Dispatch

Macrophage Activation Syndrome Complicating Adult-Onset Still’s Disease: A Diagnostic Challenge

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Abstract

We report the case of a young man who presented with high-spiking fever, erosive arthritis, and generalized lymphadenopathy. He was diagnosed as adult-onset Still’s disease (AOSD), and his clinical course was complicated by reactive macrophage activation syndrome (MAS). The sudden precipitous drop in leukocyte and platelet counts proved a valuable clue to the diagnosis of MAS in the setting of AOSD. The new American College of Rheumatology/European League Against Rheumatism classification criteria for reactive MAS complicating systemic juvenile idiopathic arthritis were applied in this patient. When MAS is associated with AOSD, treatment could be challenging. We managed this patient successfully with a combination of systemic corticosteroids and cyclosporine in the acute phase.

Keywords: Hyperferritinemia, macrophage activation syndrome, polyarthritis, Still’s disease

Introduction

Macrophage activation syndrome (MAS) is a devastating inflammatory response involving inappropriate triggering of T-lymphocytes and macrophages resulting in a proinflammatory cytokine storm. The diagnosis of reactive MAS in patients with adult-onset Still’s disease (AOSD) requires a high index of suspicion, as both diseases share many clinical and laboratory characteristics. Reported rates of occurrence of MAS in patients with AOSD vary from 12% to 56%. We describe a young male who presented with fever of unknown origin and destructive arthritis of large joints. He was diagnosed with AOSD. The early recognition of the falling platelet and leukocyte counts led to the diagnosis and timely management of MAS. We review the diagnosis and management of MAS complicating AOSD.

Case Report

A 25-year-old man, employed as a mechanic, presented to our outpatient clinic with high-grade fever, chills, rigors in addition to pain, and swelling of multiple joints for 2 weeks. Joint involvement was initially limited to the left wrist, later affecting bilateral knees followed by bilateral elbows, and finally, the right wrist in an additive pattern. He had lost 10 kg in the last month. He reported a similar episode 4 years ago, for which he was treated with aspirin considering acute rheumatic fever. Aspirin was discontinued subsequently. He had been well until this episode.

Multiple nontender firm lymph nodes, cervical (largest 1.5 cm × 1.5 cm), axillary (2 cm × 2 cm), inguinal (2 cm × 2 cm), and spleen tip were palpable on examination. Arthritis involving bilateral knees [right > left; Figure 1], bilateral wrists, and elbows was notable. Mild neutrophilic leukocytosis (13,000/cu mm), elevated erythrocyte sedimentation rate (ESR) (103 mm at 1 h), and positive C-reactive protein with normal hepatic and renal functions were found. Echocardiography showed no evidence of rheumatic carditis, and antistreptolysin O titers were <200 IU. Joint fluid analysis revealed 13,000 cells, 56% polymorphonuclear leukocytes and no crystals. Joint fluid cultures were sterile. Radiographs showed diffuse narrowing of bilateral carpometacarpal joints with destruction of articular...

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surface, suggesting a more chronic underlying inflammation than expected [Figure 2].

With fever, weight loss, generalized lymphadenopathy, joint involvement, and elevated ESR, a possibility of tuberculosis was entertained, and he was empirically started on antitubercular therapy on day 6 of admission. Brucellosis was also suspected as he reported regular consumption of raw milk. However, blood cultures were sterile, and brucella serology was negative. Fine-needle aspiration cytology indicated reactive axillary lymphadenitis. Tuberculin skin testing was negative. Contrast-enhanced computed tomographic scan confirmed the mild splenomegaly [Figure 3]. Synovial biopsy of the right wrist had features of inflammatory arthritis without granulomas. Bone marrow aspiration and biopsy on day 11 showed a reactive marrow with no granuloma. Daily spikes of 102°F–104°F fever with worsening joint pains and myalgia persisted [Figure 4]. Rheumatoid factor, anticyclic citrullinated peptide, and antinuclear antibodies by immunofluorescence were negative. Tuberculosis treatment was stopped after 4 weeks as there was clinical deterioration and no new evidence for tuberculosis emerged. Taking into account persisting quotidian fever and joint involvement, a diagnosis of AOSD was now considered.

On day 22, cytopenias emerged abruptly with hepatic and renal function derangement [Figure 5]. In view of this and hyperferritinemia (>16,500 ng/ml), MAS was strongly contemplated, especially in the background of a possible AOSD. Treatment was started with intravenous dexamethasone (10 mg/m²/day). In the ensuing 4 days, thrombocytopenia resolved and hepatic and renal parameters normalized, but quotidian fever spikes, leukocytosis, and a decline in

Figure 1: Arthritis involving bilateral knees (right > left)

Figure 2: X-ray showed diffuse narrowing of bilateral carpometacarpal joints with the destruction of the articular surface

Figure 3: Contrast-enhanced computed tomography showing mild splenomegaly

Figure 4: Temperature chart
hemoglobin persisted. He was symptomatic only during the febrile periods. By now, AOSD could be diagnosed with confidence. Since the systemic features of MAS were persisting, pulse methylprednisolone (1 g/day) along with cyclosporine (6 mg/kg) was initiated. Subsequently, fever resolved and hemoglobin improved. The patient was discharged on 1 mg/kg prednisolone along with cyclosporine and nonsteroidal anti-inflammatory drugs on day 21.

Two weeks after discharge, systemic features had resolved completely, hemoglobin had improved, but arthritis of both wrists and knees persisted. Methotrexate was started at 7.5 mg/week. Cyclosporine and prednisolone were tapered. Currently, the patient is doing well on low-dose prednisolone and methotrexate of 12.5 mg/week.

**Discussion**

The classical triad of symptoms in AOSD is high-grade (39°C) quotidian fever, salmon-colored evanescent rash, and arthralgia.[1,2] Arthralgia or arthritis commonly affects the knees, wrists, and ankles. Bilateral ankylosing wrist involvement as seen in this patient has been described.[3] Laboratory parameters reflect the ongoing inflammation with highly elevated ESR, leukocytosis, and serum ferritin. Several criteria have been proposed for AOSD, the most popular of which is Yamaguchi criteria.[4] Our patient fulfilled four of the six available criteria. The diagnosis of AOSD was challenging in this patient until week 4 of hospital stay as chronic infections and inflammatory causes needed primary consideration initially. This is anticipated, given the higher prevalence of tuberculosis and endemicity of brucellosis, whereas AOSD remains a diagnosis of exclusion.[4] MAS can be primary (familial) or secondary (reactive). The primary type occurs in childhood as familial hemophagocytic lymphohistiocytosis (HLH).[5] Secondary MAS complicates autoimmune systemic diseases, malignancies, infections, and drugs. Overproduction of interleukins 1, 16, 18 and inappropriate activation of CD8 lymphocytes and macrophages result in a clinical picture of relentless high-grade fever and hepatosplenomegaly with bone marrow evidence of hemophagocytosis by activated macrophages.[6,7] The inflammatory cytokine storm progresses to multiorgan dysfunction and unfavorable outcome. Systemic juvenile idiopathic arthritis (sJIA), AOSD, and systemic lupus erythematosus are the main systemic autoimmune diseases commonly associated with MAS. It is challenging to make a diagnosis of reactive MAS as it shares clinical characteristics and laboratory findings such as high fever, lymphadenopathy, hepatosplenomegaly, and elevated liver enzymes with AOSD.[8,9]

Recently, the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) proposed the classification criteria for reactive MAS complicating sJIA, modifying the HLH 2004 criteria using logistic regression modeling and expert consensus [Table 1].[10] Changes in laboratory values over time are highly relevant for diagnosing MAS than fulfillment of the current diagnostic criteria. Three parameters – platelet count, serum ferritin, and aspartate aminotransferase level – were most helpful for the early suspicion of MAS.[11] Our patient fulfilled these criteria at the onset of MAS. Early fall of platelet count acted as the

![Figure 5: Course of events and trend of complete blood counts showing abrupt cytopenia on day 22 of hospital stay](image)

**Table 1: American College of Rheumatology/European League Against Rheumatism classification criteria for reactive macrophage activation syndrome with systemic juvenile idiopathic arthritis successfully used in adult-onset Still’s disease**

| Ferritin >684 ng/ml and any 2 of the following |
|------------------------------------------------|
| Platelet count ≤181 x 10⁹/L |
| Aspartate aminotransferase >48 units/L |
| Triglycerides >156 mg/dl |
| Fibrinogen ≤360 mg/dl |

| Day 1 | Day 4 | Day 11 | Day 18 | Day 22 | Day 28 | Day 36 | Day 45 |
|-------|-------|--------|--------|--------|--------|--------|--------|
| Hb → TLC |
| Erosive arthritis |
| Brucella serology-negative. |
| Fever |
| Acute onset cytopenias |
| Counts improved |
| Fever/platelet count decline persistent |
| Alhebrin, arthritis reduced, Discharged |

| RA negative CRP positive |
| ATT Doxicycline |
| STEPPONICIN started |
| Doxicycline & STEPPONICIN stopped |
| Urea 108 Creatinine 1.45 mg/dL |
| Dexamethasone started |
| ATT stopped. Pulse methyl prednisolone |
| Cyclosporine |

Clinical events, Treatment decisions and trend of haematological parameters in hospital
warning sign in our patient, indicating the development of reactive MAS.

Highest observed platelet count, number of active joints in the first 3 months, and early use of methotrexate have been used to predict progression to residual joint damage at 2 years.\textsuperscript{12,13} This model places our patient at high risk for residual joint damage. This suggests that a close follow-up for joint disease activity is warranted. Development of MAS as a complication has been associated with poor prognosis and excess mortality in AOSD patients.\textsuperscript{13,14} In contrast to HLH, no specific management guidelines exist for reactive MAS. We treated this patient with dexamethasone and cyclosporine. Methotrexate was started 2 weeks later for persistent joint symptoms. The rationale for selecting this regimen was that the early use of systemic steroids, and cyclosporine has been reported to improve outcome in reactive MAS.\textsuperscript{15}

AOSD complicated by MAS remains a complex disorder challenging in diagnosis and treatment. We demonstrate, to our knowledge, the first successful adaptation of ACR/EULAR classification criteria for reactive MAS for sJIA in a patient with AOSD. Further validation can prove its applicability in a larger number of AOSD patients. At present, the earliest clue to diagnosis appears to be thrombocytopenia. Early initiation of immunosuppressive therapy may prevent multisystem involvement and mortality.\textsuperscript{16}

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Bywaters EG. Still’s disease in the adult. Ann Rheum Dis 1971;30:121-33.
2. Feuerstein JL, Klein DE, Mikhitarian MA, Mehta A. Quotidian high spiking fevers in adult still’s disease. Am J Case Rep 2017;18:580-8.
3. Medsgaer TA Jr., Christy WC. Carpal arthritis with ankylosis in late onset still’s disease. Arthritis Rheum 1976;19:232-42.
4. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashihara H, et al. Preliminary criteria for classification of adult still’s disease. J Rheumatol 1992;19:424-30.
5. Katano H, Cohen JJ. Perforin and lymphohistiocytic proliferative disorders. Br J Haematol 2005;128:739-50.
6. Deane S, Selmi C, Teuber SS, Gershwin ME. Macrophage activation syndrome in autoimmune disease. Int Arch Allergy Immunol 2010;153:109-20.
7. Larroche C, Mouthon L. Pathogenesis of hemophagocytic syndrome (HPS). Autoimmun Rev 2004;3:69-75.
8. Gerfaud-Valentin M, Janilloux Y, Iwaz J, Sève P. Adult-onset still’s disease. Autoimmun Rev 2014;13:708-22.
9. Schulert GS, Canna SW. Convergent pathways of the hyperferritinemic syndromes. Int Immunol 2018;30:195-203.
10. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis Rheumatol 2016;68:566-76.
11. Ruscitti P, Cipriani P, Masedu F, Iacono D, Ciccia F, Liakouli V, et al. Adult-onset still’s disease: Evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. BMC Med 2016;14:194.
12. Sandborg C, Holmes TH, Lee T, Biederman K, Bloch DA, Emery H, et al. Candidate early predictors for progression to joint damage in systemic juvenile idiopathic arthritis. J Rheumatol 2006;33:2322-9.
13. Ruscitti P, Cipriani P, Masedu F, Iacono D, Ciccia F, Liakouli V, et al. Adult-onset still’s disease: Evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. BMC Med 2016;14:194.
14. Ruscitti P, Cipriani P, Ciccia F, Masedu F, Liakouli V, Carubbi F, et al. Prognostic factors of macrophage activation syndrome, at the time of diagnosis, in adult patients affected by autoimmune disease: Analysis of 41 cases collected in 2 rheumatologic centers. Autoimmun Rev 2017;16:16-21.
15. Lenert A, Yao Q. Macrophage activation syndrome complicating adult onset still’s disease: A single center case series and comparison with literature. Semin Arthritis Rheum 2016;45:711-6.
16. Guilpain P, Le Quellec A. About the complexity of adult onset still’s disease and advances still required for its management. BMC Med 2017;15:5.