Macrophage activation syndrome, an important differential diagnosis for septic shock

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Abstract. Macrophage activation syndrome (MAS) is a rare and life threatening complication of rheumatic diseases. It is seen most frequently in association with systemic onset juvenile idiopathic arthritis and less commonly in other rheumatic diseases of childhood including systemic lupus erythematosus. Recognition of MAS in patients with rheumatic diseases is often challenging as it may mimic the clinical features of the underlying disease. Sometimes MAS can be the mode of initial presentation adding to the diagnostic complexity. We describe two cases of MAS in association with systemic onset juvenile idiopathic arthritis who presented with a clinical picture suggestive of septic shock. The Internal Review Board at Shands Children's Hospital and the University of Florida waived the need for approval for these case reports.

Keywords: Systemic onset juvenile idiopathic arthritis, macrophage activation syndrome, rheumatic disease

1. Introduction

Macrophage activation syndrome (MAS) is a term used most to describe hemophagocytosis associated with rheumatic diseases. Although it is seen in many rheumatic conditions, it is seen more commonly with systemic onset juvenile idiopathic arthritis (SoJIA). It is believed to be caused by the uncontrolled activation and proliferation of T cells and excessive activation of macrophages, resulting in varied symptoms due to multi-organ involvement. MAS can be difficult to diagnose early and is associated with significant mortality, between 8–22% [1]. We describe two cases

of MAS in association with SoJIA presented to our institute.

2. Case reports

2.1. Case 1

A 3-year-old Caucasian female presented to the pediatrician with high-grade fever and pharyngitis; antibiotics were prescribed for suspected upper respiratory tract infection, and she was discharged home. However, she continued to have spiking fevers and was evaluated in the emergency department 3 days (d) later. She was diagnosed with urinary tract infection based on the urinalysis, which showed positive nitrites, positive leukocyte esterase, with a total 54/hpf white blood cells. She was sent home with a sulfamethoxazole/trimethoprim

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prescription. She returned the following day with persistent fever consistently above 38.3°C and new-onset abdominal pain. In the emergency room, she appeared ill with vital signs showing tachycardia (pulse 173/min), temperature of 39.1°C, normal blood pressure (128/65 mmHg), and respiratory rate 28/min. She had significant abdominal tenderness, but the rest of the physical examination was normal. Her initial evaluation included an urgent abdominal computerized tomography (CT), which ruled out acute surgical abdomen. Ultrasound of abdomen and kidneys was done, which was unremarkable. She was admitted to the pediatric floor for possible urosepsis. She was started on ceftriaxone, and vancomycin. She continued to have high-grade fevers despite the treatment with antibiotics and antipyretics. Twenty-four hours (h) after her initial hospitalization, she deteriorated clinically and had worsening of tachycardia (pulse up to 180/min), warm extremities, bounding pulses, and widened pulse pressure (90/30 mmHg). She was transferred to the pediatric intensive care unit (PICU) in view of her hemodynamic instability and compensated shock. Physical examination at the time of admission to PICU showed diffuse abdominal tenderness but no guarding or rebound tenderness. The patient did not demonstrate hepatosplenomegaly, gallop, cardiac murmurs, rash, or arthritis. Initial management in PICU included fluid resuscitation and vasopressors including dopamine and norepinephrine. Antibiotics (ceftriaxone, vancomycin) were continued with the addition of metronidazole to broaden coverage. Ongoing investigations revealed leukocytosis of 13,500/mm³ with 78% neutrophils and 18% bands and elevated C-reactive protein (537 mg/L). Lactate was elevated to 2.5 mmol/L. Blood chemistry revealed venous bicarbonate of 12 mEq/L, blood urea nitrogen of 19 mg/dL and creatinine of 0.45 mg/dL. Technetium dimercaptosuccinic acid scan to evaluate for pyelonephritis was negative. Immunoglobulins and complement levels were normal. Further review of CT scan of the abdomen by the radiologist showed several enlarged lymph nodes (up to 1.5 cm, and hyperemic) in the mesentery in right lower abdomen suggestive of mesenteric adenitis. No inflammatory changes, free fluid or appendicoliths were noted. Gallium scan was negative. An extensive workup including urine culture, blood culture, viral studies, and pediatric antinuclear antibody tests were negative. An echocardiogram demonstrated normal anatomy and function without vegetations. Bone marrow biopsy showed 90% cellularity with multilineage hematopoiesis, granulocytic hyperplasia and erythroid hyperplasia. There was no overt involvement by

non-Hodgkin lymphoma or acute leukemia or hemophagocytosis. Flow cytometry showed normal percentage of all relevant leukocyte populations. She responded appropriately to the initial management with broad-spectrum antibiotics and vasopressors and had stable hemodynamics by the end of 48 h (day 7 of illness). She was transferred to the intermediate care unit after being afebrile for a period of 24 h (day 8 of illness). However, she continued to have recurrence of fevers up to 40°C while on the floor without any hemodynamic compromise. Her antibiotics were stopped after a 5 d course (on day 8) as all the infectious workup was negative. By the end of 2nd week (wk), her fevers decreased, and she was discharged after 2 wk of hospitalization with a presumed diagnosis of shock secondary to an unidentified pathology.

The day before discharge, she developed a polymorphic, erythematous macular rash over the abdomen. No particular significance was ascribed to the rash at that time. However, the rash became more prominent after discharge, and she had recurrence of fevers. The patient was readmitted within 48 h with fever, generalized myalgia, arthralgia, respiratory distress and shock. A summary of her vital signs included heart rate of 200/min, blood pressure of 70/30 mmHg and respiratory rate of 28/min with oxygen saturation of 91% on room air. She was directly admitted to the PICU from emergency room and was stabilized with intubation, fluid resuscitation, vasopressors including dopamine and norepinephrine. However, she remained unstable and stress dose steroids were administered resulting in stabilization of hemodynamics. Physical examination after adequate stabilization was significant for bilateral ankle and foot swelling with no other significant findings. An extensive workup for infectious diseases, malignancy, Kawasaki syndrome and vasculitis was again negative; echocardiogram did not show any coronary abnormalities and chest and abdominal magnetic resonance angiogram was negative. Bone marrow biopsy showed normal cellularity and did not show any evidence of leukemia, lymphoma or hemophagocytosis. She was treated with 2 mg/kg of intravenous gamma globulin without change in her clinical picture or laboratory studies. SoJIA at this point (arthritis, persistent fever and rash) was strongly suspected per the International League of Associations for Rheumatology criteria [2]. The diagnosis of MAS was established in this patient using the International Histiocyte Society criteria [3] which included fever, elevated ferritin (6300 ng/mL), elevated triglycerides (277 mg/dL), low natural killer (NK) cell activity and elevated soluble

interleukin-2 (IL-2) receptor level (>3000 pg/mL) by the end of 3rd wk since initial admission.

Arthritis in multiple large and small joints became more pronounced in the 4th wk and she received methylprednisolone 30 mg/kg intravenous (IV) for 3 d with a taper to 2 mg/kg/d and begun on cyclosporine (2.5 mg/kg per oral twice a day and was slowly increased to 5 mg/kg twice a day) to target a trough level of 200 ng/mL to treat SoJIA complicated by MAS. She continued to have arthritis and required initiation of etanercept (25 mg subcutaneous twice weekly). She responded well to etanercept with marked improvement in her arthritis and normalization of her ferritin level and inflammatory markers.

2.2. Case 2

A 4-year-old Caucasian male with history of Diamond-Blackfan anemia presented with fevers for 1 wk (temperature maximum of 38.9°C), vesicular rash in the mouth and bright red bleeding gums. His fevers were almost continuous responding only minimally to antipyretics. He did not have any significant family history pertinent to his illness. His physical examination was significant for vesicular rash on his palate, inside of his cheeks and lips and splenomegaly. The child was not toxic at this time and was admitted to the pediatric ward. Laboratory studies revealed pancytopenia with absolute neutrophil count of $348/\text{mm}^3$. He had an extensive workup for infectious etiology, which included blood, stool and urine bacterial and viral cultures, which were all negative. Herpes simplex virus fluorescent monoclonal antibody test of oral ulcers was negative. He had a borderline positive quantitative Epstein-Barr virus (EBV) by polymerase chain reaction (89 copies/mL) and elevated EBV-specific immunoglobulin M. CT of his face and sinuses was done in view of extensive palatal lesions and was noted to have non-specific mucosal thickening of sinuses. Further CT scan of chest, abdomen and pelvis was done to identify the cause of fevers. His CT scan chest revealed interstitial and perihilar edema. Bronchoscopy was done in view of this, and bronchoalveolar fluid cultures and stains were negative. His lumbar puncture results were normal. An extensive workup for possible vasculitis was negative. He was treated with broad-spectrum antimicrobials without resolution of his fevers. During his hospital course, there was clinical suspicion for atypical Kawasaki disease, and he was treated with 2 g/kg intravenous gamma globulin. However, he did not

respond clinically and echocardiogram did not show any abnormalities of the coronary vessels. A bone marrow biopsy was performed due to a high index of suspicion for myelodysplastic syndrome, which revealed hypocellular marrow with marked granulocytic hypoplasia and T-cell lymphocytosis. There was no overt morphologic or detectable phenotypic evidence of acute leukemia or non-Hodgkin's lymphoma. The CD4/Cd8 T-cell ratio was inverted (0.43). There were adequate numbers of megakaryocytes without overt atypia. Islands of erythroid maturation were present but slightly decreased. In situ hybridization study for EBV encoded ribonucleic acid showed rare positive cells in the bone marrow. The bone marrow picture was therefore attributed to EBV infection. In view of hypocellular marrow, filgrastim was initiated, and he received packed red blood cells for symptomatic anemia. IV antimicrobials were discontinued after 1 wk in view of negative cultures. He continued to have fevers into his 2nd wk of admission. During this time, he deteriorated clinically with tachycardia, significantly delayed capillary refill time of 6 seconds, hypotension all consistent with cold septic shock. His lactate was elevated to 14.3 mmol/L. He was admitted to the PICU, where he required cardio-respiratory support with vasopressors (dopamine and epinephrine) and mechanical ventilation for 5 d. Persistent high fevers without identifiable infectious and malignant etiology prompted screening for hemophagocytic lymphohistiocytosis (HLH), which was established using established International Histiocyte Society criteria [3] of fever, splenomegaly, elevated ferritin (1659 ng/mL), low NK cell activity (2%) and elevated soluble IL-2 receptor level (2342 pg/mL) in the 3rd wk. At this point, EBV was felt to have triggered his HLH. He improved clinically and recovered all cell lines on IV glucocorticoids and was discharged after full recovery in the 4th wk. He was readmitted 4 wk later with high fevers for 4 d, pustular rash on his extremities, persistent anemia and neutropenia. The mother described rash as pustular, but it was not apparent at the time of admission. Extensive workup for infectious etiology was again negative. He deteriorated clinically with tachycardia, bounding pulses and was transferred to the PICU on the 2nd d of his stay in the hospital. He needed fluid resuscitation and inotropic support (dopamine and norepinephrine) for a period of 48 h. He did not need respiratory support and had stable hemodynamics by the 5th d of admission. Continued investigations included another bone marrow aspirate, which revealed hypocellular sample with scattered

lymphocytes, monocytes and acellular debris. No large atypical cells or blasts were identified. The flow cytometry description showed CD-45 positive cells, which included mainly lymphocytes with a few monocytes. The monocytes were all mature with co-expression of CD-14 and CD-64. No CD-123 positive dendritic cells were detected. No evidence of hemophagocytosis was demonstrated in his bone marrow. On day 7 of his admission, he developed significant arthritis in multiple joints and was non-ambulatory. Though he did not have typical rash, in view of persistent high-grade fevers, myalgia, arthritis, and organomegaly, it was felt that his primary diagnosis was SoJIA per International League of Associations for Rheumatology criteria, and he presented with MAS, rather than EBV-driven HLH [2]. No further testing for genetic mutations was performed. He received IV steroids (4 mg/kg) and IV cyclosporine (1 mg/kg per dose) in the 2nd wk of illness (day 8), and he responded well to treatment within 48 h after the treatment. On day 10 of his admission, his steroids were changed to oral prednisolone 2.5 mg/kg/dose twice a day and oral cyclosporine 4 mg/kg/d with a target cyclosporine trough levels of 200 ng/mL, and he was discharged to home in stable condition at the end of his 3rd wk of hospitalization.

3. Discussion

Macrophage activation syndrome is seen commonly with systemic onset juvenile idiopathic arthritis (JIA) [1]. JIA is one of the most common rheumatic diseases in children. The management of JIA is improved significantly in recent decades decreasing the morbidity. SoJIA is seen in up to 10–15% of all JIA patients, but the percentage is higher in severe JIA cases [4]. At onset, it is clinically well distinguished from other forms of JIA by the prominence of extra-articular features such as spiking fevers, a salmon-colored skin rash, lymphadenopathy and serositis. However, diagnosis is often challenging, since the disease can mimic infections and malignancies. The affected children look very ill, especially during fever spikes, and may present with a life-threatening complication, MAS. Clinically evident MAS at the time of presentation can cloud the diagnostic picture of SoJIA due to alterations in laboratory values, and is reported to be present in up to 8% of patients at the time of diagnosis [5]. MAS is characterized by the excessive activation of well-differentiated macrophages, resulting in fever,

hepatosplenomegaly, lymphadenopathy, severe cytopenia, serious liver disease, intravascular coagulation, neurological involvement, and the presence of hemophagocytosis on bone marrow. Hemophagocytosis is a characteristic feature seen in primary HLH (autosomal recessive inheritance), and also in secondary HLH (i.e. acquired HLH). Secondary HLH occurs after strong immunologic activation and is seen in association with systemic infections, immunodeficiency, underlying malignancy or rheumatic diseases. The term MAS has been used almost exclusively to describe secondary HLH in association with rheumatic diseases. It is seen most commonly with systemic SoJIA and has also been reported with systemic lupus erythematosus, juvenile dermatomyositis, and Kawasaki disease. [6–9]. It is believed to be caused by the uncontrolled activation and proliferation of T cells and excessive activation of macrophages, resulting in persistent high fever, hepatosplenomegaly, lymphadenopathy, and cytopenia affecting more than one cell line, liver disease, intravascular coagulation, and neurological involvement. The frequency of MAS in SoJIA is reported to be between 7–13% [1, 10] with a reported mortality varying from 8–22% [10–12]. However, these numbers may not be a true reflection and significantly underestimate the incidence of MAS given the difficulties associated with diagnosis and nomenclature. Numerous triggers have been associated with development of MAS in SoJIA which include infections, (EBV being the most common though multiple agents have been implicated) drugs (non steroidal anti-inflammatory agents, disease modifying anti-rheumatic drugs) and even conditioning for autologous stem cell transplant therapy, and filgrastim [10, 11]. Some of the drugs used for the management of MAS themselves have been associated (anakinra and etanercept) to MAS [13, 14].

According to the guidelines of the International Histiocyte Society, in the absence of a molecular diagnosis consistent with HLH, diagnosis requires at least five of the following eight criteria: (a) fever, (b) splenomegaly, (c) cytopenias, (d) hypertriglyceridemia and/or hypofibrinogenemia, (e) hyperferritinemia, (f) elevated soluble IL-2 receptor alpha (IL-2Ra), (g) decreased NK cell activity, and (h) hemophagocytosis in bone marrow [3]. However, the diagnosis of MAS is problematic in SoJIA and other rheumatic diseases as it may have an atypical and insidious course in some patients and criteria are not always fulfilled at the time of presentation. Although the above criteria are used for diagnosis of MAS, some of these are also features of active SoJIA, including fever, lymphadenopathy,

Table 1
Diagnostic guidelines for macrophage activation system complicating systemic juvenile idiopathic arthritis* [15]

Laboratory criteria
1. Thrombocytopenia ($\leq 262,000/\text{mm}^3$)
2. Elevated levels of aspartate aminotransferase ($> 59 \text{ U/L}$)
3. Leucopenia ($\leq 4,000/\text{mm}^3$)
4. Hypofibrinogenemia ($\leq 250 \text{ mg/dL}$)
Clinical criteria
1. Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
2. Hemorrhages (purpura, easy bruising, mucosal bleeding)
3. Hepatomegaly ($\geq 3 \text{ cm}$ below the costal arch)
Histopathological criterion
1. Evidence of macrophage hemophagocytosis in the bone marrow aspirate

*The diagnosis of MAS requires the presence of any 2 or more laboratory criteria or 2 or 3 or more clinical and/or laboratory criteria. A bone marrow aspirate for the demonstration of hemophagocytosis may be required only in doubtful cases.

hepatosplenomegaly, anemia, elevated IL-2 receptor level and hyperferritinemia. This led to the proposal of new set of diagnostic guidelines by Ravelli et al. [15] for macrophage activation system complicating systemic JIA as described (Table 1).

A recent survey showed that pediatric rheumatologists worldwide gave diagnostic importance to five of the eight features included in the guidelines suggested [16]. These being, decreased platelet count, elevated liver enzymes, falling leukocyte count, hypofibrinogenemia, and evidence of macrophage hemophagocytosis in the bone marrow. All three clinical criteria (central nerve system dysfunction, hemorrhagic manifestations, and liver enlargement) included in the diagnostic guidelines by Ravelli et al. [15] did not make it to the nine top features most frequently given the highest ranks by the respondents. Among the HLH diagnostic criteria [3], only five (fever, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, evidence of macrophage hemophagocytosis in the bone marrow, and hyperferritinemia) entered the top nine features, whereas three (splenomegaly, low or absent NK cell activity, and increased soluble IL-2 receptor alpha [CD25]) did not. This observation suggests that there still is no consensus among the pediatric rheumatologists about the diagnosis of MAS complicating SoJIA. This further signifies the importance of early suspicion and aggressive management to improve the prognosis of this potentially fatal condition.

There is no established protocol for the treatment of MAS in pediatric population [3]. Unlike primary HLH, etoposide is rarely required [17] in MAS associated with SoJIA since therapies to control the underlying systemic arthritis itself often rapidly treat MAS. The guidelines of the International Histiocyte Society

suggest initial 8 wk of chemotherapy for the treatment for MAS. The immediate aim of chemotherapy is suppression of the increased inflammatory response and control of cell proliferation. Corticosteroids have been used with and without intravenous immunoglobulins with variable response rate [17]. Effective treatment of MAS with cyclosporine and IV cyclophosphamide has been reported in isolated cases [18, 19]. Risks and benefits should be carefully considered given the side effects of these, especially with cyclophosphamide (myelosuppression). Biologics including anakinra or a tumor necrosis factor inhibitor (etanercept, infliximab) are used in more severe cases and with multi-organ involvement. Anakinra, interleukin-1 receptor antagonist, has been reported to induce sustained remission of MAS together with corticosteroids [20]. Tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, is an effective cytokine inhibitor and has been reported to effectively control the symptoms and rise in inflammatory markers like C-reactive protein [21].

In conclusion, MAS is potentially fatal and its diagnosis and management is complicated particularly in patients not previously diagnosed with SoJIA, systemic lupus erythematosus or other rheumatic condition. Given the rarity of SoJIA and other rheumatic disorders in children, it is very low in the list of differential diagnoses for shock. Often the diagnosis is delayed, as it is difficult to distinguish from active underlying rheumatic disease, infections and malignancies. Thorough physical examination, comprehensive work up for autoimmune, infectious causes, and malignancy; along with a high index of suspicion may help in early diagnosis, successful treatment and improved prognosis of this interesting disorder.

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