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Editorial

Hyperferritinemia Wins Again: Defining Macrophage Activation Syndrome in Pediatric Systemic Lupus Erythematosus

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Macrophage activation syndrome (MAS) is a potentially life-threatening condition of hyperinflammation that can be secondary to an underlying chronic rheumatic condition, commonly systemic juvenile idiopathic arthritis (sJIA) but also childhood-onset systemic lupus erythematosus (cSLE). MAS is characterized by excessive activation of T lymphocytes and macrophages that lead to overproduction of cytokines and results in cytopenia, liver dysfunction, and coagulopathy[1]. It is critical to recognize MAS early in order to initiate the appropriate treatment quickly and prevent morbidity and mortality. However, in MAS secondary to rheumatic conditions, it can be difficult to distinguish MAS from active disease due to overlapping inflammatory features. Criteria to diagnose MAS in children with sJIA have been developed and initially validated[2,3]. Guidelines to diagnose MAS in children with SLE have been previously proposed though not further validated[4]. In the current issue of *The Journal of Rheumatology*, Gerstein and colleagues present novel criteria to discriminate MAS from active disease in patients with newly diagnosed cSLE, especially in those who are hospitalized, and compare the performance of their developed criteria to existing criteria[5].

In this report, the authors retrospectively reviewed hospitalizations of patients newly diagnosed with cSLE at a single center and divided patients into 2 cohorts from 2003–2007 and 2008–2013. They selected patients who were febrile, with no prior corticosteroid exposure, and with no evidence of infection. These criteria identified 34 patients in the 2003–2007 cohort and 41 patients in the 2008–2013 cohort. The diagnosis of MAS was based on expert opinion of the treating clinician during the hospital admission and validated by an independent investigator. Out of the total cohort of febrile, hospitalized patients with new diagnosis of cSLE, 26% of patients had a diagnosis of MAS. While there were no statistically significant differences based on clinical features between the 2 patient groups with and without MAS, use of the recursive partitioning technique allowed for identification of cutoff laboratory values to differentiate patients with MAS from those without MAS. The team developed 3 sets of criteria utilizing data from each subcohort and the total cohort. Interestingly, hyperferritinemia and cytopenia—specifically leukopenia and lymphopenia—were identified as the key features to distinguish MAS from active cSLE disease. The first set of criteria included ferritin ≥ 669 μg/L. The second set of criteria included (1) ferritin ≥ 1107 μg/L, and (2) lymphocyte count < 0.72 × 103/mm^3. The third and best-fitting model using the total cohort included (1) ferritin ≥ 669 μg/L and (2) white blood cells < 2.25 × 103/mm^3.

This work provides a critical step forward in the goal to improve our identification of patients with MAS complicating cSLE, especially in newly diagnosed, hospitalized patients. By applying existing hemophagocytic lymphohistiocytosis (HLH) and MAS criteria to the current dataset, the authors demonstrated improved performance of their newly developed criteria for MAS in cSLE. The 2004 HLH diagnostic guidelines[6] had low sensitivity of 47% when applied to a subset of the patients who had a bone marrow aspirate/biopsy performed. While the specificity was high at 93%, we agree with the authors that reliance on a procedure that is difficult to complete in critically ill patients or other specialized testing with limited availability could result in a delay of diagnosis. Preliminary criteria for MAS in cSLE proposed by the PReS Lupus Working Group[4] demonstrated 100% sensitivity but only 25% specificity, likely due to lower laboratory threshold values. The authors suggest a potential algorithm that combines both the PReS Lupus Working

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Group criteria and their newly defined criteria to improve identification of MAS in cSLE. Additional validation with an independent patient cohort could help further determine optimal application of these criteria for use in routine clinical care.

Notably, the authors' findings are consistent with existing criteria for MAS in sJIA, especially the ferritin threshold of 600–700 μg/L. Both the current report and previous work in sJIA use clinician diagnosis as the gold standard; therefore, there may be bias in how these criteria are developed with clinicians using existing criteria in their diagnostic assessment. However, the authors of the current report also incorporated response to therapy in their MAS diagnosis verification procedure to increase confidence in the presence of MAS. While there was a high prevalence of MAS observed in 26% of the patients in this cohort, it is possible that MAS still remains underdiagnosed in cSLE, as has been observed in sJIA[7,8]. Use of a more objective gold standard to diagnose in a prospective manner is challenging to study due to the rarity of these conditions.

It is also interesting that while the authors retrospectively searched for hospitalizations within 12 months of cSLE diagnosis, all cases of MAS occurred within 30 days of cSLE diagnosis. This is consistent with repeated reports in the literature of MAS occurring with the initial presentation of cSLE[9,10]. Therefore, we should have a high suspicion of MAS in patients with newly diagnosed cSLE, especially if febrile and hospitalized. A previous comparison of MAS between cSLE and sJIA demonstrated lower ferritin levels in cSLE compared to sJIA, but more frequent multiorgan failure[11]. Data from US hospitalized children showed a delay in time to first ferritin level in patients with cSLE compared to sJIA[12]. While there is evidence that treating cSLE disease activity is often sufficient to also treat secondary MAS due to almost universal use of methylprednisolone in cSLE induction, many patients require additional therapy, including anakinra, calcineurin inhibitors, and intravenous Ig, to more specifically target MAS[13]. Moreover, higher mortality across cSLE and sJIA patients with MAS was observed when referred to a tertiary care center ≥ 15 days after the onset of MAS symptoms[14]. Therefore, early recognition is critical to initiate appropriate intervention and prevent adverse outcomes.

In addition to improving pediatric rheumatologist awareness of MAS in cSLE, it is also important to educate other clinicians on the prevalence and significance of these conditions. Further, working to implement systematic changes to screening procedures would improve the reliability of MAS evaluation in patients with cSLE and prevent diagnostic delay. Studies by Halyabar, *et al* and Hoyt, *et al* have demonstrated that developing and implementing a standard approach to the management of patients with fever and ferritin > 500 μg/L across disciplines[15] decreased time to MAS diagnosis from 8.4 to 2.8 days and decreased mortality from 25% to 6.7%[16]. This provides support that serum ferritin could serve as an important screening tool in hospitalized febrile patients to achieve earlier recognition and intervention on MAS. In fact, ferritin ≥ 627 μg/L has been shown to be 89% specific with 95% sensitivity to identify patients with MAS compared to all febrile hospitalized patients[17].

In summary, the findings of Gerstein and colleagues is an important contribution to the field by providing additional tools to recognize MAS as a complication of newly diagnosed cSLE and to distinguish MAS from active disease. As fever and pancytopenia are frequently present during cSLE presentation, the addition of serum ferritin to the evaluation may help to identify MAS early during hospitalization and save lives. Continued work in this area is needed to further validate and reliably implement a screening protocol based on identified criteria.

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