

# Methotrexate as a Suspected Trigger of Macrophage Activation Syndrome in Juvenile Idiopathic Arthritis

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## Abstract

A four year old girl with systemic onset juvenile idiopathic arthritis (SOJIA) developed macrophage activation syndrome (MAS) shortly after starting methotrexate. We observed methotrexate is a likely trigger of MAS in SOJIA. Possibly, there are only two case reports suggesting methotrexate triggered MAS. We reviewed the literature for possible mechanisms.

**Key words:** Macrophage activation syndrome; Methotrexate; Systemic Onset Juvenile Idiopathic Arthritis

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## Introduction

Macrophage activation syndrome (MAS) is a devastating complication of systemic onset juvenile idiopathic arthritis (SOJIA) with uncertain aetiopathogenesis. Ravelli et al<sup>1</sup> had suggested that methotrexate may be a triggering factor for MAS in SOJIA although Eraso et al<sup>2</sup> and others refuted their observations. Role of methotrexate in inducing MAS in SOJIA is contemplated in the case report.

## The Case

A four year old girl admitted with fever for one year and evanescent rash with multiple joint pains for ten months. She was diagnosed as a case of SOJIA according to ILAR guideline<sup>3</sup>. Child was taking ibuprofen for one month before admission. Upon admission, we classified her as "systemic arthritis with active arthritis" according to American College of Rheumatology guidelines<sup>4</sup> and started methotrexate. The next day, she developed pruritus and high-grade, non-remittent fever, with abdominal pain and lethargy. New-onset lymphadenopathy and hepatosplenomegaly were observed and fresh tests revealed bicytopenia and low fibrinogen with elevated CRP, transaminases, INR, triglyceride and ferritin (Table 1). She was diagnosed to have developed MAS and died four days later.

## Discussion

Ravelli et al<sup>1</sup> had found methotrexate as a possible trigger of MAS in SOJIA, whereas Sterba et al<sup>5</sup> found methotrexate induced MAS in dermatomyositis. Similar to our scenario, Ravelli et al<sup>1</sup> also found sharp fever and pruritus after 24 hours of introducing methotrexate along with increase of ferritin from 207 to 10143 and other features of MAS within next 72 hours.

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**Table 1:** Main blood reports before and after initiating methotrexate

Parameters	On admission	After starting Methotrexate
Hemoglobin (g/dl)	7.2	6.2
WBC (per cc)	14400	9100
Platelet (per cc)	468000	140000
CRP (mg/dl)	70.4	147
ESR (mm)	74	14
SGOT (unit/litre)	36	1095
SGPT (unit/litre)	16	118
INR	-	2.02
Ferritin (nanogram/dl)	701	40990

Besides the temporal association between methotrexate and MAS, we also reviewed the literature to look for biological plausibility.

MAS occurs when certain trigger factors lead to excessive activation of cytotoxic CD8+ T cells, with hypersecretion of proinflammatory cytokines. NSAIDs, gold salts, sulfasalazine, penicillamine<sup>1</sup> canakinumab, etanercept and adalimumab used in SOJIA are known to cause MAS, but role of methotrexate is doubtful<sup>2</sup>. Furhman et al. noted methotrexate-induced-alveolitis, with increased CD4+ and CD8+ T-cells in the broncho-alveolar lavage among a few methotrexate-treated patients<sup>6</sup>. Dobrzanski et al<sup>7</sup> found single-dose-treatment with methotrexate enhanced T-cell mediated type1 responses. Hatachiet al<sup>8</sup> reported development of CD+ T-cell lymphoproliferative disorder with EBV genome in a RA patient, during methotrexate therapy. Neurath et al<sup>9</sup> observed that while methotrexate reduced interleukin and TNF production in synovial fluid, the levels of these cytokines were unaffected in peripheral blood. They also observed that TNF production was reduced from T-lymphocytes, but not from macrophages. Also at anti-rheumatoid doses, although methotrexate decreases pro-inflammatory cytokines, but cell proliferation is negligibly affected. Infact, at anti-rheumatoid dose, the blood concentration of methotrexate is one-tenth its concentration in synovial fluid<sup>9</sup>. Hence, its actions in the joints and in extra-articular tissues may be different. We

speculate that in few SOJIA patients, methotrexate may actually increase the cytotoxic T-lymphocytes in extra-articular regions, and initiate MAS.

Halevey et al.<sup>10</sup> reported leucocytoclastic vasculitis in the small vessels of a Rheumatoid Arthritis (RA) patient treated with Methotrexate, which proves the potential ability of Methotrexate to induce autoimmune inflammation in RA.

Methotrexate is an anti-folate drug. It is relevant that another anti-folate drug, sulphamethoxazole-trimethoprim, rarely causes DRESS (Drug rash with eosinophilia and systemic symptoms)<sup>11</sup>, which is an acute immune-mediated reaction causing macrophage and T-lymphocyte activation and cytokine release, reminiscent of drug-induced MAS.

Thus we feel that methotrexate is a possible cause of MAS in SOJIA.

## Conclusion

This case report may open the debate whether methotrexate, a common drug, has this potentially lethal side effect in SOJIA. Paediatricians who are well informed of such possibility will have a higher index of suspicion about methotrexate during their daily practice. This will contribute to salvaging more patients as well as enrichment of the medical literature with more similar case reports.

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