

## Case Report

# Macrophage Activation Syndrome Following Initiation of Etanercept in a Child with Systemic Onset Juvenile Rheumatoid Arthritis

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**ABSTRACT.** Systemic onset juvenile rheumatoid arthritis (JRA) accounts for 10–15% of all JRA. Macrophage activation syndrome (MAS), which can also be considered as secondary hemophagocytic lymphohistiocytosis, is a potentially life-threatening complication of systemic onset JRA. We describe a child with systemic onset JRA who developed MAS after initiation of etanercept therapy. (*J Rheumatol* 2003;30:401–3)

*Key Indexing Terms:*MACROPHAGE ACTIVATION SYNDROME  
JUVENILE RHEUMATOID ARTHRITISETANERCEPT  
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Systemic onset juvenile rheumatoid arthritis (JRA) accounts for 10–15% of all JRA<sup>1</sup>. Macrophage activation syndrome (MAS), which can also be considered as secondary hemophagocytic lymphohistiocytosis, is a potentially life-threatening complication of systemic onset JRA. MAS is one of the leading causes of morbidity and mortality in patients with systemic onset JRA. MAS is characterized by persistent high fever, pancytopenia, mild to serious derangements of liver cell function, purpura, encephalopathy, and disseminated intravascular coagulation. A number of triggers have been implicated in the pathogenesis of MAS, including viral infections, non-steroidal antiinflammatory drug therapy, gold salts, sulfasalazine, and methotrexate (MTX)<sup>2–7</sup>. We describe a child with systemic onset JRA who developed MAS after initiation of etanercept therapy.

**CASE REPORT**

A 4.5-year-old girl first presented in February 1998 with systemic onset JRA. The diagnosis was made on the basis of an 8 week history of fever with a quotidian pattern, characteristic systemic onset JRA rash, and polyarthritis. Laboratory investigation showed a hemoglobin of 105 g/l, white blood cell (WBC) count  $17.4 \times 10^9/l$  with 59% neutrophils, and a platelet count of  $420 \times 10^9/l$ . Erythrocyte sedimentation rate (ESR) was 115 mm/h. Her disease course was characterized by persistent systemic symptoms and severe polyarticular arthritis. She was initially treated with indomethacin (3 mg/kg/day), followed by pulse methylprednisolone, oral prednisone (up to 2 mg/kg/day)

and intraarticular steroids. Her disease was unresponsive to treatment with MTX (20 mg/m<sup>2</sup>/wk) and IV immunoglobulin. She did not tolerate cyclosporin. Three and a half years after disease onset, the systemic features were well controlled with oral prednisone (3 mg/day) and ibuprofen with no fever or rash, but she had persistent polyarthritis. She was prescribed etanercept (0.4 mg/kg twice a week). Laboratory investigation before starting etanercept showed hemoglobin 117 g/l, WBC  $14.0 \times 10^9/l$ , platelet count  $344 \times 10^9/l$ , ESR 59 mm/h; alanine aminotransferase (ALT) was 12 (normal 0–40) and aspartate aminotransferase (AST) was 23 (normal 0–45 U/l).

After 4 doses of etanercept she developed a mildly pruritic nontender giant urticarial rash adjacent to the sites of injections of etanercept on both arms (Figure 1). Four days later she developed persistent fever and a diffuse urticarial rash that was mildly pruritic. There was a significant improvement in her arthritis and no evidence of hepatosplenomegaly or lymphadenopathy. Her ESR dropped to 2 mm/h and she developed a relative cytopenia with a hemoglobin of 99 g/l and platelet count  $122 \times 10^9/l$ . AST, D-dimer, ferritin, and fasting triglycerides were all elevated (Table 1). Blood and urine cultures were negative. Serological tests for infection including Epstein-Barr virus (EBV), parvovirus, and cytomegalovirus (CMV) antibodies were negative. A diagnosis of MAS was made on the basis of clinical and laboratory findings, and she was treated with 2 pulses of IV methylprednisolone (30 mg/kg/dose) followed by high dose oral prednisone. Etanercept was stopped and she made a good clinical recovery, with resolution of fever and rash within 2–3 days. The serial laboratory tests also improved, as shown in Table 1.

**DISCUSSION**

MAS or secondary hemophagocytic lymphohistiocytosis is a clinical entity caused by the excessive activation and proliferation of well differentiated macrophages, and is associated with a heterogeneous group of conditions including infections and neoplastic and autoimmune conditions<sup>6,8</sup>. It is more commonly seen in systemic onset JRA than in any other pediatric rheumatic disease. The characteristic features are high spiking temperature, hepatosplenomegaly, pancytopenia, coagulation abnormalities, liver dysfunction, and raised triglyceride and ferritin concentrations. The pathognomonic features of this syndrome are the numerous well differentiated macrophages

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Figure 1. The etanercept injection site in arm showing giant urticaria.

Table 1. Laboratory variables before and after starting etanercept.

Variable (normal range)	Before Etanercept	2 Weeks Later*	4 Weeks Later	10 Weeks Later
Hb, g/l (120–160)	117	99	124	148
WBC $\times 10^9/l$ (4–10)	14.0	6.5	14.4	14.2
Platelets $\times 10^9/l$ (150–400)	344	122	227	225
D-dimer, ng/ml (0–449)	NA	3220	2930	828
ESR, mm/h (1–10)	59	2	56	3
Fibrinogen, g/l (1.6–4.0)	NA	1.96	4.35	3.14
AST, U/l (0–45)	23	95	44	23
Ferritin, $\mu g/l$ (22–400)	NA	964	1413	15,3

\*Etanercept stopped, high dose corticosteroids started. NA: not available

(histiocytes) actively phagocytosing hematopoietic elements seen in bone marrow aspirates or on biopsies of liver, spleen, or lymph nodes.

There are currently no validated criteria for the diagnosis of MAS in systemic onset JRA. The diagnosis of MAS was made in our patient on the basis of the clinical and laboratory picture, which was not in keeping with a flare of her systemic disease and could not be attributed to an identifiable infection. We did not proceed with bone marrow biopsy in an attempt to establish a tissue diagnosis of hemophagocytosis because she responded so well to conventional therapy.

Etanercept is a recombinant human tumor necrosis factor (TNF)- $\alpha$  receptor Fc fusion protein that effectively binds TNF- $\alpha$  and inhibits its activity. Etanercept has been shown to

be beneficial in children with polyarticular JRA<sup>9</sup>, but there are few reports regarding its effectiveness in systemic onset JRA<sup>10,11</sup>.

Injection site reactions to etanercept in children are common<sup>9</sup> and urticarial reactions at injection sites are well described<sup>12</sup>. Our patient developed giant urticaria adjacent to the injection sites after 4 doses of etanercept and then went on to develop MAS. In the absence of an identifiable infection or any other change in medication, etanercept is the most likely triggering factor. To our knowledge MAS has not been described in association with etanercept before. Indeed, TNF- $\alpha$  levels are elevated in MAS<sup>13–15</sup> and etanercept has been successfully used to treat established MAS in one child with systemic onset JRA<sup>16</sup>.

A recent report of injection site reactions from etanercept speculates that the drug could act as a hapten, binding some unknown extracellular/intracellular epidermal protein component or receptor and mediating an inflammatory flare through CD8 T lymphocytes<sup>17</sup>. Biopsy of these skin lesions showed an inflammatory infiltrate, with most of the cellular infiltrate being composed of cells with an HLA-DR/CD3/CD4/CD8 phenotype, indicating an activated mature cytotoxic T lymphocyte lineage.

The mechanism whereby etanercept can trigger MAS is unclear, but the development of MAS following a giant urticarial eruption at the injection sites suggests that this drug reaction may play a role. We suggest that the development of giant urticaria at injection sites of etanercept in a patient with systemic onset JRA may herald the development of MAS. Such patients should discontinue etanercept and should be closely monitored for the evolution of this serious and potentially life-threatening complication.

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