Case Report

Does Red-Man Reaction Stimulate Macrophage Activation Syndrome in Children with Systemic Juvenile Idiopathic Arthritis?

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ABSTRACT. Macrophage activation syndrome (MAS) is a major cause of death in patients with systemic juvenile idiopathic arthritis (JIA). We describe 4 patients who developed MAS during or after vancomycin treatment. Vancomycin should be used with great care in patients with systemic JIA. (J Rheumatol 2007;34:2491–4)

Key Indexing Terms:
RED-MAN SYNDROME
MACROPHAGE ACTIVATION SYNDROME
SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS
VANCOMYCIN

Systemic-onset juvenile idiopathic arthritis (JIA) is characterized by chronic arthritis with high spiking fever, salmon-pink evanescent rash, hepatosplenomegaly, lymphadenopathy, and serositis[1]. Most deaths of patients with systemic JIA are secondary to macrophage activation syndrome (MAS), immunosuppression-related infection, or cardiac complications[2]. MAS can be precipitated by virtually any infectious agent and modifications in drug therapy[3].

We describe 4 patients who developed MAS during or after vancomycin treatment.

CASE REPORTS

Patient 1. A 9-year-old boy diagnosed with systemic JIA 2 years previously was admitted with a high spiking fever, rash, hepatosplenomegaly, and lymphadenopathy. There were no findings of MAS. Echocardiographic examination showed he had a bicuspid aortic valve and slight aortic insufficiency. He was treated with aspirin (80 mg/kg/day). Although there was no evidence of infective endocarditis on echocardiographic examination, he was treated for infective endocarditis. Vancomycin and amikacin were prescribed because methicillin-resistant coagulase-negative *Staphylococcus* was grown on hemocultures. He was without fever and rash for 5 days but, on the sixth day of vancomycin infusion, fever and characteristic rash suddenly reappeared, and hypotension developed. The rash did not respond to antihistamine therapy. In the followup period, massive gastrointestinal bleeding occurred. He began to lose consciousness. Bicytopenia and biochemical abnormalities were found and his bone marrow revealed hemophagocytosis. Massive blood-product support was given: hemorrhage was controlled by factor VII (4 doses) and fibrinogen replacement (3 doses × 1 g). Prothrombin time (PT) and activated partial thromboplastin time (aPTT) reduced to within normal levels by the seventh day of intensive care and the necessity for blood transfusions decreased. After infections were excluded, pulse steroid, cyclophosphamide, and intravenous immunoglobulin (IVIG) therapies were given, but the patient died due to repeated severe lung infection, renal failure, and severe hemorrhage.

Patient 2. A 13-year-old boy diagnosed with systemic JIA 6 years previously was admitted with chest pain and cough. He had been treated with naproxen (10 mg/kg/day), methotrexate (MTX; 10 mg/m^2/day), and methylprednisolone (0.5 mg/kg/day). He had slight pericardial effusion on echocardiographic evaluation, but there were no findings of tamponade or fibrin. Although no proven bacterial or viral agents were found, vancomycin and ceftriaxone were prescribed. However, on the fourth day after vancomycin infusion, fever, flushing of the face, rash on the trunk, respiratory distress, nausea, and vomiting occurred, and hypotension developed. In the followup period, shoulder pain developed, and bleeding occurred from the catheter site, upper and lower gastrointestinal (GI) system, and urinary system. His pericardial effusion was not increased and his left ventricular functions were found to have returned to normal. However, his renal and liver functions worsened (Table 1). Bone marrow examination revealed hemophagocytosis and in the followup period renal failure developed. He underwent hemodialysis but peritonitis occurred and he lapsed into a comatose state. Bleeding from the catheter site and upper and lower GI system reappeared. A hematoma was found in the bladder. Although intensive support (fibrinogen, fresh-frozen plasma, pulse steroid therapy, IVIG, etoposide, granulocyte-colony stimulating factor, antifungal) was given, the patient died on the 14th day of admission. There were no infections isolated from the pericardial effusion during the postmortem examination.

Patient 3. A 7-year-old girl diagnosed with systemic JIA 3 years previously was admitted with cough, fever, rash, bilateral subcutaneous nodules on the extensor side of her arms, hepatomegaly (4 cm), and splenomegaly (2 cm). She had been treated with aspirin (80 mg/kg/day), MTX (10 mg/m^2/week), and methylprednisolone (0.5 mg/kg/day). Phenoxymethylpenicillin was prescribed for an upper respiratory tract infection but during the fourth day of admission, respiratory symptoms increased and pneumonic infiltration was seen on chest radiograph. Vancomycin and gentamicin were prescribed for pneumonia. On the tenth day after vancomycin infusion, characteristic rash, respiratory distress, nausea, and hypotension developed. Liver and renal functions worsened, and pancytopenia and intestinal bleeding occurred. Tumor

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Table 1. Patients' clinical and laboratory findings.

MAS Diagnostic Criteria*	Case 1		Case 2		Case 3		Case 4		Normal
	Pre-MAS	Post-MAS	Pre-MAS	Post-MAS	Pre-MAS	Post-MAS	Pre-MAS	Post-MAS	Values[17]
Fever	+	+	+	+	+	+	+	+	—
Splenomegaly	+	+	–	+	+	+	–	+	—
Cytopenia									
White blood cell count, mm^3	7850	3860	19070	750	10900	1200	4170	1200	—
Hemoglobin, g/dl	8.6	5.3	10.3	5.4	9.6	4.9	11.2	5.9	11.5–16
Hematocrit, %	27.2	15.9	32.1	15.6	31.5	17	34.9	18.2	35–46
Platelets ($\times 10^3/mm^3$)	202	36	434	21	423	97	37	35	150–400
Hypertriglyceride, mg/dl	98	574	233	531	177	198	180	498	31–138
Hypofibrinogenemia, mg/dl	343.6	27.8	45	26	759	357	160	146	200–400
Ferritin, ng/ml	1223	43058	4884	15834	797.4	211	898.9	26026	7–140
Hemophagocytosis (bone marrow)	**	+	**	+	**	+	**	+	—
Supportive findings									
Cerebral symtoms	–	–	–	–	–	–	–	+	—
Conjugated hyperbilirubinemia, mg/dl	0.6	3.1	0.06	9.0	0.3	2.3	0.91	7.44	0–0.2
Aspartate, IU/l	47	489	17	5417	31	48	18	2600	5–55
Alanine, IU/l	13	135	9	1447	20	20	30	265	5–45
Lactate dehydrogenase, IU/l	385	1361	684	2300	1367	1402	267	14010	120–500
C-reactive protein, mg/l	35.4	171.4	160	195.5	20.8	112	121	142	< 5
ESR, mm/h	90	3	76	45	75	45	50	23	< 20

* sCD25 and NK function tests not available; ** bone marrow examination at admission not available. MAS: macrophage activation syndrome; Pre-MAS: on admission; Post-MAS: after symptoms worsened.

lysis syndrome was suspected due to sudden clinical and laboratory worsening, and so her medications were discontinued. However, her clinical state did not change. Bone marrow aspirations and biopsy revealed hemophagocytosis. The symptoms improved with IVIG, dexamethasone, netilmycin, methicillin, imipenem, and fluconazole therapies by the 34th day after the clinical worsening. She has been followed up for 5 years and has experienced only arthritis symptoms.

Patient 4. A 7-year-old boy diagnosed with systemic JIA 2 years previously was admitted with uncontrolled fever, arthritis, and heart murmur. He was treated with naproxen (15 mg/kg/day) and methylprednisolone (1 mg/kg/day). Echocardiographic examination showed he had slight aortic and mitral insufficiency. He was treated for infective endocarditis. On hemoculture, *Streptococcus hemolyticus* was found and vancomycin plus ceftriaxone treatment was begun. This was changed to vancomycin plus imipenem on the fourth day, and amikacin was added on the seventh day due to persistent fever. Disseminated characteristic rash, fever, respiratory distress, and hypotension developed after vancomycin infusion on the ninth day. During the febrile period, 5-minute tonic-clonic convulsion occurred and intestinal bleeding also became evident. Bone marrow examination revealed hemophagocytosis. In the followup period, his respiratory pattern worsened, oxygen saturation decreased, and renal failure developed. He was treated for multiorgan failure in the intensive care unit. He was supported by a ventilator and hemodialysis. His condition improved after pulse methylprednisolone and IVIG therapies. He has been followed for 5 years and continues to be treated with naproxen, methylprednisolone, and MTX. Due to persistent arthritis, tumor necrosis factor-α (TNF-α) antagonist (etanercept) has been added to his treatment. He is now doing well.

DISCUSSION

One of the most important complications of systemic JIA is its association with MAS. This life-threatening complication is caused by excessive activation and proliferation of T cells and macrophages. Such activation leads to an overwhelming systemic inflammatory reaction[3,4] that generally develops in the earlier phases of the underlying disease and may occasionally be the presenting manifestation, although occurrence as late as 14 years after diagnosis has been reported. In our patients, MAS developed at least 2 years into the followup period. In most patients, the primary disease is clinically active at the onset of MAS, but the syndrome may also develop during quiescent phases[4].

According to Maeno, *et al*[5] bone marrow may be an essential organ in the pathogenesis of systemic JIA. Reduced perforin expression might be responsible for the increased incidence of MAS in systemic JIA. It is likely to be induced by certain cytokines or chemokines that are abundant in active systemic JIA[6]. In the study by Grom, *et al*[7] natural killer (NK) cells, NKT cells, and CD8+ cells were assessed for perforin expression by flow cytometry, and they found mildly increased levels of perforin expression in CD8+ and CD56+ cytotoxic cells. NK cell dysfunction is a distinguishing feature of systemic JIA and MAS[8]. Typically, MAS patients with a chronic disease become acutely ill and present with fever, lymphadenopathy, hepatosplenomegaly, profound depression of one or more blood cell lines, low erythrocyte sedimentation rate (ESR), raised liver cell enzymes, and abnormalities of the clotting profile[9,10]. Hyperferritinemia has been recognized as an important laboratory marker of MAS[11]. Rapid elevation of serum ferritin concentrations may indicate transition from systemic onset disease to MAS[12].

The life-threatening complication of MAS is caused by excessive activation and proliferation of T cells and macrophages. Bone marrow reveals numerous well differenti-

ated macrophages actively phagocytosing hematopoietic elements[3,4,13]. However, it should be noted that hemophagocytosis is only one of the diagnostic criteria for MAS and is not necessary for a diagnosis to be made if other criteria are present, e.g., fever, pancytopenia, hyperferritinemia, etc.

In several reports, triggering of MAS coincided with modifications in drug therapy, most notably administration of gold preparations, MTX, sulfasalazine, and TNF-blocking agents[3]. These associations, however, should be interpreted cautiously because many of the described patients had very active underlying rheumatic disease and MAS might already have been developing when the drug therapies were begun. Our patients were admitted due to findings of infection and were prescribed antibiotics. Some of them had findings of active systemic JIA but their rheumatic disease was controlled by antiinflammatory therapy. We were only able to confirm the precipitating agent as coagulase-negative *Staphylococcus* in Patient 1 and *S. hemolyticus* in Patient 4 during the pre-MAS period. Our patients' initial ESR were high but, after clinical worsening, they decreased. In a patient with persistently active systemic JIA, a fall in the ESR and platelet count, particularly in combination with an increase in D-dimer levels, should raise suspicion of impending MAS[3]. No drug treatment modifications were made and no antiinflammatory drugs were administered. We suspect our patients' symptoms were linked to vancomycin infusion. The patients' initial symptoms were very severe and the nurses were accused of administering an incorrect drug infusion by the families, although the therapies were administered at the correct dosage. The most important complication of vancomycin infusion is red-man syndrome, i.e., sudden hypotension, flushing, and/or maculopapular/erythematous rash on the face, neck, chest, and upper extremities. Rarely, cardiac arrest or seizures have been reported to occur: our Patient 4 experienced tonic-clonic convulsion during the febrile period[14]. However, convulsion is a central nervous system (CNS) MAS symptom and we could not examine the cerebrospinal fluid[15]. The reaction usually begins a few minutes after start of infusion, but may not occur until after completion of infusion, and usually resolves spontaneously one to several hours after discontinuation[14]. Red-man syndrome has been considered to be a mild reaction, occurring primarily on the first dose, with subsequent reactions, if present, of lesser severity. However, the reaction in our patients developed during Day 4 to Day 10. Although this timing distinguishes it from a classic vancomycin reaction, we believe it to be a delayed red-man reaction, the delay possibly being caused by excessive inflammatory processing activation. Vancomycin-induced hypotension appears to result from a negative inotropic and vasodilating action produced in part by the release of histamine, which is directly related to the infusion rate[14]. It was thought that red-man syndrome occurred secondary to impurities in the formulation. Our patients were receiving concurrent antiinflammatory and antibiotic therapies. Systemic inflammation continued, but MAS symptoms were evident after red-man syndrome.

The immediate aim of treatment is to suppress the severe hyperinflammation of MAS that is responsible for the life-threatening symptoms. Fever, pancytopenia, liver damage, and CNS symptoms can all be attributed to the action of cytokines released by activated lymphocytes and histiocytes. The second aim is to kill pathogen-infected antigen-presenting cells and thus remove the stimulus for the ongoing but ineffective activation of NK and T-suppressor cells[15]. The treatment overview of the HLH-2004 protocol consists of cyclosporin A, dexamethasone, and etoposide initially[16]. However, for patients who have moderate symptoms, immunosuppressive and immunomodulatory drugs such as corticosteroids, immunoglobulins, or cyclosporin A may be given initially[15]. In our clinic, to achieve rapid reversal of coagulation abnormalities, we administered intravenous methylprednisolone pulse therapy (30 mg/kg/day for 5 consecutive days), followed by 2–3 mg/kg/day in 2 divided doses, and IVIG therapy. Immunosuppressive treatment such as cyclophosphamide, azathioprine, and cyclosporine was also given.

We believe that our cases raise a question over the use of vancomycin in children with systemic JIA. Our cases suggest that the red-man reaction may stimulate the onset of MAS and that vancomycin should be used with caution when treating patients with systemic JIA.

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