Case Report

# Etanercept in the Treatment of Macrophage Activation Syndrome

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***ABSTRACT.*** Macrophage activation syndrome (MAS), a recognized complication of systemic juvenile rheumatoid arthritis (sJRA), has been associated with significant morbidity and mortality. Dysregulation of macrophage-lymphocyte interactions leading to uncontrolled proliferation of highly activated macrophages and massive release of proinflammatory cytokines including tumor necrosis factor-α (TNF-α) appears to be central to the pathogenesis of this syndrome. Until now the mainstay of therapy has been corticosteroids and cyclosporin A. We describe a patient with MAS and sJRA successfully treated with the anti-TNF agent etanercept. The outcome in this patient suggests etanercept might be an effective therapeutic agent in MAS. (J Rheumatol 2001;28:2120–4)

*Key Indexing Terms:*
ETANERCEPT
JUVENILE RHEUMATOID ARTHRITIS
MACROPHAGE ACTIVATION SYNDROME
TUMOR NECROSIS FACTOR

Macrophage activation syndrome (MAS), a clinical syndrome caused by the excessive activation and proliferation of well differentiated macrophages, is associated with a heterogeneous group of conditions including infectious, neoplastic, and rheumatologic diseases[1]. The pathognomonic features of this syndrome are found on bone marrow aspiration: numerous, well differentiated macrophages (or histiocytes) actively phagocytosing hematopoietic elements. Such cells may be found in various organs and may account for many of the systemic features of this syndrome. For this reason the term reactive hemophagocytic lymphohistiocytosis has also been used to describe this condition. Prompt recognition and management are essential to avoid the significant morbidity and mortality associated with this condition. Traditionally children with MAS have been managed with corticosteroids and more recently cyclosporin A (CSA)[2-4]. The availability of the anti-tumor necrosis factor-α (TNF-α) agent etanercept prompted us to evaluate if etanercept could be effective therapy for MAS, a condition known to be associated with elevated levels of TNF-α[2].

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*Supported in part by National Institutes of Health grant P30-HD28827, the Children's Hospital Research Foundation of Cincinnati, and the Schmidlapp Foundation.*

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*Submitted October 6, 2000; revision accepted March 12, 2001.*

## CASE REPORT

A previously healthy 7-year-old boy presented with a 5 week history of migratory arthralgias, double quotidian spiking fevers, rash, abdominal pain, and chest pain. Besides ibuprofen as needed, he had not taken any medications. On examination he had an evanescent pink maculopapular rash of the trunk and extremities, with a positive Koebner's sign. Mild generalized lymphadenopathy and hepatosplenomegaly were present. He had a pericardial rub and breath sounds were decreased over the left lower lung fields. Ankle motion was painful bilaterally. Laboratory evaluation revealed erythrocyte sedimentation rate (ESR) 72 mm/h, leukocytosis (32.0 × $10^9$/l), hemoglobin 11.3 g/dl, and platelet count 176 × $10^9$/l. Antistreptolysin O (ASO) and throat cultures were negative. Radiographs of the chest showed mildly increased cardiopericardial silhouette and a small left pleural effusion. Echocardiograms confirmed the presence of a small pericardial effusion. A presumptive diagnosis of systemic juvenile rheumatoid arthritis (sJRA) was considered and treatment with ibuprofen 40 mg/kg/day in 4 divided doses was continued. Four days later, however, his condition deteriorated acutely. The fever became persistent. He developed large hemorrhagic areas on the feet and a purpuric rash on the thighs and arms, and effusions in both knees. The chest pain and fatigue worsened and the pleural and pericardial effusions increased, prompting hospitalization. Laboratory evaluation at this time showed that the platelet count decreased from 176 to 99 × $10^9$/l, hemoglobin decreased from 11.3 to 9.8 g/dl, and white blood cell (WBC) count dropped from 32.0 to 17.9 × $10^9$/l (Table 1). Investigations for infectious etiology (blood cultures, titers for cytomegalovirus, parvovirus, mycoplasma, hepatitis B and C, and ASO) were negative. Epstein-Barr virus serology indicated a past infection. C3 and C4 were depressed (C3 61.2 mg/dl, C4 < 10 mg/dl); antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibodies were negative, as were antibodies to RNP, Ro, La, Sm, and Jo-1. Ferritin was significantly elevated at 22,593 ng/ml (normal 11–122 ng/ml) and triglycerides were also elevated at 190 mg/dl (normal 32–129 mg/dl).

Bone marrow aspiration revealed hypercellularity with a left shift, normal megakaryocytes, and hemophagocytosis of leukocytes and erythroid precursors (Figure 1). No malignant cells were detected. Biopsy

of the purpuric skin lesions revealed leukocytoclastic vasculitis with mild extravasation of erythrocytes, particularly in the superficial dermis (Figure 2). The vasculitic component was present inconsistently. The most consistent feature was abundance of the perivascular infiltrates, composed, in many instances, exclusively of lymphocytes and macrophages, particularly in the mid and deep dermis, and to a minor extent in subcutaneous fat. There were many areas in which the presence of perivascular infiltrates was not associated with vasculitic changes in the blood vessels. The immunophenotype of the perivascular mononuclear cells indicated a mixture of T lymphocytes and macrophages. The macrophages reacted with the common macrophage marker CD68 and also with Factor XIIIa and fasciin, epitopes that identify a subset of non-Langerhans macrophages[5]. The reactions with antibodies to CD1a (a marker for Langerhans cells) and CD20 (a marker for B cells) were both negative.

MAS was diagnosed and the patient was treated with 3 daily pulses of intravenous solumedrol (30 mg/kg), which resulted in improvement of clinical and laboratory variables. However, when steroids were changed to oral administration at 2 mg/kg/day in 3 divided doses, fevers, chest pain, and hemorrhagic rash recurred. Platelet count again dropped from 160 to 38 × $10^9$/l, and WBC count decreased from 10.3 to 3.8 × $10^9$/l. ESR fell sharply from 91 to 45 mm/h, most likely reflecting decreasing serum fibrinogen levels. In contrast, C3 and C4 levels were increasing (108 and 10.1 mg/dl, respectively). An increase in steroid dose to 3 mg/kg/day in 3 divided doses resulted in resolution of clinical symptoms and in the recovery of blood cell counts. Although symptoms were well controlled with high dose oral steroids, ESR returned to high levels and remained persistently elevated (80–126 mm/h). Two further attempts to decrease the prednisone to < 3 mg/kg/day in the next 2 weeks were met with recurrence of the fevers, chest pain, and rash. The rash was hemorrhagic, similar to the one observed with the earlier episodes. Hence 4 weeks after the onset of MAS etanercept 0.4 mg/kg/dose twice weekly was added. This was followed by dramatic improvement in symptoms within 24 h after the first dose. This improvement was paralleled by a decrease in ESR to 15 mm/h after just 4 doses of etanercept. Over the next 5 weeks the prednisone was tapered completely without recurrences of his symptoms. He continued to improve subjectively, with improving laboratory values. After a total of 11 weeks of therapy, etanercept was discontinued. Four months later, he remains asymptomatic taking no medications, with normal laboratory measures.

## DISCUSSION

Although the acute clinical deterioration in our patient, associated with a sharp fall in blood cell counts and the presence of leukohemophagocytoses in the bone marrow, established the diagnosis of MAS, the primary underlying disease was harder to ascertain. He did have daily high spiking fevers, evanescent maculopapular rash with Koebner's phenomenon, arthralgias, arthritis of the knees that lasted about 8 weeks, and lymphadenopathy, all favoring a diagnosis of sJRA. However, a complete resolution of all symptoms makes us still consider an infectious etiology in the differential diagnosis. The early occurrence of MAS prompted us to treat his disease aggressively, possibly modifying the course of the primary condition, such as sJRA.

The exact cause of MAS is poorly understood[6]. Clinically, MAS has similarities with other conditions, such as accelerated phase of Chediak-Higashi syndrome and familial hemophagocytic lymphohistiocytosis (FHL). FHL was recently shown to be the result of mutations in the perforin gene leading to decreased expression of this protein[7]. It is of great interest that 2 groups from the USA and Europe recently described defective perforin function in patients with sJRA as well[8,9]. It has been suggested that perforin, a cytotoxic protein that lymphocytes secrete to kill virus infected cells, may also control lymphocyte proliferation[7,10]. Therefore, in both conditions perforin deficiency may lead to persistent lymphocyte activation associated with production of large quantities of interferon-γ and granulocyte-macrophage colony stimulating factor, 2 important macrophage activators. Subsequently, the sustained macrophage activation results in tissue infiltration and in the production of high levels of TNF-α, interleukin 1 (IL-1), and IL-6 that play a major role in the various clinical symptoms and tissue damage.

Successful use of CSA in the treatment of FHL provided a rationale for the use of CSA in the treatment of MAS presenting as a complication of sJRA[2-4]. First, Stephan, *et al* and later Mouy, *et al*, in a series of 5 patients with MAS associated with JRA found that CSA was indeed effective in treating this condition[2,4]. All patients became afebrile within 24–48 h of starting CSA, and the hematological disturbances normalized within a few days. However, 3 of the 5 patients had a recurrence of disease when the CSA was tapered (3 mg/kg/day in one and at around 1 mg/kg/day in two others), and all responded to an increase in the dose of CSA. Other groups have confirmed these observations.

CSA is a potent immunosuppressant. It exerts its major effects by suppression of the early steps in T cell activation, leading to a failure to activate the transcription of "early activation" genes, such as those encoding for cytokines[11]. CSA may also affect function of macrophages, including production of IL-6[12], IL-1, and TNF-α[13]. In addition, CSA has been shown to inhibit expression of inducible nitric oxide synthase and cyclooxygenase-2 in macrophages, leading to decreased production of NO and prostaglandin $E_2$[14]. CSA also inhibits the expression of key cell surface costimulatory molecules, thus altering the antigen-presenting function of dendritic cells for T cell activation[15]. Thus, from a primary effect largely but not entirely confined to T cells, a wide variety of other effects are mediated, leading to profound and therapeutically useful immunosuppression, which explains the effectiveness of CSA in patients with hemophagocytic syndromes. However, mortality associated with these syndromes remains high.

In MAS, the clinical picture quickly evolves into a fulminant process often associated with acute hemorrhagic diathesis. The coagulation abnormalities observed in this syndrome have been interpreted by several authors as "consumption coagulopathy" triggered by the vasculitic component of the disease[16,17]. Others have proposed that severe liver dysfunction induced by macrophages infiltrating the liver parenchyma may lead to decreased production of fibrinogen and vitamin K dependent factors, thus increasing risk for bleeding[2,18]. Our patient developed severe acute hemorrhagic diathesis in the absence of signif-

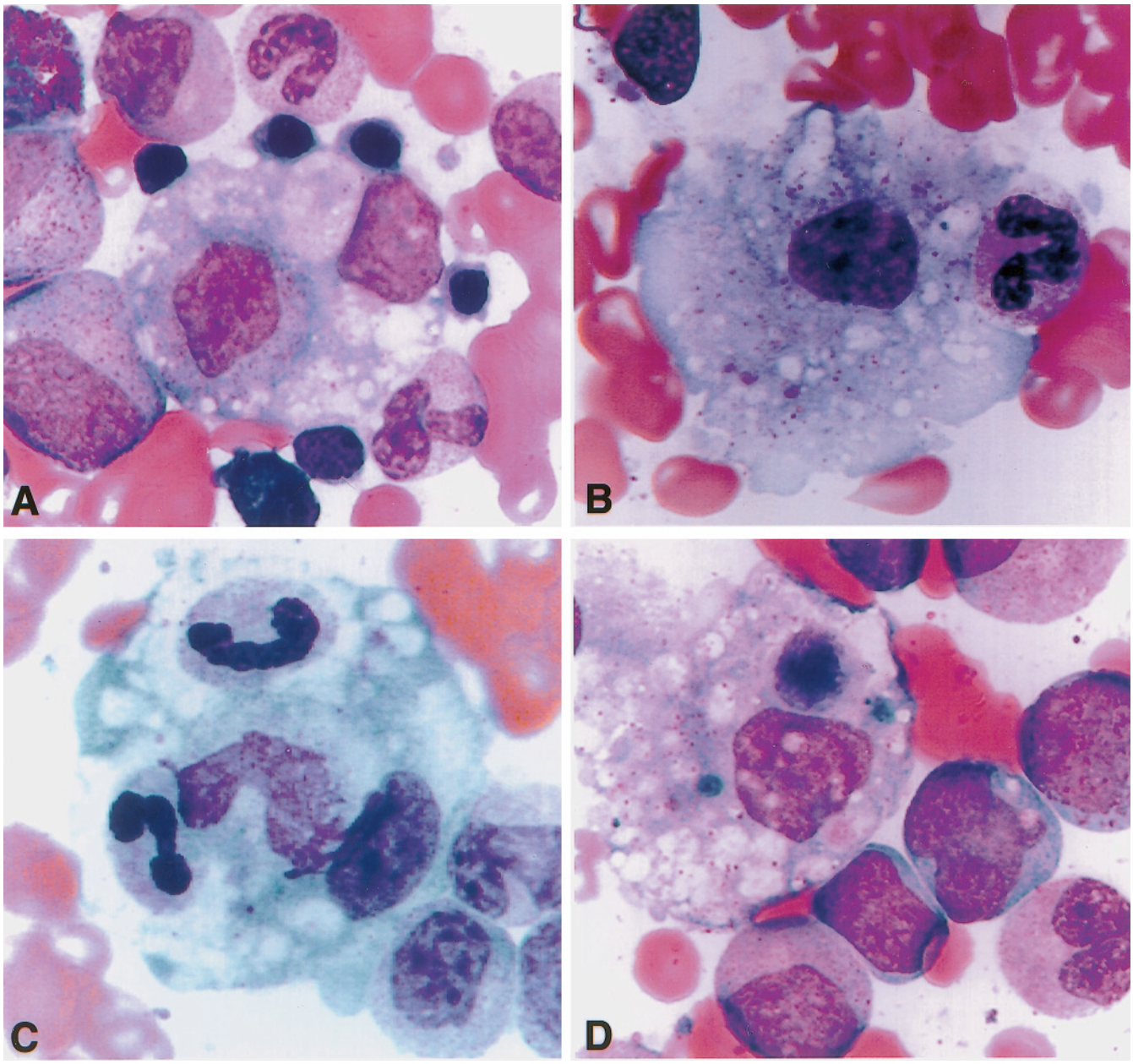


*Figure 1*. Bone marrow aspirate specimen revealing activated macrophages (H&E stain, original magnification ×1000). A. Myelocyte within activated macrophage. In addition, there are multiple adherent red blood cell and myeloid precursors. B. Activated macrophage engulfing a neutrophilic band form. C. Neutrophilic band forms and metamyelocyte within an activated macrophage. Nuclei of band forms appear condensed. D. Activated macrophage with hemosiderin deposits and a degenerating phagocytosed nucleated cell.

icant liver dysfunction. The vasculitic component in the skin lesions was inconsistent. The most striking feature was the intense perivascular infiltration of the dermis with activated macrophages and T cells, a pattern consistent with the observations described by Smith, *et al*[19]. There is ample evidence that activated macrophages themselves may have significant procoagulant activity[20-23]. Thus, in inflammatory response, they can be induced to produce fibrin stabilizing factor XIIIa[20] and hemostatic tissue factor[21,23]. Tissue factor expressed on monocytes and on TNF-α stimulated vascular endothelial cells has been shown to be central to the pathogenesis of disseminated intravascular coagulation accompanying septicemia[22]. Massive accumulation of activated macrophages in the skin lesions in our patient suggests that similar mechanisms may be relevant to the development of coagulation abnormalities in MAS as well. Regardless of the exact mechanism underlying coagulopathy, a rapid reversal of these events is critical to ensure a good overall outcome.

Excessive amounts of TNF-α have been implicated in the pathogenesis of disseminated intravascular coagulation in

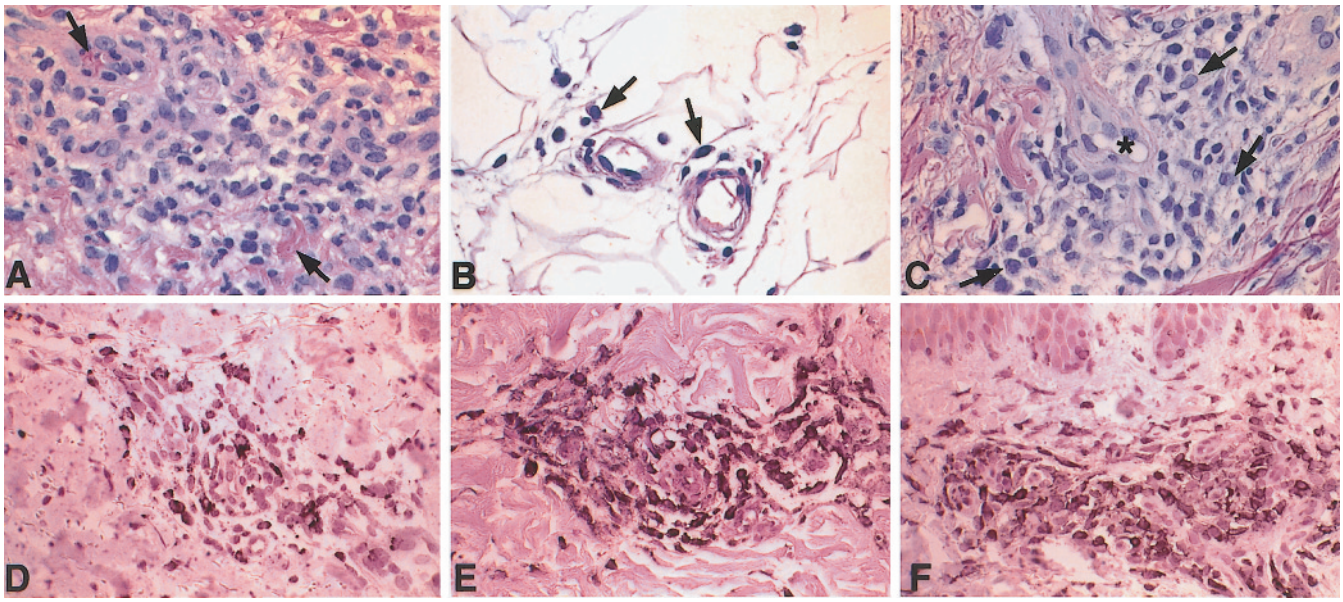


*Figure 2*. Skin biopsy specimen (A, B, C show H&E stain; D, E, F show immunostaining; original magnification ×250). A. Leukocytoclastic vasculitis in superficial dermis shows polymorphonuclear perivascular infiltrate with scattered neutrophils and nuclear debris. Arrows indicate vessel lumens. B. Slight mononuclear cell infiltrate (arrows) surrounding vessels in subcutaneous fat. C. Predominantly mononuclear cell perivascular infiltrate (arrows) in mid-dermis. *: vessel lumen. D. Stain for CD68+ cells. E. Stain for CD45RO+ cells. F. Stain for factor XIIIa positive cells. Immunoreactivity was detected using the avidin-biotin peroxidase method. The reaction product was enhanced with nickel sulfate.

both clinical[24] and experimental[25] situations. Increased serum levels of TNF-α, a major macrophage derived proinflammatory cytokine, have been described in several cases of MAS[2,26]. In addition, the importance of TNF-α in the development of coagulation abnormalities in sJRA was stressed by de Benedetti, *et al* in a study that demonstrated strong correlation between the serum levels of soluble TNF receptors and prolongation of partial thromboplastin time and decrease in prothrombin activity[27]. Thus fast blocking of TNF-α activity may provide another efficient way to reduce consequences of the excessive activation of macrophages, particularly at later stages of the syndrome. Excellent clinical response to etanercept in our patient supports this hypothesis. We conclude that etanercept may be an effective therapeutic agent in MAS in conjunction with corticosteroids, and function as a steroid sparing agent. The role of etanercept to function effectively used alone or in combination with CSA needs to be evaluated.

## ACKNOWLEDGMENT

The authors thank Murray H. Passo, MD, and David N. Glass, MD, for critically reviewing the manuscript, and Alicia Emley for assistance with the photomicrographs.

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