaly and cytopenia, subsequently diagnosed with MAS. Even in a tropical country such as India, where malaria and tuberculosis is very prevalent, a child with massive hepatosplenomegaly should be suspected to have macrophage activation syndrome after ruling out common conditions.

CASE PRESENTATION

A 4-year-old girl presented to us with high-grade fever, abdominal distension, loss of weight and appetite for 2 months.

Her medical history revealed that she had fever associated with polyarthritis 2 years ago when she was investigated thoroughly and was diagnosed with So-JIA after ruling out all other likely diagnoses such as infections, malignancies, systemic lupus erythematosus and other common collagen vasculitides.

She was treated with steroids at that time for which she reportedly had good response and defaulted from treatment beyond 6 months. When she had a

recurrence of the same symptoms, the family sought alternative medicine; hence, she was not followed up for at least 1 year in any medical hospital.

- ▶ Antenatal H/O—normal
- ▶ Natal H/O—normal
- ▶ Postnatal H/O—normal
- ▶ Immunization H/O—immunised as per national immunisation schedule until 4 years
- ▶ Nutritional H/O—no calorie gap, no protein deficit
- ▶ Family H/O—unremarkable

Now, on examination, her temperature was 104°F. She was pale with bilateral cervical lymph nodes of 3 cm. Her liver was enlarged with a firm consistency and a span of 12 cm. Her spleen was also enlarged 3 cm along its long axis. The rest of her systemic examination was normal.

INVESTIGATIONS

Initial laboratory investigations revealed a total white cell count of 15 580 cells/mm³ with polymorphonuclear cells being 43% and lymphocytes contributing 52% of total count. Haemoglobin was 7.2 g/dL, platelet count was 75 000/mm³, erythrocyte sedimentation rate (ESR) was mildly elevated (30 mm at first hour).

Her liver enzymes, clotting profile and renal function parameters were within normal limits.

Workup for infective aetiology including tuberculosis, dengue, malaria and enteric fever; rheumatological disorders including rheumatic factor and antinuclear antibodies for systemic lupus erythematosus were negative.

Her ophthalmological evaluation did not reveal any abnormality.

Her blood and urine culture were sterile.

She had persistent fever despite therapeutic intervention with broad spectrum antibiotics and repeat blood investigations after a week showed falling haemoglobin 5.5 g/dL, platelet count 61 000/mm³, total white cell count 8430/mm³.

Her serum ferritin conducted at this point was 16 500 ng/dL and lactate dehydrogenase was 2311 U/L.

In view of persistent fever not responding to antibiotics and cytopenia with a background of SoJIA and with marked hyperferritinaemia, she was worked up for MAS. Bone marrow aspiration showed mild erythroid hyperplasia with cells suggestive of macrophages showing ingested nuclei (figure 1 shows macrophages with ingested nuclei).

DIFFERENTIAL DIAGNOSIS

Her D/D after clinical examination was

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Figure 1 Peripheral smear showing emperipolesis—macrophage with ingested nuclei.

- Relapse of SoJIA
- Malaria
- Dengue
- Leptospirosis
- Leukemia
- MAS

We placed infectious diseases and a relapse of SoJIA higher up on her differential because they are common and highly likely in our country especially with this form of clinical presentation. We would like to stress on the fact that it is prudent and hence appropriate to rule out these common conditions first before considering the rarer complication that is MAS. Although a bone marrow aspiration was performed to exclude MAS, the possibility of malignancy was also ruled out simultaneously.

A few clinical points can help differentiate a relapse of SoJIA from MAS. When a patient develops MAS, they typically have little to no symptoms of SoJIA. There is also a paradoxical fall in ESR and a highly elevated serum ferritin. These were noted in our patient.

TREATMENT

After her initial laboratory investigations, she was started on parenteral broad spectrum antibiotics pending the initial reports and was later on stopped after confirmation.

Once we confirmed MAS, she was initiated on intravenous methylprednisolone 300 mg daily for 3 days when her fever reduced and she was switched over to oral prednisolone 2 mg/kg/day.

OUTCOME AND FOLLOW-UP

Her symptoms subsided and her blood parameters normalised. She was discharged home after 4 days of steroids on oral prednisolone. She is currently doing well on follow-up.

DISCUSSION

MAS is a severe, potentially lethal complication of childhood systemic inflammatory disorders, primarily SoJIA. It is characterised by pancytopenia, hepatosplenomegaly, liver insufficiency, coagulopathy, hyperferritinemia and neurological symptoms and is thought to be caused by the activation and uncontrolled proliferation of T lymphocytes and macrophages, leading to cytokine overproduction.^{4 5}

The exact incidence of MAS in childhood systemic inflammatory disorders is not entirely clear.⁶ It may be more common than previously thought.^{7 8} In one study by Moradinejad, Ziaee,⁹ the reported incidence of MAS in Still's disease was 8.2% with a mortality rate of 40%.⁹ Up to 100 cases have been reported in the literature until 2002. Although it generally develops in the early phase of JIA, it has been known to occur up to 14 years after diagnosis.

While most of the pathogenesis is unclear, what is understood is that there is a widespread dissemination of hyperactivated lymphocytes and macrophages with cytokine release. The symptoms produced are compatible with the biological effects of several T lymphocyte and macrophage-derived proinflammatory cytokines such as tumour necrosis factor (TNF) α , interleukin (IL)-1,6 and interferon γ .¹⁰ In addition, a sharp increase in ferritin, often more than 10 000 ng/mL has been reported in the acute phase of MAS.⁸

It generally presents in an acute and dramatic fashion. Table 1 shows diagnostic guidelines for the diagnosis of MAS.¹¹ Typically, patients become acutely ill with the sudden onset of non-remitting high fever, profound depression in all three blood cell lines (ie, leukopenia, anaemia and thrombocytopenia), hepatosplenomegaly, lymphadenopathy and elevated serum liver enzyme levels. High levels of triglycerides and lactic dehydrogenase and low sodium levels are consistently observed. Characteristically, a paradoxical fall in ESR (due to a fall in fibrinogen) is observed despite the proposed inflammatory state of MAS. This helps to differentiate between a flare up of JIA and the onset of MAS complicating JIA.

The treatment strategy for MAS is usually based on the parenteral administration of high doses of corticosteroids. High-dose intravenous immunoglobulins, cyclophosphamide, plasma exchange and etoposide have questionable benefit. The use of cyclosporine A was recently advocated due to its efficacy in other disorders affecting macrophages. It has been shown to

Table 1 Diagnostic guidelines for macrophage activation syndrome

Preliminary diagnostic guidelines for macrophage activation system complicating svstemii. Luvenile idiopathic arthritis

Laboratory criteria

- Decreased platelet count ($\leq 262 \times 10^9/L$)
- Elevated levels of aspartate aminotransferase ($> 59 U/L$)
- Decreased white blood cell count ($\leq 4.0 \times 10^9/L$)
- Hypofibrinogenemia ($\leq 2.5 g/L$)

Clinical criteria

- Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
- Hemorrhages (purpura, easy bruising, mucosal bleeding)
- Hepatosplenomegaly (≥ 3 cm below the costal arch)

Histopathological criterion

- Evidence of macrophage hemophagocytosis in the bone marrow aspirate

affect macrophage production of IL-6, IL-1 and TNF- α and to inhibit the expression of inducible nitric oxide synthetase and cyclo-oxygenase two in macrophages, leading to decreased production of nitric oxide and prostaglandin E₂.^{12 13} In a recent study, etanercept was found to have poor efficacy in systemic onset JIA.⁷ Results of observational studies with anakinra, an IL-1-receptor antagonist, are promising.¹⁴

DIAGNOSTIC RULE

The diagnosis of MAS requires the presence of any two or more laboratory criteria or of any two or three or more clinical and/or laboratory criteria. A bone marrow aspirate for the demonstration of haemophagocytosis may be required in doubtful cases.¹¹

Learning points

- ▶ When a patient with systemic onset juvenile idiopathic arthritis (SoJIA) presents with lymphadenopathy, hepatosplenomegaly and cytopenia, macrophage activation syndrome (MAS) should be considered.
- ▶ SoJIA and MAS
 - Can be clinically differentiated by lack of SoJIA symptoms and a fall in erythrocyte sedimentation rate coupled with a sharp increase in serum ferritin and lactate dehydrogenase.
 - Serum ferritin
 - Not just a marker of iron stores, it is also an acute phase reactant;
 - Very high levels, as in this case, is suggestive of MAS.

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managed by JXS, NB and YNVR. The diagnosis was aided by the pathological services provided by PN.

Competing interests None.

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