The Journal of Rheumatology 2020;47:1461–3
doi:10.3899/jrheum.191274

The Journal of Rheumatology

Editorial

The Storm Beneath the Storm: MAS-HLH in Inflammatory Myopathies

Grant S. Schulert[1]

Hemophagocytic lymphohistiocytosis (HLH) represents a potentially life-threatening episode of overwhelming inflammation characterized by activation of T lymphocytes, hemophagocytic macrophages, and marked hyperferritinemia[1,2]. Historically, HLH has been classified as having a primary, genetic cause (familial HLH) or occurring secondary to an identified trigger including various infections, malignancies, or rheumatic diseases. When occurring in the setting of inflammatory or autoimmune disease, rheumatologists call secondary HLH the macrophage activation syndrome (MAS), and it is reflected as MAS-HLH in the updated Histiocyte Society nomenclature[3]. Episodes of MAS-HLH have been reported in nearly all rheumatic diseases, but are most commonly recognized in patients with systemic juvenile idiopathic arthritis (sJIA) or adult-onset Still disease (AOSD), systemic lupus erythematosus (SLE), Kawasaki disease, and certain monogenic autoinflammatory disorders[4,5]. In contrast, the inflammatory myopathies including dermatomyositis (DM) and polymyositis (PM) have typically been considered low-risk for development of MAS-HLH. In the current issue of *The Journal*, Liang and colleagues[6] present a large series of patients with adult idiopathic inflammatory myopathies that challenges this conventional wisdom, and suggest that MAS-HLH may represent an underappreciated cause of mortality in these disorders.

In this report, the authors identified 424 adult patients admitted to their institution over an 8-year period with DM, PM, or clinically amyopathic dermatomyositis (CADM)[6]. Interestingly, they found that 18 (4.2%) satisfied the 2004 diagnostic criteria for HLH[7]. This is in comparison to historical data for sJIA, which suggests that up to 17% may experience MAS-HLH[8]. The patients identified here with inflammatory myopathies complicated by MAS-HLH had a much higher short-term mortality rate than those without MAS-HLH (78% vs 7%). Liang and colleagues further performed a case-control study, matching those patients with MAS-HLH 1:4 by age and sex with myopathy patients who did not have MAS-HLH[6]. Cases and controls had broadly similar clinical features of their underlying myopathies including disease duration, skin findings, degree of arthritis, autoantibody status, and concomitant interstitial lung disease (ILD). This analysis did identify several factors that were associated with MAS-HLH, including on-admission disease activity [as assessed by the MYOACT (Myositis Disease Activity Assessment Visual Analogue Scale) score], acute exacerbation of ILD, gastrointestinal hemorrhage, infection, liver dysfunction, and hyperferritinemia. However, in multivariate logistic regression, only on-admission disease activity, worsening ILD, and infection were associated with risk for MAS-HLH. The authors also found that mycophenolate mofetil (MMF) was used more frequently in patients who did not develop MAS-HLH, although this did not reach significance in the multivariate analysis[6]. Given the relatively low number of patients, the authors were not able to identify any significantly different clinical features between the subtypes of inflammatory myopathies, although patients with CADM had a trend toward lower mortality rates.

Previous reports in the literature of MAS-HLH complicating inflammatory myopathies are largely single case reports, with the largest prior series detailing 4 such patients[9]. Systematic reviews of MAS-HLH have similarly identified only scattered reports in patients with myositis, a fraction of those found in patients with sJIA, AOSD, and SLE[10]. This dogma may have led to a confirmation bias, where clinicians do not expect to find MAS-HLH and therefore fail to investigate its presence. The findings of

Dr. Schulert is supported by the US National Institutes of Arthritis and Musculoskeletal and Skin Disorders, National Institutes of Health, K08-AR072075.

[1]G.S. Schulert, MD, PhD, Division of Rheumatology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA.

Address correspondence to Dr. G.S. Schulert, Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45208 USA. Email: Grant.schulert@cchmc.org.

See Secondary hemophagocytic lymphohistiocytosis, *page 1532*

Liang, *et al*[6] suggest that this complication may occur much more commonly than previously recognized, and notably occurs in patients with the worst outcomes. Recognition of MAS-HLH is further complicated by the lack of diagnostic criteria for patients with inflammatory myopathies. In this study, authors used the HLH-2004 criteria, which are generally considered insensitive in the setting of rheumatic diseases[11], suggesting that the incidence of MAS-HLH highlighted in the present study may even be underrepresented. A recent report did find that the 2016 classification criteria for MAS-HLH in the setting of sJIA[12] may be very useful in patients with juvenile dermatomyositis (JDM)[13]. At least 8/12 patients with JDM-associated MAS-HLH satisfied the classification criteria, but the analysis was hampered by lack of key criteria (notably triglycerides and fibrinogen) in several patients. This demonstrates the urgent need for development and validation of criteria for early recognition of MAS-HLH in patients with inflammatory myopathies.

The clinical features identified here as associated with MAS-HLH, as well as prior case reports, may provide important clues toward recognition of this complication. The most consistent finding in this study was that MAS-HLH was associated with high levels of disease activity, as measured by the MYOACT. This is consistent with MAS-HLH in the setting of other rheumatic diseases including sJIA and SLE, where episodes frequently occur at diagnosis or disease flares[14,15]. Liang and colleagues also highlighted other findings that are unusual for inflammatory myopathies but common in MAS-HLH, including liver dysfunction and hyperferritinemia. Indeed, several prior case reports of MAS-HLH in the setting of myopathies similarly describe a shared disease course: atypical clinical features including liver dysfunction, central nervous system (CNS) involvement, and pan-cytopenia; initial improvement with corticosteroids followed by rapid worsening; and marked hyperferritinemia leading to ultimate diagnosis[16,17,18,19]. The association between MAS-HLH and worsening ILD is also particularly interesting. Several case reports of MAS-HLH in DM have detected antimelanoma differentiation-associated gene 5 (*MDA5*) autoantibody, which is strongly associated with ILD[19,20,21]; however, the authors note that *MDA5* presence was not assessed in most patients in the present study. In addition, chronic lung disease in children with sJIA is strongly associated with history of MAS-HLH[22]. This may suggest pathophysiologic overlap between risk for ILD and MAS-HLH in patients with rheumatic disease. The occurrence of MAS-HLH in a distinct subset of patients may also suggest potential genetic risks; for example, from hypomorphic variants in the lymphocyte cytolytic pathway genes, as has been proposed for other rheumatic diseases, most notably sJIA[23].

Taken together, the findings of Liang and colleagues[6] suggest that the life-threatening cytokine storm of MAS-HLH is an underappreciated cause of mortality in patients with inflammatory myopathies. Treating clinicians should be alert to signs of emerging MAS-HLH in such patients, particularly liver dysfunction, CNS involvement, and unexplained cytopenias. In particular, obtaining a serum ferritin level in such patients could either largely rule out MAS-HLH, or suggest the need for further evaluation. The best treatment approach for MAS-HLH in this setting is unknown, although case reports have detailed the successful use of intravenous immunoglobulin, calcineurin inhibitors, and plasmapheresis[17,19,20]. Interestingly, Liang, *et al* found an association between use of MMF and protection from MAS-HLH[6], suggesting that such T lymphocyte–targeting therapies may be beneficial in preventing emergence of this complication. Whether more targeted therapy such as cytokine blockade may be similarly beneficial remains unknown, but further supports the need for multisite and international collaborative approaches to address this cytokine storm.

REFERENCES

1. Risma K, Jordan MB. Hemophagocytic lymphohistiocytosis. Curr Opin Pediatr 2012;24:9-15.
2. Schulert GS, Canna SW. Convergent pathways of the hyperferritinemic syndromes. Int Immunol 2018;30:195-203.
3. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016;127:2672-81.
4. Bracaglia C, Prencipe G, De Benedetti F. Macrophage activation syndrome: different mechanisms leading to one clinical syndrome. Pediatr Rheumatol 2017;15:5.
5. Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. Rheumatology 2019;58:5-17.
6. Liang J, Xu D, Sun C, Chen W, Cao H, Lin J. Hemophagocytic lymphohistiocytosis: prevalence, risk factors, outcome, and outcome-related factors in adult idiopathic inflammatory myopathies. J Rheumatol 2020;47:1532-40.
7. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
8. Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine-directed therapies. Annu Rev Med 2015;66:145-59.
9. Yajima N, Wakabayashi K, Odai T, Isozaki T, Matsunawa M, Miwa Y, et al. Clinical features of hemophagocytic syndrome in patients with dermatomyositis. J Rheumatol 2008;35:1838-41.
10. Atteritano M, David A, Bagnato G, Beninati C, Frisina A, Iaria C, et al. Haemophagocytic syndrome in rheumatic patients. A systematic review. Eur Rev Med Pharmacol Sci 2012;16:1414-24.
11. Davì S, Minoia F, Pistorio A, Horne A, Consolaro A, Rosina S, et al. Performance of current guidelines for diagnosis of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Arthritis Rheumatol 2014;66:2871-80.
12. 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.
13. Poddighe D, Dauyey K. Macrophage activation syndrome in juvenile dermatomyositis: a systematic review. Rheumatol Int 2019 Sep 16 (E-pub ahead of print).
14. Grom AA, Horne A, De Benedetti F. Macrophage activation

syndrome in the era of biologic therapy. Nat Rev Rheumatol 2016;12:259-68.
15. Borgia RE, Gerstein M, Levy DM, Silverman ED, Hiraki LT. Features, treatment, and outcomes of macrophage activation syndrome in childhood-onset systemic lupus erythematosus. Arthritis Rheumatol 2018;70:616-24.
16. Yamashita H, Matsuki Y, Shimizu A, Mochizuki M, Takahashi Y, Kano T, et al. Hemophagocytic lymphohistiocytosis complicated by central nervous system lesions in a patient with dermatomyositis: a case presentation and literature review. Mod Rheumatol 2013;23:386-92.
17. Kaieda S, Yoshida N, Yamashita F, Okamoto M, Ida H, Hoshino T, et al. Successful treatment of macrophage activation syndrome in a patient with dermatomyositis by combination with immunosuppressive therapy and plasmapheresis. Mod Rheumatol 2015;25:962-6.
18. Bazan-Socha S, Zolcinski M, Szostek M, Jurczyszyn A, Rucinska M, Demczuk S, et al. A fatal case of acquired hemophagocytic lymphohistiocytosis (macrophage activation syndrome) in the initial course of dermatomyositis with anti-Jo-1 antibody. Int J Rheum Dis 2017;20:2171-4.
19. Yoshimatsu Y, Kotani T, Fujiki Y, Oda K, Kataoka T, Yamairi K, et al. Successful treatment with intravenous high-dose immunoglobulin for cardiomyopathy in dermatomyositis complicated with rapid progressive interstitial pneumonia. Int J Rheum Dis 2019;22:321-4.
20. Wakiguchi H, Hasegawa S, Hirano R, Kaneyasu H, Wakabayashi-Takahara M, Ohga S. Successful control of juvenile dermatomyositis-associated macrophage activation syndrome and interstitial pneumonia: distinct kinetics of interleukin-6 and -18 levels. Pediatr Rheumatol Online J 2015;13:49.
21. Nagashima T, Kamata Y, Iwamoto M, Okazaki H, Fukushima N, Minota S. Liver dysfunction in anti-melanoma differentiation-associated gene 5 antibody-positive patients with dermatomyositis. Rheumatol Int 2019;39:901-9.
22. Schulert GS, Yasin S, Carey B, Chalk C, Do T, Schapiro AH, et al. Systemic juvenile idiopathic arthritis–associated lung disease: characterization and risk factors. Arthritis Rheumatol 2019; 71:1943-54.
23. Zhang M, Behrens EM, Atkinson TP, Shakoory B, Grom AA, Cron RQ. Genetic defects in cytolysis in macrophage activation syndrome. Curr Rheumatol Rep 2014;16:439.