CASE REPORT

Novel use of rituximab in macrophage activation syndrome secondary to systemic lupus erythematosus

Zachary Junga,¹ Rodger Stitt,² Christopher Tracy,² Michael Keith²

¹Department of Medicine,
Walter Reed National Military
Medical Center, Bethesda,
Maryland, USA

²Department of Rheumatology,
Walter Reed National Military
Medical Center, Bethesda,
Maryland, USA

Correspondence to

Dr Zachary Junga,
jungaz@gmail.com

Accepted 8 August 2017

SUMMARY

Macrophage activation syndrome (MAS) is a rare disease characterised by aberrant immune hyperactivation of T lymphocytes and macrophages driven by cytokine dysfunction. The HLH-2004 protocol is commonly used for the treatment of MAS, but significant toxicities are associated. We describe a case of MAS secondary to systemic lupus erythematosus in a young female that responded well to rituximab in lieu of etoposide. She continues to be in remission 1 year following the completion of rituximab infusion and is maintained on hydroxychloroquine. This case highlights the need for further research on the use of rituximab and other available biologics in the setting of MAS in order to help guide further alternative treatment decisions.

BACKGROUND

Macrophage activation syndrome (MAS), also known as secondary or reactive haemophagocytic lymphohistiocytosis (HLH) syndrome, is a rare disease characterised by aberrant immune hyperactivation of T lymphocytes and macrophages driven by cytokine dysfunction. Clinical features include fever, hyperferritinaemia, haepatomegaly, lymphadenopathy, cytopaenias and encephalitis. MAS differs from primary HLH in that it is triggered by an infection, autoimmune process or malignancy, whereas primary HLH is caused by an underlying genetic abnormality.¹ The HLH-2004 treatment protocol, which is the largest study to date on the treatment of primary HLH includes etoposide, cyclosporine, dexamethasone and intrathecal methotrexate. A patient must meet five of the eight following features to fulfil the HLH-2004 diagnostic criteria: fever, splenomegaly, cytopaenia, hypertriglyceridaemia and/or hypofibrinogenemia, low/absent natural-killer-cell activity, hyperferritinaemia and high soluble interleukin-2 receptor levels.² The treatment protocol has been used by some as a surrogate to the treatment of MAS given its similar disease manifestation. Significant toxicities have been associated with the treatment regimen, and it has been predominantly studied in primary HLH, which likely has a different pathogenesis. There is no consensus on alternative, less toxic treatments for MAS. We describe a case of MAS secondary to systemic lupus erythematosus (SLE) that responded well to rituximab

in lieu of etoposide in the HLH-2004 protocol treatment.

CASE PRESENTATION

A 22-year-old African-American female presented to an outside hospital with nausea, vomiting and diarrhoea for 4 days. She also had progressive fatigue, fevers and weakness for 12 weeks and had lost a total of 12 pounds. She had a family history of SLE in her mother and was evaluated several months prior for concern of new onset SLE manifested by malar rash, inflammatory arthritis, positive antinuclear antibody and high titre anti-Smith and antiribonucleoprotein antibodies. She was lost to follow-up after initial evaluation and never started any medications for SLE. Her malar rash and arthritis had resolved spontaneously by the time of her presentation to the emergency room. She had no other pertinent medical history and was not taking any medications.

INVESTIGATIONS

Initial physical examination revealed a temperature of 102.7°F, heart rate of 125 beats/min, blood pressure of 108/67 mm Hg and respiratory rate of 16 breaths/min. Her lower abdomen was diffusely tender to palpation without peritoneal findings or organomegaly. The remaining physical examination was unremarkable. Initial laboratory evaluation revealed normal liver-associated enzymes and complete blood count. Serum chemistry showed mild hyponatremia and hypokalaemia. D-dimer was elevated to 954 ng/mL. Chest radiograph, CT pulmonary angiogram and abdominal ultrasound were unremarkable.

Her heart rate and serum chemistry abnormalities normalised with intravenous fluids. Blood, urine and viral cultures were obtained. A single dose of metronidazole was given in the emergency room. She was admitted to the hospital for observation and antibiotics were held. She continued to have fever, nausea, vomiting, and diarrhoea over the next 24 hours. A CT scan of the chest, abdomen and pelvis with contrast showed non-specific mesenteric lymph node enlargement and an enlarged external iliac lymph node measuring 12 mm. On hospital day 2, she underwent an excisional biopsy of the external iliac lymph node, which was remarkable for necrosis and scant cellularity on flow cytometry. Gram stain and culture were negative. The

CrossMark

To cite: Junga Z, Stitt R, Tracy C, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221347

Table 1 Infectious evaluation

Blood culture	No growth
Urine culture	No growth
Stool culture	No growth
Viral culture	Negative
<i>Clostridium difficile</i> PCR	Negative
Dengue IgM	Negative
HIV ab	Negative
Hepatitis A virus IgM	Negative
Hepatitis B virus core IgM	Negative
Hepatitis B virus surface antigen	Negative
Antistreptolysin O titre	Negative
Brucella titre	Negative
Cytomegalovirus IgM	Negative
Epstein-Barr virus IgM	Negative
Epstein-Barr PCR	Negative
Herpes simplex virus IgM	Negative
Cerebral spinal fluid culture	Negative
Cerebral spinal fluid protein	30 mg/dL (15–45 mg/dL)
Cerebral spinal fluid cell count	1 cell/ μ L (0–5 cells/ μ L)

gastrointestinal symptoms improved by hospital day 4, but she continued to have high grade fevers to 103°F without a specific pattern throughout the day, so intravenous, broad spectrum antibiotics were started. Initial and serial blood and urine cultures showed no growth. A broad infectious evaluation was unremarkable (table 1). Antibiotics were stopped on hospital day 8 because there was no improvement in fevers.

Additional lab tests were ordered. Antinuclear antibody titre was 1:2560 in a speckled pattern, double-stranded DNA antibodies were negative, extractable nuclear antigen panel was notable for high titre Smith and ribonuclear antibodies, complement 3 and 4 were normal and urinalysis was unremarkable. Beta-2-glycoprotein antibodies, anticardiolipin antibodies and lupus anticoagulant were negative. CT angiography of the abdomen and pelvis showed anasarca and fatty liver but no evidence of vasculitis. By hospital day 10, she developed a new headache. A CT scan of the head, MRI of the brain and a lumbar puncture were all normal. Cerebral spinal fluid Gram stain and culture were negative. It was noted that her haemoglobin, platelet count and white blood count had been decreasing throughout her hospitalisation with nadirs of 6.9 mg/dL, 99 000/ μ L and 1500/ μ L (absolute neutrophil count of 1000/mL), respectively. In addition, her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had been steadily climbing with peak of 402 IU and 379 IU, respectively, with interval development of splenomegaly on examination. A blood smear showed hypocoagulability but was otherwise unremarkable. A bone marrow biopsy showed hypocellularity without haemophagocytosis and was otherwise unremarkable. Further laboratory testing revealed a lactate dehydrogenase of 2664 U/L, ferritin >7500 ng/mL, triglyceride 452 mg/dL and fibrinogen 161 mg/dL.

DIFFERENTIAL DIAGNOSIS

1. MAS
2. Systemic lupus flare
3. Sepsis
4. Lymphoma

Figure 1 Ferritin (ng/mL) level over time from initial diagnosis to remission.

TREATMENT

A diagnosis of MAS was made based on the following HLH-2004 criteria: fever, markedly elevated ferritin, pancytopenia, hypofibrinogenaemia and hepatosplenomegaly with exclusion of other likely causes. She was started on the HLH-2004 treatment protocol with etoposide, cyclosporine and dexamethasone. Intrathecal methotrexate was held due to absence of central nervous system findings. On discharge, she requested to have her outpatient care transferred to our clinic to be near her family.

At the time of presentation to our clinic, she had received 2 weeks of HLH-2004 protocol. Ferritin and liver-associated enzymes had improved but continued to be elevated to 1060 ng/mL and AST 31 U/L and ALT 161 U/L, respectively (figure 1). Despite improvement in serum ferritin and liver-associated enzymes, her pancytopenia had become worse. The discordance was concerning for etoposide toxicity and continued disease activity. In addition, our patient declined to continue etoposide due to neuropathic symptoms in her upper extremities and severe nausea and vomiting. Etoposide was discontinued, and she was treated with 4 weekly doses of rituximab 375 mg/m² (total dose 620 mg). Cyclosporine and dexamethasone were continued per the HLH-2004 protocol (10 mg/m² with taper over 8 weeks).

OUTCOME AND FOLLOW-UP

Her clinical symptoms, complete blood count, ferritin and triglycerides all normalised (figure 1). She remains disease free 1 year following the last dose of rituximab and is currently maintained on hydroxychloroquine.

DISCUSSION

In this case, we describe an individual with MAS secondary to SLE. Our patient met diagnostic criteria for the HLH-2004 protocol and had a calculated HScore of 253 with 99.5% probability of having MAS, making us confident in her diagnosis.^{2,3} Haemophagocytosis was not seen on the bone marrow aspirate; however, this is not a sensitive or specific finding. In one study, only 70% of patients diagnosed with HLH had haemophagocytosis

on bone marrow aspirate, which may be secondary to tissue sampling and/or timing in the disease process.⁴ Our patient responded initially to the HLH-2004 protocol but could not tolerate etoposide after 2 weeks of therapy. Despite substituting rituximab for etoposide after only 2 weeks of therapy, she has had a sustained response and is currently in remission a year later with no disease activity.

HLH treatment was revolutionised by the advent of the HLH-94 study, which improved the long-term survival from 4% to a reported 5-year survival rate of greater than 50%. The treatment protocol included etoposide and dexamethasone for 8 weeks with the addition of methotrexate if there was evidence of CNS involvement. All patients were younger than 16 years and were excluded if they had an underlying rheumatic disease. Most patients likely had a genetic cause for their HLH, though the genes were not completely understood at the time of enrollment and were not tested.⁵ Although mortality vastly improved, the treatment protocol can have significant toxicities, notably cytopenias, infection, alopecia and severe nausea, vomiting and diarrhoea. The HLH-94 study and the HLH-2004 protocol are often extrapolated to the MAS population, but there is a paucity of data on its efficacy in this disease process. Studies have shown that MAS behaves differently than HLH and has an overall better prognosis.⁶ Weaver *et al*⁷ have argued that the common link between HLH and MAS is more likely hyperinflammation and, as such, treatment should be individualised to the underlying disease process. The ideal treatment regimen would be personalised to the patient's cytokine profile reflected by the underlying disease; however, we still lack understanding on which cytokines are the best to target.^{7,8} Currently, biological agents that precisely target cytokines in the pathogenesis of MAS are being developed with mixed results.⁹

Biological therapies are promising, but we have to look for a readily available therapy in our arsenal until an effective cytokine antagonist is commercially available for the treatment of MAS. Some experts advocate for disease-specific treatment of the underlying rheumatic disease rather than a one-size-fits-all approach with the HLH-2004 treatment protocol.¹⁰

Rituximab may be an effective treatment option for MAS by modulating various parts of the cytokine cascade along with the adaptive and innate immunity either as a monotherapy or an adjunct to the HLH-2004 protocol as was done with our patient, especially for underlying SLE.^{11,12} Our literature review found few published cases of rituximab successfully used in the treatment of MAS secondary to SLE.^{13,14} Although we cannot prove a causal relationship in this single case report, it does raise several questions. Can rituximab be used as monotherapy in treatment of MAS secondary to SLE? Is it possible to get by with a truncated course of etoposide? Does rituximab therapy result in a more sustained response given its long therapeutic effect? The future for treatment of MAS likely lies in the medicines that more precisely modulate the immune system to specifically target the cause of immune dysregulation. It is well known in the rheumatology community that rituximab has far less toxicity than etoposide and is much better tolerated by patients. There is a need for further research on rituximab's use in the treatment of MAS.

Learning points

- ▶ Macrophage activation syndrome (MAS) is difficult to diagnose.
- ▶ Rituximab may be an effective treatment option for MAS secondary to systemic lupus erythematosus (SLE), especially for maintenance of remission.
- ▶ The optimal treatment regimen for MAS should be directed at the underlying disease process. Universal treatment protocols like the HLH-2004 protocol may not be the best therapeutic option for every patient.

Contributors ZJ drafted the article and agrees to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved. RS analysed and interpreted the data and revised the manuscript critically for important intellectual content. CT and MK analysed and interpreted the data and revised the manuscript critically for important intellectual content as well as providing final approval of the version published.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Ravelli A, Minoia F, Davi S, *et al*. 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.
- 2 Henter JL, Horne A, Aricó M, *et al*. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124–31.
- 3 Fardet L, Galicier L, Lambotte O, *et al*. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014;66:2613–20.
- 4 Rivière S, Galicier L, Coppo P, *et al*. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. *Am J Med* 2014;127:1118–25.
- 5 Trottestam H, Horne A, Aricó M, *et al*. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood* 2011;118:4577–84.
- 6 Fukaya S, Yasuda S, Hashimoto T, *et al*. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. *Rheumatology* 2008;47:1686–91.
- 7 Weaver LK, Behrens EM. Hyperinflammation, rather than hemophagocytosis, is the common link between macrophage activation syndrome and hemophagocytic lymphohistiocytosis. *Curr Opin Rheumatol* 2014;26:562–9.
- 8 Shimizu M, Nakagishi Y, Yachie A. Distinct subsets of patients with systemic juvenile idiopathic arthritis based on their cytokine profiles. *Cytokine* 2013;61:345–8.
- 9 Shimizu M, Yokoyama T, Yamada K, *et al*. Distinct cytokine profiles of systemic-onset juvenile idiopathic arthritis-associated macrophage activation syndrome with particular emphasis on the role of interleukin-18 in its pathogenesis. *Rheumatology* 2010;49:1645–53.
- 10 Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood* 2015;125:2908–14.
- 11 Wiesik-Szewczyk E, Olesinska M. B-cell targeted therapy in systemic lupus erythematosus: potential of rituximab. *Biologics* 2012;6:347–54.
- 12 Xu D, Stedman A, Zhang L. CD20 antibody primes B lymphocytes for type I interferon production. *PLoS One* 2013;8:e67900.
- 13 So MW, Koo BS, Kim YJ, *et al*. Successful rituximab treatment of refractory hemophagocytic lymphohistiocytosis and autoimmune hemolytic anemia associated with systemic lupus erythematosus. *Mod Rheumatol* 2014;24:855–7.
- 14 Bakshi J, Hassan S, D'Cruz D, *et al*. Rituximab therapy in refractory macrophage activation syndrome secondary to systemic lupus erythematosus. *Lupus* 2013;22:1544–6.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow