Hypocomplementemia Associated with Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis and Adult Onset Still's Disease: 3 Cases

To the Editor:

Macrophage activation syndrome (MAS) is a life-threatening complication seen in association with childhood inflammatory diseases, most commonly in systemic juvenile idiopathic arthritis (sJIA)[1,2,3]. MAS has also been described in the setting of adult-onset Still's disease (AOSD), systemic lupus erythematosus, drug reactions, and viral infections[4,5].

Decrease in C3 has been documented in patients with lupus and MAS[4]; however, to our knowledge, hypocomplementemia has not been previously described as associated with MAS in sJIA or AOSD. We describe 2 patients with sJIA, and a third with AOSD, who developed MAS with hypocomplementemia during the acute phase of illness.

Patient 1, a 9-year-old boy, presented with high quotidian fever, evanescent rash, and arthritis. He had leukocytosis (24 × 10^9/l) with elevated markers of inflammation: erythrocyte sedimentation rate (ESR) 52 mm/h and C-reactive protein (CRP) 17.3 mg/dl. Liver enzymes and renal function were normal. Ferritin was 5623 ng/ml. Serologic tests for Epstein-Barr virus, parvovirus, cytomegalovirus, Lyme disease, mycoplasma, and group A streptococcus were negative. Complement levels, obtained by the primary intensive care team, showed slightly increased C3 (166 mg/dl) and normal C4 (32 mg/dl). He was discharged with a diagnosis of new-onset sJIA and prescribed indomethacin. Several days later, he returned to clinic with worsening symptoms and petechial rash. Laboratory results are shown in Table 1. Ferritin was markedly elevated. C3 and C4 were profoundly decreased. Aspartate aminotransferase (AST) was mildly elevated and platelets declined over several days from 522 × 10^9/l to 167 × 10^9/l. Antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-Smith, anti-RNP, anti-Ro, and anti-La autoantibodies were negative. He was diagnosed with MAS secondary to sJIA and treated with pulses of methylprednisolone (30 mg/kg/dose) and intravenous immunoglobulin (IVIG; 2 g/kg); he had improvement of symptoms and decrease of ferritin levels to 1533 ng/ml. Complement levels and ferritin measured 2 weeks after steroid pulse had normalized. He has been managed subsequently with anakinra. Since starting anakinra, he has been stable, with occasional flares of mild rash and arthritis due to periodic noncompliance.

Table 1. Laboratory characteristics of patients with macrophage activation system in a setting of sJIA/AOSD during acute and recovery phase of illness. Normal ranges in parentheses.

Characteristic	Patient 1	Patient 2	Patient 3
Ferritin (10–280 ng/ml)			
Acute MAS	> 5000	6,129	12,558
Recovery	245	75	356
C3 (79–152 mg/dl)			
Acute MAS	43	74	20
Recovery	186	152	159
C4 (16–38 IU/l)			
Acute MAS	< 10	< 5	< 5
Recovery	32	21	23
AST (10–40 IU/l)			
Acute MAS	76	70	208
Recovery	25	13	19
International normalized ratio (0.8–1.2)			
Acute MAS	1.2	1.6	1.3
Recovery	1.1	1.2	1.0
White blood cell count (4.5–14.5 × 10^9/l)			
Acute MAS	24	34.6	13.5
Recovery	15.6	6.5	12.1
Platelets (156–369 × 10^9/l)			
Acute MAS	167	5–80 (range)	43
Recovery	434	432	352
CRP (0–0.74 mg/dl)			
Acute MAS	45	18.72	31.2
Recovery	0.22	0.25	2.5

sJIA: systemic juvenile idiopathic arthritis; AOSD: adult-onset Still's disease.

Patient 2, an 11-year-old girl, presented with high fever, left ankle arthritis, and abdominal pain. She was transferred to our institution from an outside hospital with a fine erythematous, blanching rash and respiratory distress. She arrived in shock with hypotension requiring intubation. She continued to have high fevers (highest 41.3°C) and rash. Initial and subsequent laboratory results are shown in Table 1. They were significant for leukocytosis, elevated ferritin, and elevated markers of inflammation. C3 and C4 concentrations obtained due to unclear clinical setting were low. A bone marrow biopsy showed hemophagocytosis. Extensive evaluation for infectious agents was negative, with the exception of positive serology for adenovirus at the lowest detectable titer. ANA and specific lupus autoantibodies were negative. She was diagnosed with MAS and treated with pulses of methylprednisolone (30 mg/kg/dose) and IVIG, followed by high-dose oral prednisone (2 mg/kg/day). Fevers and hypotension resolved. She developed a large pericardial effusion that required drainage. Following this, she developed thrombocytopenia, with persistent platelet counts of 5 to 25 × 10^9/l. At this point complement levels were found to have normalized. Due to persistent thrombocytopenia, cyclosporine was begun at 2 mg/kg/day, which resulted in improvement of platelet counts. Several months later, after recurrence of pericarditis and fever, she was given anakinra. Since starting anakinra, she has been stable. Soluble CD25 level, near the end of disease course, was 11,670 pg/ml (normal < 2500 pg/ml), and natural killer function was decreased, at 0.3 lytic units.

Patient 3, a 17-year-old girl, presented with fever, arthralgia, wrist swelling, and rash. Initial laboratory findings were notable for elevated markers of inflammation (ESR 40 mm/h and CRP 16.44 mg/dl). She was initially managed with indomethacin, but over 2 weeks she developed quotidian fever and evanescent rash with Koebner phenomenon, and began to appear more ill. Laboratory evaluation at that time showed acute anemia (hemoglobin 8.0 g/dl) and thrombocytopenia (platelet count 95 × 10^9/l), and acute renal and liver dysfunction, with creatinine 1.7 mg/dl, alanine aminotransferase 153 IU/l, aspartate aminotransferase 208 IU/l. She developed hypotension, acute respiratory distress, and mild cardiac dysfunction. Initial and subsequent laboratory results are shown in Table 1. Complement levels, obtained due to observations of previous patients with hypocomplementemia and MAS, were markedly decreased. Ferritin was elevated. Bone marrow biopsy did not show hemophagocytosis, but rare hemophagocytosis was seen on a peripheral blood smear. An extensive infectious investigation was negative. ANA, ANCA, and all extractable nuclear antigens were negative. She was diagnosed with Still's disease with progression to MAS and was treated with pulse methylprednisolone 30 mg/kg/dose for 3 days, followed by high-dose oral prednisone (30 mg BID), with improvement of clinical condition within days, decline in liver enzymes, and normalization of serum creatinine. She had normalization of complement levels and ferritin by 6 weeks after her critical illness. She was subsequently tapered slowly on steroids, and continues a low maintenance dose.

The diagnosis of MAS is often a challenge as it may mimic a flare of the underlying disease. Accurate and reasonably rapid discrimination of MAS from other mimicking conditions is important to avoid delay of treatment. Occult hemophagocytosis at high rates has been reported in patients with sJIA without other evidence of MAS[6]. Diagnostic guidelines specific for MAS complicating sJIA were proposed by Ravelli, *et al* in 2005[7]. However, these criteria have not yet been validated. Marked hyperferritinemia (> 10,000 ng/ml) has also been found to be a strong indicator of MAS[8].

Hypocomplementemia was not among the 13 laboratory criteria evaluated by Ravelli and colleagues, and it has not been noted as a feature of MAS complicating sJIA in our review of the literature. Further study may show this to be a useful laboratory discriminator in the critical phase of illness. Addition of hypocomplementemia as one of the discriminating features of MAS complicating sJIA may add to the overall sensitivity and specificity of diagnostic criteria.

The molecular mechanisms underlying hypocomplementemia may be related to the markedly increased production of a urokinase-like plasminogen activator by activated macrophages in MAS[9]. Plasminogen activator converts plasminogen to form plasmin, which is believed to activate the complement system[10,11].

Further clinical cases may show hypocomplementemia to be a feature of MAS associated with sJIA, and to be useful as a discriminating laboratory feature for cases progressing to MAS.

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J Rheumatol 2011;38:2; doi:10.3899/jrheum.100833