The History of Macrophage Activation Syndrome in Autoimmune Diseases

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The aim of this chapter is to present an overview of the history of macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (HLH).

In 1952, Farquhar et al. first described a familial disease that was clinically characterized by fever, hepatosplenomegaly, skin rash, lymphadenopathy, and central nervous system (CNS) involvement. Laboratory investigation showed a pancytopenia, a low ESR, abnormal liver function tests (LFTs), an abnormal prothrombin time (PT), and an abnormal cerebral spinal fluid examination (CSF) [1]. They termed this syndrome familial hemophagocytic reticulosis (FHR). The term was later changed to familial hemophagocytic lymphohistiocytosis (FHLH) and then just hemophagocytic lymphohistiocytosis (HLH). In 1997, the HLH Study Group defined primary HLH and secondary HLH. Both illnesses were characterized by activation of the mononuclear phagocytic system. Secondary HLH included virus-associated hemophagocytotic syndrome (VAHS) [now called infection-associated hemophagocytic syndrome (IAHS)], malignancy-associated hemophagocytic syndrome (MAHS), and HLH following prolonged intravenous nutrition, including administration of soluble lipids (fat overload syndrome). There was no mention of rheumatic diseases as a cause of secondary HLH [2]. HLH criteria were further updated in 2004, and these are the criteria that are currently used [3].

Secondary HLH

In 1939, Scott et al. described four patients with HLH and reviewed five patients found in the literature. These patients were described as having "atypical Hodgkin's disease." The patients had the following clinical features in common: fever, wasting,

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generalized lymphadenopathy, and hepatosplenomegaly with jaundice and purpura. Laboratory investigations showed anemia, thrombocytopenia and marked leukopenia. Post-mortem examination revealed hyperplasia of histiocytes throughout the lymphoreticular tissue, and, importantly, there was evidence of profound erythrophagocytosis by histiocytes. The cellular proliferation with active phagocytosis was most prominent in the medullary portion of node, spleen, and periportal areas of liver. The authors therefore termed this syndrome histiocytic medullary reticulosis (HMR) [4]. Even as late as 1973, a large review of histiocytic disorders still referred to HMR as a malignancy and felt it was a 'well differentiated form of reticulum cell sarcoma' [5]. It was not until 1979 that Risdall et al. introduced the term viral-associated hemophagocytic syndrome (VAHS) to differentiate HMR from malignant histiocytic disorders. It should be noted however, that 5 out of 19 patients described did not have a documented, or any evidence of, infection at the time of diagnosis of VAHS [6]. Despite this and other publications, even as late as in 1984 HMR was still occasionally called a malignant disorder, although the term "reactive" was beginning to gain usage [7]. It soon became recognized that his syndrome was associated with multiple hematologic malignancies as well as viruses (reviewed in [8]). However, the term macrophage activation syndrome (MAS) was not coined until 1993.

MAS in Rheumatic Diseases

Difficulty in Diagnosis of MAS in Rheumatic Diseases

The term MAS appears to be used only when secondary HLH is associated with an autoimmune disease and has led to confusion in terminology and diagnosis. Furthermore, it can be difficult to be sure of the diagnosis of secondary HLH in autoimmune diseases (MAS) as a result of the great overlap of the clinical and laboratory features between HLH and the underlying autoimmune disease. This is likely because activation of the immune system, including macrophages, is characteristic of autoimmune disease while the diagnostic criteria for HLH were based on the differentiation of this disease entity from other diseases of histiocytes rather than from patients with chronic activation of the immune system as seen in autoimmune diseases. Therefore, absolute levels of many of the diagnostic features may not be relevant in patients with autoimmune diseases. Furthermore, the criteria have not been validated in either pediatric or adult cases of MAS [9]. This was first recognized in patients with systemic juvenile idiopathic arthritis (sJIA) [10] but also applies to patients with other autoimmune diseases including systemic lupus erythematosus (SLE) which is frequently associated with levels of both soluble interleukin-2 receptor (sIL-2R) and ferritin (both part of the diagnostic criteria of HLH) within levels in the diagnostic criteria of HLH, while fibrinogen is often not below HLH diagnostic levels. The latter observation is likely the result of the elevation of

baseline fibrinogen levels, as it is an acute phase reactant. Similarly, triglycerides maybe elevated in patients on corticosteroids. By contrast, elevated liver function tests (LFTs), generalized lymphadenopathy, hypoproteinemia, hyponatremia, and decreased HDL in MAS are frequently seen although only considered supportive of the diagnosis of HLH according to 2004 criteria [3].

MAS in Juvenile Idiopathic Arthritis (JIA)

The first use of the term "activated macrophages" in patients with what we now refer to as sJIA was in 1985 by Hadchouel et al. [11]. They described seven patients who developed sudden onset of fever with altered level of consciousness bleeding and hepatosplenomegaly. Laboratory investigations showed a fall in fibrinogen, hemoglobin, white blood cell count, platelets, and ESR with increased fibrin split products, and LFTs. In three patients, it was following a second injection of gold (vide infra), while in the other 4 there was either evidence of a recent infection, non-steroid anti-inflammatory drug (NSAID) use, or no known cause. Liver biopsy showed evidence of diffuse Kupffer cell hyperplasia. Many of the Kupffer cells contained ceroid or lipofuscin pigments but were without evidence of "excessive phagocytosis" and no erythrophagocytosis. Bone marrow examination in two patients showed large macrophages with phagocytosed material but no erythrophagocytosis. They concluded that the main histological feature was macrophage activation and hypothesized that these activated macrophages secreted enzymes that lead to the clinical picture. The first published paper which used the term macrophage activation syndrome in its title was in 1993 [12]. This paper described four patients with childhood-onset rheumatic diseases who clinically had fever, hepatosplenomegaly, pancytopenia, low ESR, abnormal LFTs, and hypofibrinogenemia. Bone marrow aspiration showed active hemophagocytosis. In two patients, there was evidence of high levels circulating cytokines. In 1994, it was then proposed that activated macrophages can lead to this syndrome, including the low fibrinogen and increased fibrin degradation products commonly seen in these patients [13].

Although these papers referred to the above defined MAS as a disease entity, previous publications described patients with sJIA who had this clinical syndrome. However, the authors used different names to describe the clinical and laboratory findings in these patients. It is likely that the first report was in 1971. This paper described seven patients with abnormal LFTs accompanied by a fall in ESR, platelets, hemoglobin, and/or white blood cell (WBC) count. Many of the patients had a new-onset macular rash which was different from the rash of sJIA and/or increased adenopathy, and/or hepatosplenomegaly. It is likely that at least some of these patients had MAS. In one patient each, the clinical syndrome was present a) shortly following diagnosis; b) following second injection of gold; and c) with concomitant EBV infection [14]. The next reports were not until 1983 when two papers appeared that described patients with sJIA who developed a picture of disseminated intravascular coagulation (DIC)/consumptive coagulopathy [15, 16].

Silverman et al. described seven patients with sJIA who had a fall in hemoglobin, platelet count, fibrinogen, and ESR with elevated LFTs, PT, and/or PTT, and fibrin split products. In two patients, this clinical picture occurred following the second injection of gold salts, while in the other five it was either at presentation or during a time of disease flare. In two patients, this syndrome recurred [16]. The other paper, by De Vere-Tyndall et al., described two patients with sJIA who developed a fall in hemoglobin, platelet count, ESR, with elevation of PT/PTT, fibrin degradation products, and evidence of active bleeding. In one patient, it followed a third injection of gold and in the other following an infection [15]. A paper from 1985 reported a patient with sJIA who developed what appears to be MAS during an episode of chickenpox. A bone marrow aspiration was reported as showing histiocytic medullary reticulosis (hemophagocytosis). The final diagnosis was VAHS [17]. In the same year, a patient with sJIA developed the clinical syndrome of MAS during a Coxsackie infection. Bone marrow aspiration showed hemophagocytosis, and the patient was reported to have histiocytic medullary reticulosis [8]. sJIA is now the most commonly cited cause of MAS and classification criteria have been proposed [18], although systemic lupus erythematosus (SLE) in MAS may account for more patients in total (see below).

Although MAS in patients with JIA is most commonly seen in patients with sJIA, it has also been described in other JIA subtypes [19].

MAS in Systemic Lupus Erythematosus (SLE)

Despite the recognition of MAS as early as 1985 in sJIA and in adult-onset Still disease (AOSD), it was until 1991 that the first recognized case of MAS in patients with SLE was described in the literature [20]. However, in 1979, Risdall et al. described a case of virus-associated MAS in a patient with SLE [6]. The reason for this late recognition in SLE is likely for two reasons: (1) As described above, there are many overlapping clinical and laboratory features of SLE and MAS; and (2) Unlike sJIA patients, SLE is known to have a significant mortality even at presentation. However, since then, there have many cases series and large cohorts of patients with both childhood-onset SLE (cSLE) and adult-onset SLE (aSLE) [21].

In adults, SLE is the most common rheumatic disease leading to MAS, and most reviews report that SLE is responsible for the majority of cases of MAS in adult rheumatic diseases (described below). The incidence of MAS in aSLE has been reported to be between 0.9 and 4.6% [22]. A report from France in 2017 reported 89 patients with aSLE and MAS [23]. A review of the literature of MAS in patients with rheumatic disease showed that the most common reported cause was sJIA with SLE second. However, similar to what is seen in aSLE, in our hospital, we see more cases of MAS secondary to SLE than sJIA (unpublished data), although others have reported that MAS occurs more frequently in sJIA than cSLE [24]. In childhood, MAS has been associated with Kikuchi's disease with and without associated SLE [25].

MAS in Kawasaki Disease (KD)

The first reported case in the literature of MAS secondary to KD appeared in a 1995 article that described a 32-month-old boy from Japan who developed HPS during KD that was resistant to treatment. It is interesting to note that this patient had elevated interferon-gamma (IFN-γ) levels at the time of MAS but not earlier during the course of his KD [26]. A systematic review of MAS in KD, as of September 2016, reviewed 67 cases of MAS in the literature, and two reported new cases. The first four case reports suggested that MAS occurred late following the diagnosis of KD (range 20–24 days after onset first symptom) and following failure of IVIG treatment (2–5 courses). The systemic review demonstrated that in KD, MAS either preceded (6%) or was simultaneous with KD presentation (21%). The initial observation that MAS in KD tended to be in older children was confirmed in a systemic review, as 34/69 KD patients were >5 years old [27]. Similar to what has been described in other causes of MAS, mild MAS may be seen in KD, and, in fact, Choi suggested that all patients with refractory KD should be considered to have 'occult' MAS [28]. A systematic review of MAS in rheumatic disease patients in 2012 reported that in 6% of patients MAS was associated with KD [29]. Conversely, MAS occured in 1.9–4.7% of KD patients [30, 31]. In 2016, it was suggested that HLH criteria may not be a good indicator of MAS in KD and suggested the possibility of testing the MAS using sJIA 2016 MAS criteria [32].

MAS in Adult Rheumatic Diseases

The first patient with adult rheumatoid arthritis (RA) with MAS was described in 1977 [33]. Interestingly, although the authors concluded it was HMR presenting as RA, the patient had a 4-year history of joint pains, but at the time of presentation the patient developed pancytopenia, a fall in ESR, hepatosplenomegaly, and generalized lymphadenopathy, and died. Postmortem examination of lymph nodes, liver, and spleen revealed histiocytic infiltrate with marked erythrophagocytosis. By 2007, 11 cases secondary to RA had been reported in the Japanese literature [34]. A review of 30 cases of MAS in adults showed that it occurred in order of frequency: SLE—18 cases, ASOD—3 cases, and 2 cases each in patients with RA, polymyositis/dermatomyositis (PM/DM), systemic sclerosis (SSc), and Sjögren syndrome (SS), and one case in a patient with vasculitis [35]. MAS has also been reported in adults with polyarteritis nodosa, mixed connective tissue disease, pulmonary sarcoidosis, Goodpasture disease, Behcet disease, granulomatosis with polyangiitis, and ankylosing spondylitis [29, 36–38]. It has been proposed that the EULAR/ACR/PRINTO classification criteria for MAS can be used in AOSD [39].

Therapy of MAS

As MAS was first recognized in rheumatic diseases in sJIA, the initial treatment was dictated by the treatment of sJIA and included steroid, high dose oral or pulse, and IVIG. If this failed, then treatment was either initiated with HLH 1994 (mostly etoposide) or cyclosporine alone [40, 41]. By the early 2000s, the drug of choice for patients who failed steroid and IVIG therapy was cyclosporine [42], although other authors reported success with anti-TNF agents [43]. Calcineurin inhibitors (cyclosporine or tacrolimus) remain alternatives in patients who fail or are dependent on high doses steroids and IVIG. A key to the use of a calcineurin inhibitor is likely its earlier introduction. In the mid-2000s, other therapies included the use of antithymocyte globulin [44, 45] or monoclonal anti-CD25 antibodies [46, 47], but these therapies are not routinely used. Currently, many investigators suggest that IL-1 inhibition, in particular, anakinra, with its short half-life, is the drug of choice when a calcineurin inhibitor does not control the MAS or is contra-indicated [48–51]. However, the doses of anakinra that are required to control MAS may exceed the standard daily dose, and more frequent dosing may be required [51, 52]. There is at least a theoretical word of caution for the use of IL-1 inhibition in SLE patients with MAS as blocking the IL-1-TNF (Th1 pathway) may lead to production of Th2 cytokines which have been implicated in the pathogenesis of SLE. This issue remains to be resolved.

In resistant cases, treatment with the HLH-2004 protocol should be considered. Hematologists who treat patients with HLH are frequently involved in the treatment of patients with MAS. They tend to advocate the use of dexamethasone rather than prednisone and the early use of the HLH-2004 protocol for steroid/IVIG failures. The rationale for the use of dexamethasone over prednisone is that dexamethasone penetrates the CSF better than prednisone and patients with HLH frequently have CNS involvement. Certainly, when CNS involvement is seen in patients with MAS then dexamethasone should be used but its routine use in MAS is not as clear. There have not been any studies that compare prednisone to dexamethasone in MAS. The use of the HLH-2004 protocol and, in particular, the use of etoposide is frequently advocated by hematologists and resisted by rheumatologist because of its significant immunosuppressive properties and the potential for the development of malignancy [3]. Patients treated with etoposide are at high risk for sepsis, including invasive infection with opportunistic organisms leading to death. However, severe unresponsive MAS also leads to death. The current protocol at our institution is the use of IVIG and high dose prednisone, including pulse methylprednisolone, with the early introduction of a calcineurin inhibitor. If response is unsatisfactory, then the rapid introduction of anakinra is advocated with escalating doses and decreasing time between doses to get a rapid response to avoid the requirement for life-support. The requirement for admission to an intensive care unit is associated with a poor prognosis, and all attempts should be made to prevent this, including the consideration of the use of the HLH-2004 protocol.

Newer, more specific therapies directed against other cytokines may available in the future. A mouse model of MAS showed there was a significant upregulation of the interferon-gamma (IFN-γ) pathway. Mice were treated with an anti-IFN-γ antibody showed a significant improvement in survival which was associated with a significantly decreased level of circulating chemokines, CXCL9 and CXCL10, and downstream pro-inflammatory cytokines [53]. In patients with active MAS and other secondary for types of HLH, levels of IFN-γ and of IFN-γ-induced chemokines were markedly elevated during times of active MAS. Furthermore, in patients with sJIA and active MAS, these levels were higher than in patients with active sJIA without MAS [54].

A second cytokine, interleukin-18 (IL-18), which is upstream of IFN-γ, may also be important in the pathogenesis of MAS, and blocking its action may be another potential therapeutic target. As early as 2001, elevated levels of IL-18 were found in patients with active AOSD [55]. A mutation in the NLRC4 gene leads to infantile enterocolitis and recurrent MAS, which is associated with increased production of IL-18, and treatment with recombinant IL-18 binding protein (IL-18BP) was associated with resolution of MAS [56, 57]. Furthermore, it was shown that very high serum IL-18 levels were associated with the development MAS in patients with sJIA [58]. In the CpG-treated IL-18BP(−/−) mouse model of MAS, levels of IFN-γ and IFN-γ -associated chemokines were significantly increased as compared to wild-type mice, and the use of IL-18BP decreased the severity of both MAS and the IFN-γ response [59].

Animal Models

Animal models can be useful to suggest important pathogenic mechanism of human disease and to test potential therapies. I will briefly review the history of animal of HLH and MAS.

In 2004, Jordan et al. developed a murine model of HLH by infecting a perforin-deficient (pfp−/−) mouse strain with lymphocytic choriomeningitic virus (LCMV). These mice had multiple clinical and histologic features of HLH. There was evidence of activated CD68+ macrophages and elevated levels of both IFN-γ and, to a lesser extent, IL-18. Depletion experiments showed that CD8+ T cells secreting IFN-γ were required for the development of the HLH-like syndrome and death [60]. This model was used to demonstrate that perforin is required for the functioning of a reciprocal interaction between CD8+ T cells and dendritic cells, whereby antigen-primed DCS activate T cells, while primed CD8+ T cells suppress DC function (T cell activation) [61]. An animal model of familial HLH type4 (FHL4) has also been developed in a Stx11-deficient mouse. This model was used to show the importance of T-cell exhaustion as an important factor for determination of disease severity in HLH [62]. The generation of doubly or triply heterozygous for mutations in HLH-associated genes (perforin, Rab27a, and syntaxin-11) demonstrated that the accumulation of multiple monoallelic mutations increased the risk of developing HLH [63].

The results of this study suggest that double heterozygotes for HLH genes may develop HLH.

The development of animal models for secondary HLH or MAS has been less successful. Models using either repeated stimulation of TLR9 or chronic typhoid fever have been less helpful in gaining insights in HLH/MAS [64, 65]. However, the mouse model using repeated stimulation of TLR9 was used to show the importance of tissue levels of IFN-γ, and that CXCL9 and CXCL10 blood levels were important, and that neutralization of tissue IFN-γ correlated with CXCL9 and CXCL10 blood level normalization [66]. A CMV model of secondary HLH developed only a mild phenotype, and depletion of CD8+ T cells could not inhibit or cure the HLH-like syndrome [67]. More promising was the development of EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in a human CD34+ cell-transplanted humanized mouse model [68].

In two different murine models of HLH, JAK1/2 inhibitor or anti-IFN-γ antibody treatment prevented full-blown HLH when given after the development of disease [69, 70]. In the CMV-prf−/− model, treatment with IL-18 binding protein (BP) decreased hemophagocytosis and reversed liver as well as spleen damage and cytokine production by CD8+ T and NK cells [71]. Although these results are encouraging, there have not been clinical trials of these treatments undertaken in MAS.

Genetics

The history of the genetics of HLH began as early as 1999 [72]. Subsequently, autosomal recessive defects in PRF1, UNC13D, STX11, and STXBP2 genes were shown to be responsible for types 2, 3, 4, and 5 types of primary or familial HLH (FHL). These four genes are important in perforin-mediated lymphocyte cytotoxicity. Similarly, autosomal recessive mutations in RAB27A and LYST genes were shown to lead to secondary HLH seen in Griscelli syndrome type 2 (GS2) and Chédiak–Higashi syndrome (CHS). Patients with X-linked lymphoproliferative disease and mutations in SH2D1A or XIAP will frequently present with secondary HLH that is often triggered by Epstein–Barr virus (EBV) infection (reviewed [73]). Monogenic mutations leading to macrophage activation and autoinflammatory disease have been associated with MAS. One example is a defect in the NLRC4 inflammasome that leads to an early onset systemic inflammatory disease with MAS [74]. MAS had been seen in multiple auto-inflammatory diseases, including cryopyrin-associated periodic syndrome, mevalonate kinase deficiency, familial Mediterranean fever, and tumor necrosis factor receptor-associated periodic syndrome [75].

Testing of FHL-associated genes in patients with sJIA has shown that there is an increased frequency of heterozygous, but not homozygous, mutations patients with a history of MAS as compared to those without a history of MAS [76–79]. These mutations were associated with decreased perforin gene expression and/or function [79]. Similarly a heterozygous mutation in the perforin gene was found in a patient with adult RA who died of MAS [73].

The recognition and understanding of MAS pathophysiology has come a long way in the last several decades. New diagnostic criteria and the availability of agents targeting inflammatory cytokines should help survival of patients with rheumatic diseases who go on to develop MAS. The future is looking more encouraging for these patients, in terms of preventing fatal outcomes.

References

1. Farquhar, J. W., & Claireaux, A. E. (1952). Familial haemophagocytic reticulosis. *Archives of Disease in Childhood, 27*, 519–525.
2. Henter, J. I., Arico, M., Egeler, R. M., et al. (1997). HLH-94: A treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. *Medical and Pediatric Oncology, 28*, 342–347.
3. Henter, J. I., Horne, A., Arico, M., et al. (2007). HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatric Blood & Cancer, 48*, 124–131.
4. Scott, R., & Robb-Smith, A. (1939). Histiocytic medullary retiuculosis. *Lancet, 2*, 194–198.
5. Cline, M. J., & Golde, D. W. (1973). A review and reevaluation of the histiocytic disorders. *The American Journal of Medicine, 55*, 49–60.
6. Risdall, R. J., McKenna, R. W., Nesbit, M. E., et al. (1979). Virus-associated hemophagocytic syndrome A benign histiocytic proliferation distinct from malignant histiocytosis. *Cancer, 44*, 993–1002.
7. Stark, B., Hershko, C., Rosen, N., Cividalli, G., Karsai, H., & Soffer, D. (1984). Familial hemophagocytic lymphohistiocytosis (FHLH) in Israel. I. Description of 11 patients of Iranian-Iraqi origin and review of the literature. *Cancer, 54*, 2109–2121.
8. Heaton, D. C., & Moller, P. W. (1985). Still's disease associated with Coxsackie infection and haemophagocytic syndrome. *Annals of the Rheumatic Diseases, 44*, 341–344.
9. Otrock, Z. K., Daver, N., Kantarjian, H. M., & Eby, C. S. (2017). Diagnostic challenges of hemophagocytic lymphohistiocytosis. *Clinical Lymphoma, Myeloma & Leukemia, 17s*, S105–Ss10.
10. Parodi, A., Davi, S., Pringe, A. B., et al. (2009). Macrophage activation syndrome in juvenile systemic lupus erythematosus: A multinational multicenter study of thirty-eight patients. *Arthritis and Rheumatism, 60*, 3388–3399.
11. Hadchouel, M., Prieur, A. M., & Griscelli, C. (1985). Acute hemorrhagic, hepatic, and neurologic manifestations in juvenile rheumatoid arthritis: Possible relationship to drugs or infection. *The Journal of Pediatrics, 106*, 561–566.
12. Stephan, J. L., Zeller, J., Hubert, P., Herbelin, C., Dayer, J. M., & Prieur, A. M. (1993). Macrophage activation syndrome and rheumatic disease in childhood: A report of four new cases. *Clinical and Experimental Rheumatology, 11*, 451–456.
13. Prieur, A. M., & Stephan, J. L. (1994). Macrophage activation syndrome in rheumatic diseases in children. *Revue du Rhumatisme, 61*, 447–451.
14. Kornreich, H., Malouf, N. N., & Hanson, V. (1971). Acute hepatic dysfunction in juvenile rheumatoid arthritis. *The Journal of Pediatrics, 79*, 27–35.
15. De Vere-Tyndall, A., Macauley, D., & Ansell, B. M. (1983). Disseminated intravascular coagulation complicating systemic juvenile chronic arthritis ("Still's disease"). *Clinical Rheumatology, 2*, 415–418.
16. Silverman, E. D., Miller 3rd, J. J., Bernstein, B., & Shafai, T. (1983). Consumption coagulopathy associated with systemic juvenile rheumatoid arthritis. *The Journal of Pediatrics, 103*, 872–876.
17. Morris, J. A., Adamson, A. R., Holt, P. J., & Davson, J. (1985). Still's disease and the virus-associated haemophagocytic syndrome. *Annals of the Rheumatic Diseases, 44*, 349–353.

18. Ravelli, A., Minoia, F., Davi, S., 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. *Annals of the Rheumatic Diseases, 75*, 481–489.
19. Park, J. H., Seo, Y. M., Han, S. B., et al. (2016). Recurrent macrophage activation syndrome since toddler age in an adolescent boy with HLA B27 positive juvenile ankylosing spondylitis. *Korean Journal of Pediatrics, 59*, 421–424.
20. Wong, K. F., Hui, P. K., Chan, J. K., Chan, Y. W., & Ha, S. Y. (1991). The acute lupus hemophagocytic syndrome. *Annals of Internal Medicine, 114*, 387–390.
21. Borgia, R. E., Gerstein, M., Levy, D. M., Silverman, E. D., & Hiraki, L. T. (2018). Features, treatment, and outcomes of macrophage activation syndrome in childhood-onset systemic lupus erythematosus. *Arthritis & Rhematology, 70*, 616–624.
22. Granata, G., Didona, D., Stifano, G., Feola, A., & Granata, M. (2015). Macrophage activation syndrome as onset of systemic lupus erythematosus: A case report and a review of the literature. *Case Reports in Medicine, 2015*, 294041.
23. Gavand, P. E., Serio, I., Arnaud, L., et al. (2017). Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients. *Autoimmunity Reviews, 16*, 743–749.
24. Aytac, S., Batu, E. D., Unal, S., et al. (2016). Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus. *Rheumatology International, 36*, 1421–1429.
25. Khan, F. Y., Morad, N. A., & Fawzy, Z. (2007). Kikuchi's disease associated with hemophagocytosis. *Chang Gung Medical Journal, 30*, 370–373.
26. Ohga, S., Ooshima, A., Fukushige, J., & Ueda, K. (1995). Histiocytic haemophagocytosis in a patient with Kawasaki disease: Changes in the hypercytokinaemic state. *European Journal of Pediatrics, 154*, 539–541.
27. Garcia-Pavon, S., Yamazaki-Nakashimada, M. A., Baez, M., Borjas-Aguilar, K. L., & Murata, C. (2017). Kawasaki disease complicated with macrophage activation syndrome: A systematic review. *Journal of Pediatric Hematology/Oncology, 39*, 445–451.
28. Choi, U. Y., Han, S. B., Lee, S. Y., & Jeong, D. C. (2017). Should refractory Kawasaki disease be considered occult macrophage activation syndrome? *Seminars in Arthritis and Rheumatism, 46*, e17.
29. Atteritano, M., David, A., Bagnato, G., et al. (2012). Haemophagocytic syndrome in rheumatic patients. A systematic review. *European Review for Medical and Pharmacological Sciences, 16*, 1414–1424.
30. Kang, H. R., Kwon, Y. H., Yoo, E. S., et al. (2013). Clinical characteristics of hemophagocytic lymphohistiocytosis following Kawasaki disease: Differentiation from recurrent Kawasaki disease. *Blood Research, 48*, 254–257.
31. Latino, G. A., Manlhiot, C., Yeung, R. S., Chahal, N., & McCrindle, B. W. (2010). Macrophage activation syndrome in the acute phase of Kawasaki disease. *Journal of Pediatric Hematology/Oncology, 32*, 527–531.
32. Han, S. B., Lee, S. Y., Jeong, D. C., & Kang, J. H. (2016). Should 2016 criteria for macrophage activation syndrome be applied in children with Kawasaki disease, as well as with systemic-onset juvenile idiopathic arthritis? *Annals of the Rheumatic Diseases, 75*, e44.
33. Crow, J., & Gumpel, J. M. (1977). Histiocytic medullary reticulosis presenting as rheumatoid arthritis. *Proceedings of the Royal Society of Medicine, 70*, 632–634.
34. Katoh, N., Gono, T., Mitsuhashi, S., et al. (2007). Hemophagocytic syndrome associated with rheumatoid arthritis. *Internal Medicine, 46*, 1809–1813.
35. Fukaya, S., Yasuda, S., Hashimoto, T., et al. (2008). Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: Analysis of 30 cases. *Rheumatology, 47*, 1686–1691.
36. Dhote, R., Simon, J., Papo, T., et al. (2003). Reactive hemophagocytic syndrome in adult systemic disease: Report of twenty-six cases and literature review. *Arthritis and Rheumatism, 49*, 633–639.

37. Basnet, A., & Cholankeril, M. R. (2014). Hemophagocytic lymphohistiocytosis in a patient with Goodpasture's syndrome: A rare clinical association. *American Journal of Case Reports, 15*, 431–436.
38. Lou, Y. J., Jin, J., & Mai, W. Y. (2007). Ankylosing spondylitis presenting with macrophage activation syndrome. *Clinical Rheumatology, 26*, 1929–1930.
39. Ahn, S. S., Yoo, B. W., Jung, S. M., Lee, S. W., Park, Y. B., & Song, J. J. (2017). Application of the 2016 EULAR/ACR/PRINTO classification criteria for macrophage activation syndrome in patients with adult-onset still disease. *The Journal of Rheumatology, 44*, 996–1003.
40. Fishman, D., Rooney, M., & Woo, P. (1995). Successful management of reactive haemophagocytic syndrome in systemic-onset juvenile chronic arthritis. *British Journal of Rheumatology, 34*, 888.
41. Quesnel, B., Catteau, B., Aznar, V., Bauters, F., & Fenaux, P. (1997). Successful treatment of juvenile rheumatoid arthritis associated haemophagocytic syndrome by cyclosporin A with transient exacerbation by conventional-dose G-CSF. *British Journal of Haematology, 97*, 508–510.
42. Ravelli, A., Viola, S., De Benedetti, F., Magni-Manzoni, S., Tzialla, C., & Martini, A. (2001). Dramatic efficacy of cyclosporine A in macrophage activation syndrome. *Clinical and Experimental Rheumatology, 19*, 108.
43. Prahalad, S., Bove, K. E., Dickens, D., Lovell, D. J., & Grom, A. A. (2001). Etanercept in the treatment of macrophage activation syndrome. *The Journal of Rheumatology, 28*, 2120–2124.
44. Stabile, A., Bertoni, B., Ansuini, V., La Torraca, I., Salli, A., & Rigante, D. (2006). The clinical spectrum and treatment options of macrophage activation syndrome in the pediatric age. *European Review for Medical and Pharmacological Sciences, 10*, 53–59.
45. Ozturk, K., & Ekinci, Z. (2015). Successful treatment of macrophage activation syndrome due to systemic onset juvenile idiopathic arthritis with antithymocyte globulin. *Rheumatology International, 35*, 1779–1780.
46. Tomaske, M., Amon, O., Bosk, A., Handgretinger, R., Schneider, E. M., & Niethammer, D. (2002). Alpha-CD25 antibody treatment in a child with hemophagocytic lymphohistiocytosis. *Medical and Pediatric Oncology, 38*, 141–142.
47. Olin, R. L., Nichols, K. E., Naghashpour, M., et al. (2008). Successful use of the anti-CD25 antibody daclizumab in an adult patient with hemophagocytic lymphohistiocytosis. *American Journal of Hematology, 83*, 747–749.
48. Behrens, E. M., Kreiger, P. A., Cherian, S., & Cron, R. Q. (2006). Interleukin 1 receptor antagonist to treat cytophagic histiocytic panniculitis with secondary hemophagocytic lymphohistiocytosis. *The Journal of Rheumatology, 33*, 2081–2084.
49. Durand, M., Troyanov, Y., Laflamme, P., & Gregoire, G. (2010). Macrophage activation syndrome treated with anakinra. *The Journal of Rheumatology, 37*, 879–880.
50. Miettunen, P. M., Narendran, A., Jayanthan, A., Behrens, E. M., & Cron, R. Q. (2011). Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: Case series with 12 patients. *Rheumatology, 50*, 417–419.
51. Shakoory, B., Carcillo, J. A., Chatham, W. W., et al. (2016). Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: Reanalysis of a prior phase III trial. *Critical Care Medicine, 44*, 275–281.
52. Kahn, P. J., & Cron, R. Q. (2013). Higher-dose Anakinra is effective in a case of medically refractory macrophage activation syndrome. *The Journal of Rheumatology, 40*, 743–744.
53. Prencipe, G., Caiello, I., Pascarella, A., et al. (2018). Neutralization of IFN-gamma reverts clinical and laboratory features in a mouse model of macrophage activation syndrome. *The Journal of Allergy and Clinical Immunology, 141*, 1439–1449.
54. Bracaglia, C., de Graaf, K., Pires Marafon, D., et al. (2017). Elevated circulating levels of interferon-gamma and interferon-gamma-induced chemokines characterise patients with macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases, 76*, 166–172.

55. Kawashima, M., Yamamura, M., Taniai, M., et al. (2001). Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease. *Arthritis and Rheumatism, 44*, 550–560.
56. Canna, S. W., de Jesus, A. A., Gouni, S., et al. (2014). An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. *Nature Genetics, 46*, 1140–1146.
57. Canna, S. W., Girard, C., Malle, L., et al. (2017). Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition. *The Journal of Allergy and Clinical Immunology, 139*, 1698–1701.
58. Shimizu, M., Nakagishi, Y., Inoue, N., et al. (2015). Interleukin-18 for predicting the development of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *Clinical Immunology, 160*, 277–281.
59. Girard-Guyonvarc'h, C., Palomo, J., Martin, P., et al. (2018). Unopposed IL-18 signaling leads to severe TLR9-induced macrophage activation syndrome in mice. *Blood, 131*, 1430–1441.
60. Jordan, M. B., Hildeman, D., Kappler, J., & Marrack, P. (2004). An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. *Blood, 104*, 735–743.
61. Terrell, C. E., & Jordan, M. B. (2013). Perforin deficiency impairs a critical immunoregulatory loop involving murine CD8(+) T cells and dendritic cells. *Blood, 121*, 5184–5191.
62. Kogl, T., Muller, J., Jessen, B., et al. (2013). Hemophagocytic lymphohistiocytosis in syntaxin-11-deficient mice: T-cell exhaustion limits fatal disease. *Blood, 121*, 604–613.
63. Sepulveda, F. E., Garrigue, A., Maschalidi, S., et al. (2016). Polygenic mutations in the cytotoxicity pathway increase susceptibility to develop HLH immunopathology in mice. *Blood, 127*, 2113–2121.
64. Behrens, E. M., Canna, S. W., Slade, K., et al. (2011). Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. *The Journal of Clinical Investigation, 121*, 2264–2277.
65. Brown, D. E., McCoy, M. W., Pilonieta, M. C., Nix, R. N., & Detweiler, C. S. (2010). Chronic murine typhoid fever is a natural model of secondary hemophagocytic lymphohistiocytosis. *PLoS One, 5*, e9441.
66. Buatois, V., Chatel, L., Cons, L., et al. (2017). Use of a mouse model to identify a blood biomarker for IFNgamma activity in pediatric secondary hemophagocytic lymphohistiocytosis. *Translational Research, 180*, 37–52.e2.
67. Brisse, E., Imbrechts, M., Put, K., et al. (2016). Mouse cytomegalovirus infection in BALB/c mice resembles virus-associated secondary hemophagocytic lymphohistiocytosis and shows a pathogenesis distinct from primary hemophagocytic lymphohistiocytosis. *Journal of Immunology, 196*, 3124–3134.
68. Sato, K., Misawa, N., Nie, C., et al. (2011). A novel animal model of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in humanized mice. *Blood, 117*, 5663–5673.
69. Maschalidi, S., Sepulveda, F. E., Garrigue, A., Fischer, A., & de Saint Basile, G. (2016). Therapeutic effect of JAK1/2 blockade on the manifestations of hemophagocytic lymphohistiocytosis in mice. *Blood, 128*, 60–71.
70. Das, R., Guan, P., Sprague, L., et al. (2016). Janus kinase inhibition lessens inflammation and ameliorates disease in murine models of hemophagocytic lymphohistiocytosis. *Blood, 127*, 1666–1675.
71. Chiossone, L., Audonnet, S., Chetaille, B., et al. (2012). Protection from inflammatory organ damage in a murine model of hemophagocytic lymphohistiocytosis using treatment with IL-18 binding protein. *Frontiers in Immunology, 3*, 239.
72. Stepp, S. E., Dufourcq-Lagelouse, R., Le Deist, F., et al. (1999). Perforin gene defects in familial hemophagocytic lymphohistiocytosis. *Science, 286*, 1957–1959.
73. Cetica, V., Sieni, E., Pende, D., et al. (2016). Genetic predisposition to hemophagocytic lymphohistiocytosis: Report on 500 patients from the Italian registry. *The Journal of Allergy and Clinical Immunology, 137*, 188–96.e4.

74. Mukda, E., Trachoo, O., Pasomsub, E., et al. (2017). Exome sequencing for simultaneous mutation screening in children with hemophagocytic lymphohistiocytosis. *International Journal of Hematology, 106*, 282–290.
75. Rigante, D., Emmi, G., Fastiggi, M., Silvestri, E., & Cantarini, L. (2015). Macrophage activation syndrome in the course of monogenic autoinflammatory disorders. *Clinical Rheumatology, 34*, 1333–1339.
76. Hazen, M. M., Woodward, A. L., Hofmann, I., et al. (2008). Mutations of the hemophagocytic lymphohistiocytosis-associated gene UNC13D in a patient with systemic juvenile idiopathic arthritis. *Arthritis and Rheumatism, 58*, 567–570.
77. Zhang, K., Biroschak, J., Glass, D. N., et al. (2008). Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis is associated with MUNC13-4 polymorphisms. *Arthritis and Rheumatism, 58*, 2892–2896.
78. Vastert, S. J., van Wijk, R., D'Urbano, L. E., et al. (2010). Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis. *Rheumatology, 49*, 441–449.
79. Kaufman, K. M., Linghu, B., Szustakowski, J. D., et al. (2014). Whole-exome sequencing reveals overlap between macrophage activation syndrome in systemic juvenile idiopathic arthritis and familial hemophagocytic lymphohistiocytosis. *Arthritis & Rhematology, 66*, 3486–3495.