Clinical Rheumatology (2019) 38:603–608
https://doi.org/10.1007/s10067-018-4387-5

CASE BASED REVIEW

Macrophage activation syndrome in a patient with axial spondyloarthritis on adalimumab

Rahaf Baker[1] · Jean W. Liew[2,3] · Paul D. Simonson[4] · Lori A. Soma[4] · Gordon Starkebaum[2]

Received: 25 October 2018 / Revised: 20 November 2018 / Accepted: 28 November 2018 / Published online: 7 December 2018

Abstract

Macrophage activation syndrome (MAS) is a rare and potentially fatal condition characterized by excessive activation and uncontrolled proliferation of T lymphocytes and macrophages, leading to overwhelming systemic inflammation and cytokine release. MAS has been reported with viral infections, autoimmune disorders, malignancies, and medications. We describe a case of a patient with axial spondyloarthritis (axSpA) treated with adalimumab, who presented with MAS.

Keywords Adalimumab · Axial spondylitis · Fever · Hemophagocytic lymphohistiocytosis · Macrophage activation syndrome

To the Editor:

Macrophage activation syndrome (MAS) is a rare and potentially fatal condition characterized by excessive activation and uncontrolled proliferation of T lymphocytes and macrophages, leading to overwhelming systemic inflammation and cytokine release. MAS has been reported with viral infections, autoimmune disorders, malignancies, and medications. We describe a case of a patient with axial spondyloarthritis (axSpA) treated with adalimumab, who presented with MAS.

Case report

A 34-year-old Middle Eastern man with long-standing HLA-B27-positive axSpA on adalimumab presented with several days of persistent fevers. AxSpA had been diagnosed on the basis of a history of recurrent iritis, patellar tendon enthesitis, and inflammatory lower back pain. The back pain, although initially responsive, became refractory to non-steroidal anti-inflammatory medications and a sacroiliac joint steroid injection. Adalimumab was started in April 2018, and for the next

Rahaf Baker and Jean W. Liew contributed equally to this work.

KEY POINTS • MAS is a rare condition of systemic inflammation with high mortality; having a strong index of suspicion can lower mortality in these patients.
• Medications, including TNF inhibitors, should be considered as possible triggers for MAS.
• Consider high-dose steroids and anakinra, either alone or in combination, for the treatment of MAS. If a medication is suspected, remove the offending agent.

✉ Jean W. Liew
jwliew@uw.edu

Rahaf Baker
rahafb@uw.edu

Paul D. Simonson
psimonso@uw.edu

Lori A. Soma
somal@uw.edu

Gordon Starkebaum
gas1@uw.edu

[1] University of Washington School of Medicine, Seattle, WA, USA

[2] Division of Rheumatology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA

[3] University of Washington, 1959 NE Pacific St, BB561, Seattle, WA 98195, USA

[4] Department of Laboratory Medicine, Division of Hematopathology, University of Washington School of Medicine, Seattle, WA, USA

2.5 months, he had dramatic improvement in his inflammatory back pain, and no extra-articular manifestations. In June 2018, he presented to the hospital and endorsed 4 days of high fevers with mild lower chest discomfort and cough. He described unremitting fevers that occurred multiple times daily, which were associated with significant weakness and rigors. The review of systems was otherwise negative. He had no other pertinent past medical history or medications. His family history was non-contributory. His social history was notable for moving to the USA from Saudi Arabia 10 years ago with recent, frequent travel around the USA and Mexico. He had traveled to Las Vegas for a work conference a few days prior to his presentation.

On admission, his temperature was 40.2 °C, blood pressure was 129/68 mm/Hg, and pulse was 60 beats per minute. He was ill-appearing and his physical exam was otherwise only notable for splenomegaly with tenderness on palpation. His initial labs revealed lymphopenia (absolute lymphocyte count 650 cells/μL), mild anemia (hemoglobin 12 g/dL), thrombocytopenia (132,000 cells/μL), and transaminitis (AST 53 U/L, ALT 76 U/L). Erythrocyte sedimentation rate (ESR) was 42 mm/h and C-reactive protein (CRP) was 202 mg/dL. An extensive infectious disease workup was undertaken, with all tests reported as negative (Table 1). Computed tomography (CT) of the chest, abdomen, and pelvis showed mild splenomegaly with residual thymic tissue and no lymphadenopathy.

After a week of hospitalization, the patient remained febrile despite treatment with antipyretics. He developed a transient, faint, erythematous maculopapular rash over his trunk. Further labs demonstrated elevated ferritin (2312 mg/dL), fibrinogen (871 mg/dL), and triglycerides (289 mg/dL). CRP peaked at 400 mg/dL. A diagnosis of MAS was considered. On the seventh day of hospitalization, he was started on anakinra 100 mg twice daily without adequate fever control; thus, oral prednisone 60 mg daily was added. He quickly defervesced with improvement of his condition, labs, and inflammatory markers (Fig. 1). A bone marrow biopsy, which was obtained on hospital day 7, showed erythroid hyperplasia and hemophagocytic histiocytes without evidence of malignancy (Fig. 2). Soluble interleukin-2 receptor levels, however, were low. After an 11-day hospitalization, he was discharged on prednisone 60 mg daily and anakinra 100 mg once daily. Adalimumab was completely discontinued. Upon outpatient follow-up, he had continued symptomatic improvement with normalization of the ESR, CRP, ferritin, and fibrinogen. He was tapered off prednisone over 2 months but his inflammatory back pain returned.

Discussion

MAS is a potentially fatal syndrome that can present in patients with inflammatory conditions and is considered to be similar to hemophagocytic lymphohistiocytosis (HLH) [1, 2]. The finding of abundant activated hemophagocytic macrophages, or histiocytes, has led to their classification as a histiocytic disorder [3]. The underlying pathogenesis of MAS is poorly understood, but it is proposed to be triggered by an

Table 1 Summary of workup for unexplained fever

Infectious category	Tests returned negative
Viral	Serum Ebstein-Barr virus monospot and PCR; serum cytomegalovirus PCR; serum herpes simplex virus 1 and 2 PCR, serum varicella zoster virus PCR
	Nasopharyngeal rapid influenza A and B PCR
	Respiratory viral panel PCR: bocavirus, metapneumovirus, adenovirus, parainfluenza 1–4, respiratory syncytial virus, coronavirus, rhinovirus
	Serum West Nile virus IgM and IgG
	Human immunodeficiency virus antibody/antigen 4th-generation screen
	Hepatitis B virus surface antigen, surface antibody, and core antibody
	Hepatitis C virus antibody screen
Bacterial	Group A *Streptocccus* by rapid detection
	Streptococcus pneumoniae urine antigen
	Legionella urine antigen
	Serum *Leptospira* IgM
	Syphilis IgG antibody
	Quantiferon-Gold tuberculosis
Fungal	*Histoplasma* urine antigen
	Serum *Coccidioides* IgG and IgM
	Cryptococcus serum antigen
Parasitic	Malaria thick and thin smear

PCR, polymerase chain reaction

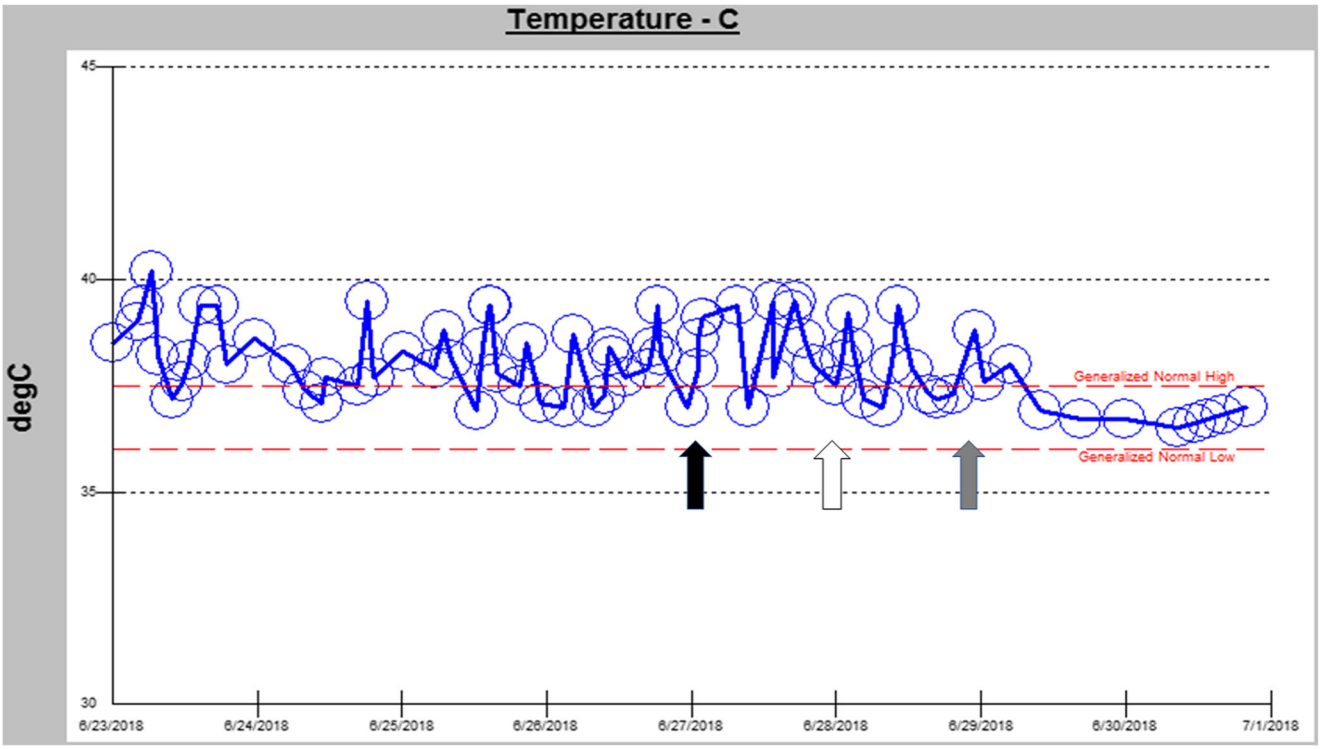

Fig. 1 Fever curve during hospital stay. The black arrow indicates the initiation of anakinra 100 mg daily. The white arrow indicates the initiation of anakinra 100mg twice daily. The gray arrow indicates the initiation of prednisone 60mg daily with continued twice daily anakinra injections

inciting event such as infection, malignancy, autoimmune conditions, or drugs, that leads to immune dysregulation [4]. The resultant overwhelming cytokine storm drives phagocytosis of blood cell precursors and the infiltration of macrophages into tissues, causing multiorgan dysfunction. Currently, there are no diagnostic criteria for MAS in adults, and the proposed classification criteria rely on our understanding from the pediatric population [1]. The findings of high fevers, cytopenias, hyperferritinemia, and hypertriglyceridemia should alert the clinician to the possibility of MAS. Although significantly elevated ferritin is specific for HLH in pediatrics, it is not as specific to HLH or MAS in the adult population [5]. Evidence of hemophagocytic cells on bone marrow biopsy is not required for diagnosis and is not always found on presentation in MAS.

The most consistent diagnosis for our patient was MAS, as he had high persistent fevers without an infectious cause, lymphopenia and anemia, marked hyperferritinemia, hypertriglyceridemia, splenomegaly, and the presence of hemophagocytes on bone marrow biopsy. The diagnosis of

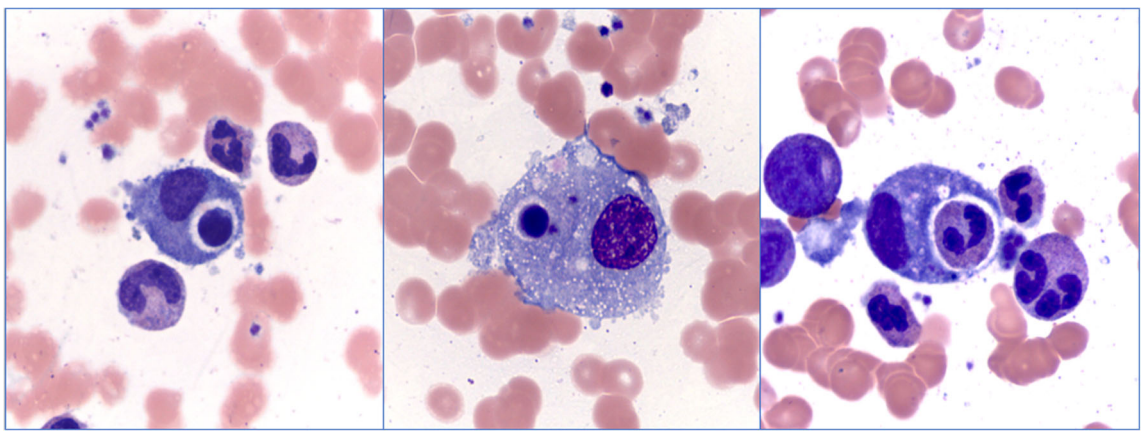

Fig. 2 Hemophagocytic histiocytes. The images are those of hemophagocytic histiocytes seen in a bone marrow aspirate smear. The left two images show histiocytes with engulfed cells, consistent with degenerated hematopoietic cells. The image on the right shows a histiocyte with an engulfed neutrophil

adult-onset Still's disease (AoSD) was excluded due to his axSpA [6]. The leading explanations for his MAS were adalimumab, an undetected viral infection, or his underlying axSpA.

Infection, particularly viral, is the most common reported cause of MAS cited in the literature [2]. Our patient had extensive infectious workup that was negative; however, his MAS may have been triggered by an undetected virus. In rheumatologic conditions, MAS has been associated with underlying activity of systemic juvenile idiopathic arthritis and AOSD, and in rare cases of systemic lupus erythematosus [1]. SpA is rarely associated with MAS; only three were found in our review of the literature (Table 2). Of these three cases, only one occurred in the absence of TNF inhibitor use or clear source of infection [7]. Our patient had well-controlled SpA that was stable prior to presentation; therefore, we felt that SpA was a less likely trigger for his MAS.

Recently, MAS has been reported more frequently in association with TNF inhibitor use, although it is unclear whether this is due to heightened clinician awareness or increasing incidence. On our literature review, we found 10 reports of MAS associated with etanercept, infliximab, or adalimumab (Table 3). Of the two cases that described the timing of MAS relative to TNF inhibitor administration, one was in a patient with RA 2 months after discontinuation of etanercept, and one was in AoSD 2 months after initiation of adalimumab [12, 14]. Four of the cases reported had associated infections, including visceral leishmaniasis, disseminated histoplasmosis, liver abscess, or primary EBV, which were felt to be the primary trigger for MAS, though the TNF inhibitor was implicated as a contributing risk factor for the infection [8, 13, 15]. It is plausible that adalimumab triggered MAS in our patient as he presented at 2.5 months after initiation of adalimumab, which is consistent with the timeline from other case reports, and he had no obvious infection.

The pathogenesis of MAS secondary to TNF inhibitors is unknown. These medications have been successful in treating some refractory cases of MAS, but their use may also rarely induce or aggravate autoimmune diseases, or trigger MAS in the setting of infection [1]. It has been proposed that TNF inhibitor blockade of macrophage activity is coupled with a compensatory immune system activation and rebound cytokine response [16]. This leads to an overall immune system dysregulation and may trigger hemophagocytosis. The explanation for this paradoxical effect on immune response will require further research.

As for the treatment of MAS, we note that in MAS associated with TNF inhibitors only, six of the eight patients had clinical and laboratory improvement after treatment with high-dose corticosteroids. Two patients died despite receiving high-dose corticosteroids; however, these patients presented with severe or late systemic disease that was previously not well controlled on prednisone [9, 12]. In the cases of MAS with an associated infection, three of the four patients received high-dose corticosteroids in addition to treatment of underlying infection, and all four patients responded well and survived [8, 13, 15]. In the three reported cases of MAS in SpA, all three patients received high-dose prednisone and clinically stabilized [7, 8]. Dual treatment with high-dose steroids and anakinra, an IL-1 receptor antagonist, induced remission in our patient. Both agents have been shown to rapidly induce remission and ameliorate the cytokine storm in refractory and severe cases of MAS [4]. Anakinra was trialed first in our patient given his prolonged and high fevers, but given the

Table 2 Case reports of MAS in patients with axial spondyloarthritis

Citation	Age	Gender	Underlying conditions	TNF inhibitor used	Treatment	Outcome
Larroche et al. [5]	37	M	Crohn's disease with axial spondyloarthritis treated on infliximab. Patient had EBV primary infection	Infliximab	IV immunoglobulin (2 g/kg) and 3 boluses of methyplrednisolone	Seroconversion 2 months later with negative EBV PCR
Larroche et al. [5]	40	M	Ankylosing spondylitis on infliximab. Patient had a liver abscess	Infliximab	Antibiotics (amoxicillin, clavulonic acid, erythromycin), IV immunoglobulin (2 g/kg), and 7 methylprednisolone boluses followed by prednisone	Healing of abscess
Lou et al. [6]	42	F	Ankylosing spondylitis	None	Prednisolone (60 mg/day)	Laboratory improvement within 2 weeks. Clinically stable without relapse at 6 months

EBV, Epstein Barr virus; *PCR*, polymerase chain reaction

Table 3 Cases of MAS reported in the literature attributed to TNF inhibitors

Citation	Age	Gender	Underlying conditions	TNF inhibitor used	Treatment	Outcome
Sterba et al. [8]	70	F	Systemic sclerosis on prednisone and etanercept	Etanercept	Stopped etanercept Initiated cyclosporin and high-dose methylprednisolone (30 mg/kg), and IVIG	Demise after 12 days with multiorgan failure requiring mechanical ventilation and hemodialysis
Aikawa et al. [7]	10	M	Systemic onset juvenile idiopathic arthritis on methotrexate, naproxen, etanercept	Etanercept	Stopped etanercept Initiated IV methylprednisolone (30 mg/kg) TID and IV cyclosporin A (2.0 mg/kg/day), followed by prednisone (1.0 mg/kg/day) and oral cyclosporine A (5.0 mg/kg/day)	Clinically stable without relapse at 3 months
Ramanan et al. [9]	4.5	F	Systemic onset juvenile idiopathic arthritis. Recently initiated etanercept	Etanercept	Stopped etanercept Two pulses IV methylprednisolone (30 mg/kg/dose) followed by high-dose oral prednisone	Resolution of fever and rash within 2–3 days, with clinical and lab improvement
Sandhu et al. [10]	42	F	Rheumatoid arthritis on prednisone and ketoprofen. Was on etanercept 2 months prior	Etanercept	Initially tobramycin and cefazolin for neutropenic fever then discontinued Initiated cyclosporine (5 mg/kg), IV immunoglobulin (0.5 mg/kg for 2 days), dexamethasone (10 mg/m^2)	Demise after 6 weeks
Molto et al. [11]	60	M	Rheumatoid arthritis on adalimumab and methotrexate. Presented with visceral leishmaniasis*	Adalimumab	Stopped adalimumab and methotrexate Initiated lipid-soluble Amphotericin B (5 mg/kg for 10 days)	Clinically stable at 1 month
Soubani et al. [12]	26	F	Adult-onset Still's disease on corticosteroids and methotrexate. Recently started adalimumab 2 months prior	Adalimumab	Stopped adalimumab Methylprednisolon pulse therapy (1 g/day for 3 days), oral prednisone (2 mg/kg/day for 1 month) then tapered Maintained on tocilizumab and low dose prednisone	In remission. Maintained on tocilizumab with resolution of fever and joint pains
Agarwal et al. [13]	21	F	Adult-onset Still's disease on adalimumab. Presented with disseminated histoplasmosis*	Adalimumab	IV amphotericin B (4 mg/kg/day) and subcutaneous anakinra (100 mg/day), and high-dose steroids	Clinically stable, discharged at 3 weeks
Chauveau et al. [14]	37	M	Crohn's disease on azathioprine and infliximab	Infliximab	Corticosteroids and broad spectrum antibiotics	Clinically improved
Larroche et al. [5]	37	M	Crohn's disease with axial spondyloarthritis treated on infliximab. Patient had EBV primary infection*	Infliximab	IV immunoglobulin (2 g/kg) and 3 boluses of methyplrednisolone	Seroconversion 2 months later with negative EBV PCR
Larroche et al. [5]	40	M	Ankylosing spondylitis on infliximab. Patient had a liver abscess*	Infliximab	Antibiotics (amoxicillin, clavulonic acid, erythromycin), IV immunoglobulin (2 g/kg), and 7 methylprednisolone boluses followed by prednisone	Healing of abscess

*The TNF inhibitor was a likely risk factor for the infection, which likely triggered the onset of MAS

EBV, Epstein Barr virus; *PCR*, polymerase chain reaction

duration of symptoms and the likely presence of other cytokines besides IL-1, it alone was not sufficient in inducing remission.

In conclusion, it is important to recognize MAS as a possible life-threatening complication of autoimmune and inflammatory diseases. Currently, the diagnosis of MAS relies heavily on the pediatric diagnostic criteria, and the treatment on case reports and case series in adults. It is important to increase awareness of this rare disease among clinicians in order to prevent mortality and improve outcomes of these patients.

Compliance with ethical standards

Disclosures None.

References

1. Ravelli A, Minoia F, Davi S et al (2016) 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Ann Rheum Dis 75:481–489
2. Schram AM, Berliner N (2015) How I treat hemophagocytic lymphohistocytosis in the adult patient. Blood 125:2908–2914
3. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, Requena-Caballero L, Jordan MB, Abdel-Wahab O, Allen CE, Charlotte F, Diamond EL, Egeler RM, Fischer A, Herrera JG, Henter JI, Janku F, Merad M, Picarsic J, Rodriguez-Galindo C, Rollins BJ, Tazi A, Vassallo R, Weiss LM, for the Histiocyte Society (2016) Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 127: 2672–2681
4. Grom AA, Horne A, De Benedetti F (2016) Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol 12: 259–268
5. Schram AM, Campigotto F, Mullally A et al (2015) Marked hyperferritinemia does not predict for HLH in the adult population. Blood 10:602–607
6. Feist E, Mitrovic S, Fautrel B (2018) Mechanisms, biomarkers and targets for adult-onset Still's disease. Nat Rev Rheumatol 14:603–618
7. Lou YJ, Jin J, Mai QY (2007) Ankylosing spondylitis presenting with macrophage activation syndrome. Clin Rheumatol 26(11): 1929–1930
8. Larroche C, Falgarone G, Dumont Fischer D, Dhote R (2010) Syndrome d'activation macrophagique sous biothérapies: deux cas. Rev Med Interne 31S:S404–S501. https://doi.org/10.1016/j.revmed.2010.10.181.
9. Sterba G, Sterba Y, Stempel C, Blank J, Azor E, Gomez L (2010) Macrophage activation syndrome induced by etanercept in a patient with systemic sclerosis. Isr Med Assoc J 12:443–445
10. Aikawa NE, Carvalho JF, Bonfa E et al (2009) Macrophage activation syndrome associated with etanercept in a child with systemic onset juvenile idiopathic arthritis. Isr Med Assoc J 11:635–636
11. Ramanan AV, Schneider R (2003) Macrophage activation syndrome following initiation of etanercept in a child with systemic onset juvenile rheumatoid arthritis. J Rheumatol 30:401–403
12. Sandhu C, Chesney A, Piliotis E, Buckstein R, Koren S (2007) Macrophage activation syndrome after etanercept treatment. J Rheumatol 34:241–242
13. Molto A, Mateo L, Lloveras N et al (2010) Visceral leishmaniasis and macrophagic activation syndrome in a patient with rheumatoid arthritis under treatment with adalimumab. Joint Bone Spine 77: 271–273
14. Soubani L, Dridi L, Abdelghani KB et al (2014) Possible macrophage activation syndrome following initiation of adalimumab in a patient with adult-onset still's disease. Pan Afr Med J 17:94
15. Agarwal S, Moodley J, Goel GA et al (2011) A rare trigger for macrophage activation syndrome. Rheumatol Int 31:405–407
16. Chauveau E, Terrier F, Casassus-Builble D et al (2005) Syndrome d'activation macrophagique apres traitement par infliximab pour maladie de crohn fistulisee. Presse Med 34:583–584