Editorial

The Big Bad Wolf: Macrophage Activation Syndrome in Childhood-Onset Systemic Lupus Erythematosus

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For decades, rheumatologists have recognized that certain patients are at risk for developing life-threatening episodes of systemic hyperinflammation and multiorgan system dysfunction, which was termed *macrophage activation syndrome* (*MAS*), due to the distinctive finding of highly activated macrophages or histiocytes with hemophagocytic activity seen in tissue.[1-3] This clinical picture, including hyperferritinemia; anemia and consumptive coagulopathy; and hepatic, neurologic, and hematologic dysfunction, was proposed by Grom and Passo as well as Ramanan and Baildam to represent a form of secondary hemophagocytic lymphohistiocytosis (HLH).[4,5] Primary HLH consists of several rare recessive disorders, typically presenting in childhood, that collectively represent defects in the perforin cytolytic pathway and lead to profound immune dysregulation.[6] Interestingly, several studies have shown that children and adults with MAS occurring in the setting of the Stills spectrum disorders—systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still disease (AOSD)—have a high prevalence of single copy, hypomorphic mutations in the genes encoding perforin (*PRF1*) or other key proteins in the cytolytic pathway.[7-9] While the most common rheumatic condition associated with MAS in pediatric rheumatology is sJIA, MAS is increasingly recognized as complicating childhood-onset systemic lupus erythematosus (cSLE). However, the mechanisms of MAS specific to patients with cSLE are largely undefined, and whether similar genetic risks are present in these patients has not been carefully examined.

In this issue of *The Journal of Rheumatology*,[10] Lahiry and colleagues describe the prevalence of HLH-related gene variants found in a large, single-center cohort of cSLE. The authors identified 19 patients in the lupus cohort at The Hospital for Sick Children in Toronto (SickKids) who had been diagnosed with MAS and underwent whole-exome sequencing (WES) and/or whole-genome sequencing (WGS). These were compared to 62 patients with cSLE who had WGS performed for suspected monogenic lupus due to early age of onset, consanguinity, or strong family history. Compared to these patients, children with cSLE-MAS were younger at SLE diagnosis, and more likely to have fever, nephritis, leukopenia, and hypocomplementemia but less likely to have rash. Most episodes of cSLE-MAS (84%) were diagnosed at SLE disease detection, and only 16% had identified infectious triggers. The study then examined WES/WGS data to identify low-frequency (minor allele frequency [MAF] < 0.05) exonic variants in 16 prespecified genes associated with familial HLH.[11] Such variants were very common, found in 60% of all cSLE patients including 32% carrying 2 or more variants. However, there was no significant differences between the proportion of cSLE-MAS and non-MAS patients with HLH-associated variants, whether considering all variants, all nonsynonymous variants, or predicted pathogenic variants. None of these variants were previously reported to be pathogenic in patients with primary familial HLH, and only one variant found in patients with cSLE-MAS had a significantly higher MAF than in the general population. In addition, no patients carried homozygous variants, although 2 patients each carried 2 heterozygous variants in *LYST* or *AP3B1*. As such, the presence of HLH-associated variants did not significantly increase the risk of cSLE-MAS in this cohort. Together, these data suggest that hypomorphic variants in the perforin cytolytic pathway may not have a major role in the pathogenesis of MAS in patients with SLE.

The findings of this study[10] challenge the evolving hypothesis of the pathogenesis of MAS, which has largely been derived from studies of patients with Stills spectrum disorders. Several independent studies have found a high proportion of patients with sJIA-MAS (35-40%) carry rare, pathogenic, hypomorphic variants in genes linked to primary HLH.[7,9,12] In particular, Kaufman and colleagues found that such variants were found significantly more often in patients with sJIA-MAS than in patients with sJIA who never experienced MAS.[9] Similarly high

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proportions of such variants have been found in patients with secondary HLH due to a variety of triggers,[13] as well as those with clinical features of MAS-HLH in the setting of fatal H1N1 influenza infection.[14] While the present study did find rare, predicted pathogenic variants in HLH-related genes in 47% of patients with cSLE with MAS, this was not different from the larger cohort of patients with SLE with WGS performed. A significant limitation of the present study is that patients with cSLE-MAS were not matched to the patients with non-MAS cSLE examined; rather, the comparator population was selected for sequencing due to concern for monogenic SLE. Thus, one possible conclusion is that hypomorphic variants in the perforin cytolytic pathway have a more general role in the pathogenesis of cSLE regardless of a patient's underlying risk of MAS. However, if these findings are confirmed with a more carefully matched population of patients with SLE, it would suggest that the mechanisms of SLE-MAS are fundamentally different from those in the Stills spectrum disorders of sJIA and AOSD.

The occurrence of MAS in patients with SLE including cSLE is increasingly recognized. In adults, SLE has long been considered the most common rheumatologic trigger of secondary MAS-HLH,[15] due in part to the much higher prevalence of SLE than in children. However, MAS can also complicate cSLE, with some studies suggesting it can be associated with more severe organ involvement and higher mortality than in adults with

SLE.[16] The largest study examining occurrence of cSLE-MAS was recently described by Borgia and colleagues from SickKids, who reported that 9% of their lupus cohort had experienced MAS, the majority concomitant with cSLE diagnosis.[17] Children with cSLE-MAS had an overall similar disease course to patients without MAS with respect to organ dysfunction and damage, but had a significantly higher mortality rate. Given that MAS and SLE can have overlapping symptoms including fever, cytopenias, hepatitis, and central nervous system involvement, prompt diagnosis of SLE-MAS is challenging and imperative. There do exist proposed diagnostic criteria for cSLE-MAS that include both clinical and laboratory variables,[18] but these have not been extensively validated. Recent work from the SickKids cohort also found that elevated serum ferritin was the best discriminator to identify MAS in cSLE,[19] and highlighted the importance of such testing in acutely ill, febrile patients with SLE.

The findings of Lahiry and colleagues challenge us to rethink and carefully consider the pathogenic mechanisms that underlie MAS in SLE.[10] The current model for MAS, derived largely from work in the Stills spectrum disorders, is that extremely very high levels of interleukin (IL)-18 drive persistent activation of lymphocytes and natural killer cells, frequently with genetic impairments in cytolytic capacity, which together cause hyperproduction of interferon (IFN)-γ that activates macrophages to release proinflammatory cytokines (Figure). This
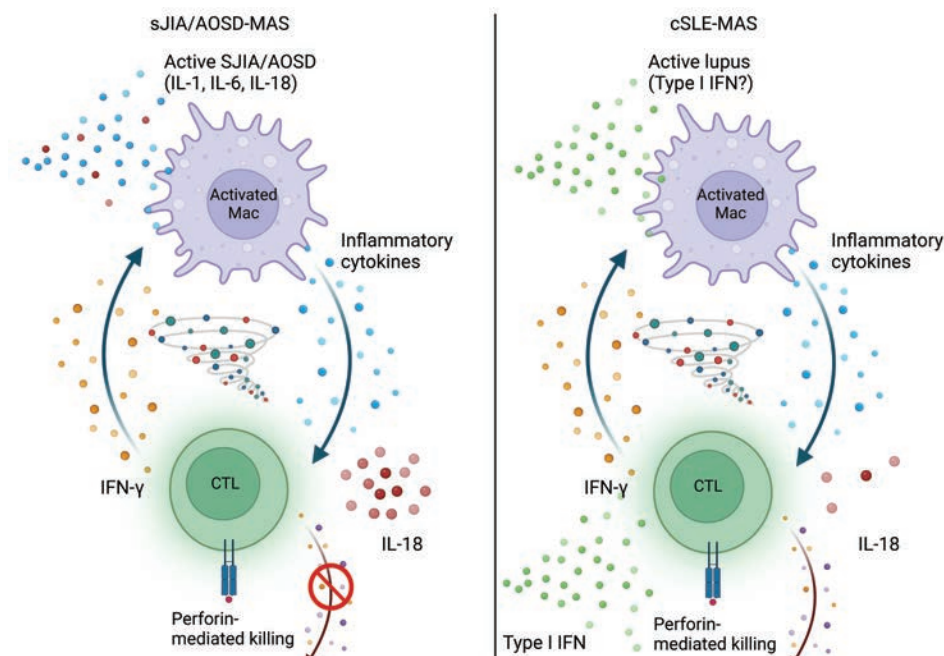

Figure. Proposed inflammatory loops in MAS. (Left) In MAS in the setting of the Stills spectrum disorders sJIA and AOSD, high macrophage-derived proinflammatory cytokines including IL-18 drive systemic inflammation. Markedly elevated IL-18 activates CTL, which have impaired perforin-mediated killing, and produce high levels of IFN-γ. IFN-γ, along with other inflammatory cytokines, further activates macrophages to perpetuate the inflammatory loop, and leads to the clinical features of cytokine storm. (Right) Highly active SLE is notable for elevated type I IFN, which could serve to amplify proinflammatory cytokine production from monocytes and macrophages. Inflammatory cytokines, possibly including IL-18 and type I IFN, could then drive activation of functionally normal CTL to produce high levels of IFN-γ to perpetuate the inflammatory loop. AOSD: adult-onset Still disease; cSLE: childhood-onset systemic lupus erythematosus; CTL: cytolytic T cells; IFN: interferon; IL: interleukin; MAS: macrophage activation syndrome; sJIA: systemic juvenile idiopathic arthritis; SLE: systemic lupus erythematosus.

inflammatory loop then becomes excessively amplified, leading to unremitting immune activation and the clinical features of multiorgan dysfunction seen in MAS.[20] The dysregulation of this cytokine-IFN-γ axis is felt to be the central driver of systemic inflammation in hyperferritinemic cytokine storm syndromes including HLH and MAS.[21] Specific therapies targeting IFN-γ have been shown to be highly effective in HLH,[22] and multiple ongoing clinical trials are targeting IL-1, IL-18, and IFN-γ in MAS (ClinicalTrials.gov: NCT02780583, NCT05001737, NCT04641442). However, even prior to the present study,[10] emerging data suggested that a fundamentally different mechanism may contribute to SLE-MAS. First, the majority of patients with cSLE-MAS appear to be diagnosed with MAS at the time of SLE disease detection and without concomitant infections[10,17]; in contrast, infectious triggers are commonly identified in sJIA-MAS, particularly in patients on biologic therapy.[23] Most notably, however, patients with SLE-MAS do not demonstrate the same degree of extreme IL-18 elevation as seen in sJIA-MAS. One recent study found that patients with MAS in the context of SLE (or juvenile dermatomyositis and Kawasaki disease) had levels of IL-18 100-fold lower than seen in sJIA-MAS, despite similar levels of IFN-γ–induced proteins including CXCL9.[24,25] This is in good agreement with work from Weiss and colleagues suggesting that markedly elevated IL-18 and IL-18/CXCL9 ratio is not broadly seen in HLH but rather distinguish a subset of hyperferritinemic cytokine storms such as MAS in the setting of sJIA and AOSD.[26] Therefore, we are left with the key unanswered question: if SLE-MAS is fundamentally different from MAS in the setting of Stills spectrum disorders, what then are the triggers, causes, and best treatments for MAS in SLE? The answer is not clear, although notably, the potential role of excessive type I IFN production as a key driver of MAS in SLE has not been well studied.[27] Answers to these questions are urgently needed to inform best practices for the diagnoses, treatment, and prevention of SLE-MAS.

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