

- and other medical decisions concerning the end of life. *Health Policy* 1992;22:1-262.
38. Pijnenborg L, van der Maas PJ, van Delden JJM, Looman gCWN. Life-terminating acts without explicit request of patient. *Lancet* 1993;341:1196-9.
 39. de Kleine MJK, de Leeuw R, Kollée LAA, Berger HM. Voortzetten of staken van levensverlengend handelen bij pasgeborenen: een onderzoek in vier centra voor neonatale intensieve zorg. *Ned Tijdschr Geneeskd* 1993;137:496-500.
 40. Pearson EB, Bose CL, Kraybill EN. Decisions about futile treatment in an intensive care nursery. *NC Med J* 1995;56:462-6.
 41. Sheldon T. Dutch court convicts doctor of murder [news item]. *BMJ* 1995;310:1028.
 42. Dutch doctor free after prosecution proves murder case. *Am Med News*, December 4, 1995:4.
 43. Leenen HJJ, Ciesielski-Carlucci C. Force majeure (legal necessity): justification for active termination of life in the case of severely handicapped newborns after forgoing treatment. *Cam Q Healthc Ethics* 1993;2:271-4.
 44. Dupuis HM. Actively ending the life of a severely handicapped newborn: a Dutch ethicist's perspective. *Cam Q Healthc Ethics* 1993;2:275-80.
 45. Huibers AK. Beyond the threshold of life: treating and nontreating of critically ill newborns in the Netherlands. *J Legal Med* 1995;16:227-45.
 46. Dutch Society of Pediatrics. Doen of laten? Grenzen van het medisch handelen in de neonatologie. Utrecht: The Society, 1992.
 47. Committee on Bioethics, American Academy of Pediatrics. Guidelines on forgoing life-sustaining medical treatment. *Pediatrics* 1994;93:532-6.
 48. U.S. Department of Health and Human Services. Child abuse and neglect prevention and treatment program. *Federal Register* 1985;50:14878-92.
 49. Harrison H. The principles for family-centered neonatal care. *Pediatrics* 1993;92:643-50.

Macrophage activation syndrome in systemic juvenile rheumatoid arthritis

The macrophage activation syndrome, 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. In this issue of *The Journal of Pediatrics*, Mouy et al.¹ discuss a novel concept of therapeutic intervention when this syndrome is manifested as a complication of systemic juvenile rheumatoid arthritis. In the original description of this condition, Risdall et al.,² in 1979, noted that macrophage activation was secondary to an immune dysregulation induced in response to viral infections in an immunocompromised host. Clinically, MAS has similarities with other conditions, such as the accelerated phase of Chédiak-Higashi syndrome and familial hemophagocytic lymphohistiocytosis.^{3,4} The cause of these mixed lymphohistiocytic inflammatory diseases is poorly understood. However, the increase in the levels of both T-cell-derived and macrophage-derived cytokines, particularly tumor necrosis factor alpha and interferon gamma (initially known as macrophage-activating factor) is of particular interest.⁴

The clinical findings in MAS are dramatic. Typically, patients with a chronic condition are acutely ill at presentation with persistent fever, lymphadenopathy, hepatosplenomegaly, profound depression of all three blood cell lines (low leukocyte, erythrocyte, and platelet counts), low erythrocyte sedimentation rate, and elevated serum liver enzyme values. These patients also have prolonged prothrombin and partial thromboplastin times, hypofibrinogenemia, and low levels of vitamin K-dependent clotting factors; in addition, they often have easy bruising and mucosal bleeding when first seen. Fibrin degradation products may be present as well. The pathognomonic features of this syndrome are

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ESR	Erythrocyte sedimentation rate
JRA	Juvenile rheumatoid arthritis
MAS	Macrophage activation syndrome

found on bone marrow aspiration: numerous, well-differentiated macrophages (or histiocytes) actively phagocytosing hematopoietic elements.⁵ Such cells may be found in various organs and may account for many of the systemic features. For this reason the term *reactive hemophagocytosis*

cytic lymphohistiocytosis has been used to classify this condition.

More recently, hematophagocytic lymphohistiocytosis has been associated with systemic JRA.⁶⁻⁸ In 1985 a few reports from various countries described a number of patients with long-standing systemic JRA who at presentation had persistent fever, mental status changes, hepatosplenomegaly, increased serum levels of liver enzymes, and a sharp fall in blood cell counts and ESR in association with hypofibrinogenemia, prolonged prothrombin time, and easy bleeding. In most of these instances, bone marrow aspiration revealed the presence of hematophagocytic histiocytes. The acute deterioration in the patients was preceded by either a viral infection or major changes in therapy, usually administration of gold preparations or nonsteroidal antiinflammatory drugs.⁷

The coagulation abnormality seen in these patients appears to represent a spectrum of clinical problems. Silverman et al.⁹ described seven patients with hematologic abnormalities similar to those observed in MAS. The clinical findings at that time were interpreted as "consumption coagulopathy," although no clinical signs of thrombosis were reported in the patients described. It was suggested that intravascular coagulation might result from decreased production of antiaggregative prostaglandin I₂ (prostaglandin) by endothelial cells and that such a decrease might be induced by nonsteroidal antiinflammatory drugs routinely used in the treatment of JRA.

In contrast, Scott et al.¹⁰ observed two patients with systemic JRA who had clinical signs of disseminated intravascular coagulation. One patient had fulminant purpura, which resulted in peripheral gangrene. The clinical findings in these two patients were explained by activation of the coagulation system. Scott et al., in their study of a large group of patients with JRA, showed that activation of intravascular coagulation was common in systemic JRA as evidenced by high levels of fibrinopeptide A, a sensitive measure of intravascular thrombus generation. The authors attributed the abnormalities to damage to endothelial cells associated with the vasculitic component of systemic JRA.

Pouchot et al.,¹¹ in a review of 62 cases of adult-onset Still disease (a disease identical to systemic JRA in patients >16 years of age), noted two patients with evidence of an acute hemorrhagic diathesis caused by disseminated intravascular coagulation.

Most of the described clinical findings, including pancytopenia with phagocytosis of bone marrow-derived elements and liver abnormalities, could be explained by the presence of histiocytic infiltrates. However, these histiocytic infil-

trates do not account for the entire spectrum of coagulation abnormalities, some of which may be related, at least in part, to liver dysfunction induced by macrophages infiltrating the liver parenchyma and secreting proinflammatory cytokines.³ This would lead to a decreased production of fibrinogen and vitamin K-dependent clotting factors and would increase the risk of bleeding. In addition, Prieur and Stephan³ suggested that activated macrophages release proteases that activate plasminogen, which leads to the formation of plasmin; this could account for the appearance of fibrin degradation products in the systemic circulation.

Smith et al.,¹² in a description of skin biopsy specimens obtained from 10 patients with cutaneous manifestations of hematophagocytic syndrome, noted the presence of microthrombi and endothelial proliferation in almost half of the patients. A possible explanation for the phenomenon is that a functionally impaired liver may have a decreased ability to degrade procoagulant factors. In addition, activated macrophages release tumor necrosis factor, which, when present in excessive amounts, is capable of inducing intravascular coagulation.³ However, the magnitude of thrombotic events in some patients¹⁰ implies that other mechanisms may be involved. The damage to endothelial cells caused by vasculitis may induce disseminated intravascular coagulation with subsequent development of consumption coagulopathy, which suggests a mechanism different from that in a "pure hematophagocytic syndrome." In summary, the coagulation abnormalities that may develop acutely in patients with systemic JRA reflect heterogeneous, underlying pathogenic mechanisms. There appears to be an overlap between two syndromes: one induced by activation of macrophages and the other caused by intravascular coagulation triggered by vasculitis.

MAS is a serious complication of systemic JRA associated with considerable morbidity and death. Therefore the early recognition of this syndrome and immediate therapeutic intervention to produce a rapid clinical response are critical. MAS can be clinically differentiated from a typical exacerbation of systemic JRA by several features that are apparent early in the course of this syndrome. Patients with an exacerbation of systemic JRA usually have a spiking daily (quotidian) or twice-daily (double quotidian) fever, evanescent rash, generalized lymphadenopathy, and hepatosplenomegaly. Symptoms of polyserositis and arthritis may also be present. A marked polymorphonuclear leukocytosis, thrombocytosis, and increased ESR with hyperfibrinogenemia are common features that reflect the activity of inflammation. Mild elevation of liver enzyme activity is also common. In contrast, persistent unremitting fever (which is different

from the quotidian fever of systemic JRA), mental status changes, and moderately elevated liver enzyme activity (occasionally seen with hyperbilirubinemia), accompanied by a sharp fall in ESR in association with hypofibrinogenemia, relative leukopenia, thrombocytopenia, prolonged prothrombin time, and easy bleeding, should raise suspicion of MAS. The diagnosis is confirmed by demonstration of hematomphagocytic histiocytes in bone marrow and lymph nodes.

The article by Mouy et al.,¹ in this issue of The Journal, reports the use of cyclosporine A to treat MAS that was manifested as a complication of systemic JRA and was refractory to corticosteroid management. Five patients with juvenile arthritis (four with systemic JRA, one with polyarticular JRA) had episodes of acute hematologic abnormalities characteristic of MAS with no apparent clinical signs of thrombosis. In two patients the presence of hematomphagocytic lymphohistiocytosis was confirmed histologically, suggesting that the clinical features were likely to be related to the activation of macrophages. Therefore the dysregulation of macrophage-lymphocyte interactions, with subsequent release of cytokines (e.g., tumor necrosis factor alpha, interferon gamma), was likely to be a major pathogenic mechanism in these patients.

Previously, cyclosporine A has been used successfully in the treatment of familial hematomphagocytic lymphohistiocytosis.¹³ Strong similarities between this disease and MAS accompanying systemic JRA provided a rationale for the authors to use cyclosporine A in the patients they described.

Cyclosporine A is a potent immunosuppressant. It exerts its major effects by the suppression of the early steps in T-cell activation, leading to a failure to activate the transcription of "early" genes, such as those encoding for cytokines. Thus, through a primary effect confined largely to T cells, a wide variety of secondary effects are mediated, leading to profound and therapeutically useful immune suppression.¹⁴

In all five patients the administration of cyclosporine A (without manipulations in steroid therapy) resulted in a rapid resolution of symptoms. In each case, fever resolved within 24 hours and hematologic disturbances within a few days. High-dose corticosteroid therapy is initially used to treat MAS, but in some patients this condition appears to be corticosteroid resistant. The data presented by Mouy et al.¹ show that when hematologic abnormalities are induced by macrophage activation, cyclosporine A not only may provide rapid control of symptoms but also may allow avoidance of excessive use of corticosteroids. In cases that appear resistant to corticoster-

oid treatment, early administration of cyclosporine A may be lifesaving.

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REFERENCES

1. Mouy R, Stephan J-L, Pillet P, Haddad E, Hubert P, Prieur AM. Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile rheumatoid arthritis: report of five cases. *J Pediatr* 1996;129:750-4.
2. Risdall RJ, McKenna RW, Nesbit ME, Drivit W, Balfour HH Jr, Simmons RL, et al. Virus-associated hematomphagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. *Cancer* 1979;44:993-1002.
3. Prieur AM, Stephan J-L. Macrophage activation syndrome in children with joint diseases. *Rev Rhum Engl Ed* 1994;61:385-8.
4. Henter J-I, Elinder G, Soder O, Hansson M, Andersson B, Andersson U. Hypercytokinemia in familial hematomphagocytic lymphohistiocytosis. *Blood* 1991;78:2918-22.
5. Reiner AP, Spivak JL. Hematomphagocytic histiocytosis: a report of 23 new patients and a review of the literature. *Medicine* 1988;67:369-88.
6. Heaton DC, Moller PW. Still's disease associated with Cox-sackie infection and haematomphagocytic syndrome. *Ann Rheum Dis* 1985;44:341-4.
7. Hadchouel M, Prieur AM, Griscelli C. Acute hemorrhagic, hepatic, and neurologic manifestations in juvenile rheumatoid arthritis: possible relationship to drug or infection. *J Pediatr* 1985;106:561-6.
8. Morris JA, Adamson AR, Holt PJL, Davson J. Still's disease and the virus-associated haematomphagocytic syndrome. *Ann Rheum Dis* 1985;44:349-53.
9. Silverman ED, Miller JJ, Bernstein B, Shafai T. Consumption coagulopathy associated with systemic juvenile rheumatoid arthritis. *J Pediatr* 1983;103:872-6.
10. Scott JP, Gerber P, Maryjowski MC, Pachman LM. Evidence for intravascular coagulation in systemic onset, but not polyarticular, juvenile rheumatoid arthritis. *Arthritis Rheum* 1985;28:256-61.
11. Pouchot J, Sampalis JS, Beaudet F et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine* 1991;70:118-36.
12. Smith KJ, Skelton HG, Yeager J, Angritt P, Wagner K, James WD, et al. Cutaneous histopathologic, immunohistochemical, and clinical manifestations in patients with hematomphagocytic syndrome. *Arch Dermatol* 1992;128:193-200.
13. Stephan JL, Donadieu J, Le Deist F, Blanche S, Griscelli C, Fischer A. Treatment of familial hematomphagocytic lymphohistiocytosis with anti-thymocyte globulins, steroids and cyclosporin A. *Blood* 1993;82:2319-23.
14. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK506. *Immunol Today* 1992;13:136-42.