RHEUMATOLOGY

Review

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Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment

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Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome, which if not promptly treated, can lead rapidly to critical illness and death. HLH is termed macrophage activation syndrome (MAS) when associated with rheumatic disease (where it is best characterized in systemic JIA) and secondary HLH (sHLH) when associated with other triggers including malignancy and infection. MAS/sHLH is rare and coupled with its mimicry of other conditions, is underrecognized. These inherent challenges can lead to diagnostic and management challenges in multiple medical specialties including haematology, infectious diseases, critical care and rheumatology. In this review we highlight the pathogenesis of MAS/sHLH including its underlying triggers, key clinical features and diagnostic challenges, prognostic factors and current treatments in adults.

Key words: macrophage activation syndrome, haemophagocytic lymphohistiocytosis, haemophagocytic syndrome, reactive haemophagocytosis, hyperferritinaemia

Rheumatology key messages

- Secondary haemophagocytic lymphohistiocytosis is underrecognized, can lead to critical illness and has a high mortality rate.
- Secondary haemophagocytic lymphohistiocytosis is triggered by infection (especially viral infection), malignancy, autoimmunity and autoinflammation.
- Secondary haemophagocytic lymphohistiocytosis, if treated promptly, responds well to a combination of corticosteroids and IL-1 blockade with anakinra.

REVIEW

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is an underrecognized hyperinflammatory condition with a high mortality, characterized by inappropriate survival of histiocytes and cytotoxic T cells (CTLs), leading to a cytokine storm, haemophagocytosis and multi-organ damage [1].

HLH terminology is problematic and there is broad agreement that an update and unification between haematology and rheumatology nomenclature will improve clarity and enhance future research [2, 3]. Currently, familial HLH (fHLH) is characterized by inherited defects of cytolytic pathway proteins (Table 1) and usually presents in infancy. Secondary, reactive or acquired HLH (sHLH) may be triggered by malignancy, infection and autoimmunity, and is seen in children, adolescents and adults [4]. When sHLH occurs in the context of autoimmunity it is termed macrophage activation syndrome (MAS). The clinical syndrome was first described in the 1980s in children complicating severe cases of systemic-onset JIA (sJIA) [5, 6]. The term MAS was first coined by Stephan *et al*. [7] and emerged in parallel with development of the The Histiocyte Society Classification of Histiocyte Disorders in 1987 [8].

MAS is well-recognized in paediatric and adolescent rheumatology as it occurs in ~10% of patients with sJIA. As a result, MAS is specifically addressed in treatment algorithms such as the latest ACR guidelines for treatment of sJIA [9–11]. Retrospective studies in sJIA, Kawasaki's disease and SLE show that MAS is underrecognized, highlighting a need for increased vigilance, understanding and education for this condition, enabling

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Table 1 Familial and acquired susceptibilities to HLH

Primary/familial susceptibility					Populations at-risk of secondary HLH or MAS
fHLH type	**Gene defect**	**Protein defect**	**Function**	Rheumatic disease	sJIA, AOSD, SLE
1	Chromosome 9 (9q21)	Unknown	Unknown	Infection	Herpes family (EBV, VZV, HSV, CMV)
2	*PRF1*	Perforin	Pore formation		HIV
3	*UNC13D*	Munc 13-4	Vesicle priming		Influenza H1N1
4	*STX11*	Syntaxin 11	Vesicle fusion		Dengue
5	*STXBP2*	Syntaxin binding protein	Vesicle fusion		Ebola
Immunodeficiency syndromes				Malignancy	Haematological malignancy (T cell, NK cell leukaemias or lymphoma, diffuse large B cell lymphoma, Hodgkin lymphoma, AML)
XLP1	*SH2D1A*	SH2D1A/SAP	Signalling pathways	Miscellaneous	Chemotherapy
XLP2	*XIAP*	XIAP	Signalling pathways		Bone marrow transplant recipients
Chediak Higashi	*LYST*	LYST	Vesicle trafficking		Pyrexia of unknown origin
Griscelli 2	*RAB27A*	RAB27A	Vesicle fusion		Multiple organ failure/critical care population
Hermansky-Pudlak 2	*AP3B1*	AP-3 complex subunit beta-1	Vesicle trafficking		Immunosuppressed patients (e.g. solid organ transplant recipients, autoimmune disease, bone marrow/stem cell transplants)

HLH: haemophagocytic lymphohistiocytosis; XLP: X-linked lymphoproliferative syndrome; VZV: varicella zoster virus; AOSD: adult onset Still's disease; AML: acute myeloid leukaemia; MAS: macrophage activation syndrome.

timely delivery of life-saving treatment [12–16]. Recent consensus classification criteria for MAS complicating sJIA have been published to facilitate research [17].

It is increasingly recognized that sHLH occurs in adult populations as a consequence of malignancy, infection, autoimmunity, autoinflammation or a combination of these factors, with the diagnosis lying at the boundaries of multiple specialities including haematology, infectious diseases, rheumatology and critical care. The syndrome of sHLH is poorly characterized, with a small evidence base. In this review we highlight the key pathogenesis, diagnosis, treatment and prognosis of sHLH in adults.

Pathogenesis

HLH is caused by a failure of normal cytolytic function of NK cells and CTLs (Fig. 1). Inability to clear antigen from infection, malignant cells or from autoimmune/autoinflammatory processes leads to inappropriate immune stimulation and a self-perpetuating hyperinflammatory state known as the cytokine storm [18–20]. Dysfunction of the innate immune system involving IL-1 is central to disease pathogenesis, highlighted by excellent clinical responses to IL-1 blockade [21–23].

In fHLH and related immunodeficiency syndromes, inheritance of defective genes involved in control of cytolysis leads to impaired NK cell and CTL cytolytic activity, resulting in uncontrolled proliferation and survival of CTLs (Table 1) [18, 20]. It is important to note that although the majority of these genetic defects present in the first few years of life, they can present rarely in adulthood [24].

Patients with sHLH have both low NK cell activity, and may have underlying hypomorphic defects in cytolytic genes found in fHLH (Table 1) [25–30]. Low NK cell activity alone is not capable of causing HLH; family members of patients with fHLH who also have low NK cell activity may never develop clinical disease, indicating that HLH requires breach of a threshold through a combination of genetic predispositions and additional triggers including infection, inflammation or malignancy (Fig. 2) [20, 29, 31–33].

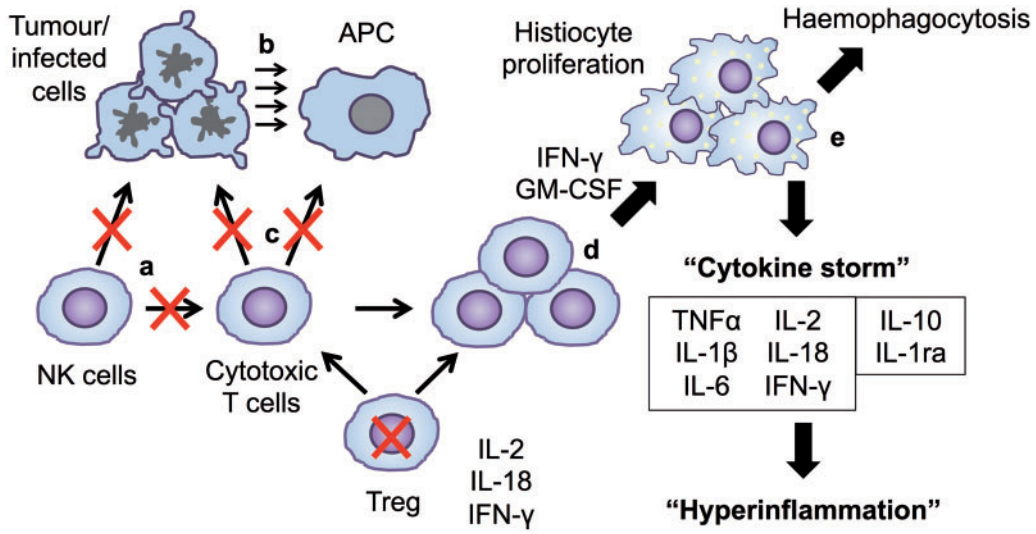
Infections can trigger sHLH by specific mechanisms disrupting normal cytolytic function, including EBV, which is capable of inhibiting (SH2 domain-containing protein 1A (SH2D1A), a protein defective in X-linked lymphoproliferative disease type 1, in whom there is susceptibility to EBV-triggered HLH [34].

Hyperferritinaemia is induced by the milieu of cytokines present in MAS/sHLH leading to upregulation of ferritin synthesis [35, 36]. It is recognized as a key clinical feature of sHLH and other hyperferritinaemic syndromes, and is itself capable of inducing NF-κB and promoting a pro-inflammatory state [37, 38].

MAS in autoimmunity

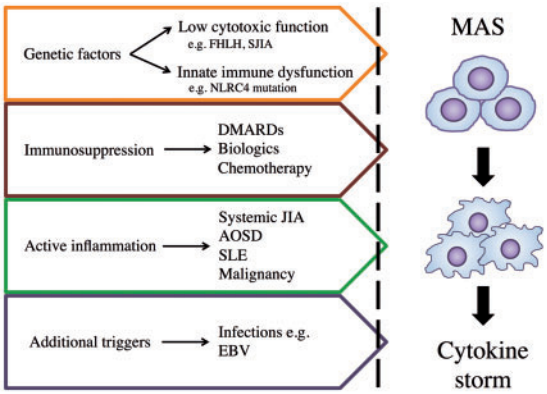
MAS is most prevalent and well-described in sJIA, where infection is identified as the trigger of MAS in approximately one-third of patients [39]. EBV and varicella zoster virus are the most frequent pathogens identified [9, 40, 41], and while some pathogens may work specifically to disrupt cytolytic pathways [34, 42–44], a broad

Fig. 1 Pathogenesis of MAS/sHLH



(**a**) Cytotoxic function of NK cells fails to clear tumour or infected cells and cytotoxic T cells. (**b**) Persistent tumour-infected cells cause persistent stimulation by persistent antigen presentation. (**c**) Cytotoxic function of CTLs fail to clear tumour cells and APCs, and Tregs are overwhelmed. (**d**) Proliferation of the population of activated CTLs induce activation and proliferation of tissue macrophages (histiocytes). (**e**) Activated histiocytes haemophagocytose and produce a cytokine storm, due to which imbalance of pro- and anti-inflammatory cytokines induces fever and hyperinflammatory haemophagocytic syndrome. MAS: macrophage activation syndrome; sHLH: secondary haemophagocytic lymphocytosis; APC: antigen-presenting cell; CTLs: cytotoxic T cells.

Fig. 2 Continuum of risk factors in the threshold model of MAS/sHLH



Multiple predispositions and triggers breach a threshold for MAS and leads to a cytokine storm. Variation in the severity of predisposing factors means not all factors/triggers are required to breach the threshold, and thus a heterogeneous population and spectrum of clinical presentations are observed. MAS: macrophage activation syndrome; AOSD: adult onset Still's disease; sHLH: secondary haemophagocytic lymphocytosis; FHLH: familial HLH; SJIA: systemic JIA.

range of viral, bacterial and fungal triggers are capable of triggering MAS. Recent trials in tocilizumab and canakinumab have demonstrated that controlling underlying inflammation is not sufficient to prevent MAS, commonly triggered by infection in this context [3, 45–48].

In adults, MAS is most prevalent in patients with Adult Onset Still's Disease (AOSD), which is estimated to occur in 10–15% of patients [49–52]. This is no surprise given the similarity between AOSD and sJIA, where molecular evidence supports that both sJIA and AOSD lie on the same continuum of a single disease entity [53, 54]. MAS may be common to both conditions as they share an autoinflammatory disease pathogenesis where activation of key innate immune pathways, including IL-1 and IL-18, give rise to systemic inflammation [53, 55, 56]. There is recent evidence that NLRC4 gain-of-function mutations can give rise to activation of IL-1 and IL-18 pathways in autoinflammatory disease complicated by MAS, lending further support to this hypothesis [57]. Similarly to patients with sJIA, MAS in AOSD can occur at the onset of disease as a consequence of active disease, in which viral triggers are frequently identified [49, 50].

SLE is more common than AOSD and therefore more cases of SLE-associated MAS are reported in the medical literature, with overall prevalence estimated between 0.9 and 9% [15, 51, 58, 59]. MAS in SLE presents at the

onset of the first SLE flare in 46% of patients, in whom hypocomplementaemia (56%) and positive anti-DNA antibodies (63%) are common. One large retrospective study applied the 2016 sJIA PRINTO Classification Criteria for MAS to patients with SLE admitted to hospital with fever, and found one-third were classified as having MAS, of whom 35% died, compared with 3% without MAS, indicating that the classification criteria could be used in patients with SLE and fever to identify MAS, and facilitate effective treatment [60]. Miscarriage and parturition have also been reported to trigger MAS in SLE [61, 62].

MAS has been reported in most rheumatic diseases, and rather than being a consequence of a specific mechanism in these conditions, concomitant immunosuppression and infections are the likely triggering factors [50, 51, 63].

sHLH in malignancy

sHLH can also occur as the consequence of malignancy, either at presentation or relapse, during treatment of the malignancy (HLH during chemotherapy) or after bone marrow transplantation. The mechanism by which malignancy leads to haemophagocytosis is unknown; however, the inflammation that is a hallmark of cancer is likely to have a prominent role [64, 65].

It is proposed that chemotherapy may cause HLH by two mechanisms: release of pro-inflammatory cytokines by tumour lysis, and by promoting a pro-inflammatory, Th1 cytokine response [66].

The most common malignancies causing sHLH are haematological malignancies, including T cell, NK-cell leukaemias or lymphomas, diffuse large B cell lymphoma and Hodgkin lymphoma, of which a significant proportion may be driven by EBV [67–69]. sHLH may also be present in up to 10% of patients receiving intensive chemotherapy for acute myeloid leukaemia [70].

It is important when assessing patients with sHLH to be mindful that, while EBV is an independent trigger of sHLH, EBV and malignancy can co-trigger sHLH in the context of an EBV-associated lymphoma, which may be very difficult to detect clinically, especially in the scenario where the presenting symptoms of both diseases are simultaneous [68, 69, 71].

HLH may occur after bone marrow transplant for haematological malignancy. In these patients, acute graft *vs* host disease is common and can mimic sHLH [72]. In the authors' experience a high index of suspicion is needed, and demonstration of hyperferritinaemia can clinch the diagnosis in this group (Carter SJ, Tattersall RS, Ramanan AV, unpublished work).

Infections and sHLH

In adults, the worldwide leading cause of sHLH is viral infection, where EBV infection is the predominant viral trigger in the USA and Asia. Other members of the herpes virus family including CMV, HSV and varicella zoster virus are common infectious triggers. HIV, influenza, Dengue and Ebola virus are other notable examples [43, 44, 63, 73–76].

Clinical and laboratory features

sHLH is a clinical syndrome with features that overlap with and mimic the symptoms and signs of other systemic illnesses such as sepsis, malignancy and rheumatic disease. To fulfill classification criteria for MAS a combination of clinical features are required (Table 2). There are no agreed diagnostic criteria to date for sHLH, but it should be considered in an unwell, feverish patient in certain at-risk populations, summarized in Table 1. A recommended diagnostic approach is summarized in Fig. 3.

In early sHLH the absolute values of laboratory results may be less helpful than a review of the trend of results, particularly when considering cytopaenias and fibrinogen. This approach mirrors the 2016 sJIA MAS classification criteria, where patients can fulfill classification for MAS even if platelet and fibrinogen counts are within the normal reference range. This highlights that normal levels of these markers are inappropriate in the context of active inflammatory disease and should prompt the clinician to consider MAS, and emphasizes the need for close monitoring in both trends in clinical status and laboratory parameters [17].

One of the key populations in which sHLH is underrecognized is in critically ill patients with multiple organ damage. In a study of patients who died of critical illness, up to 65% of patients had histiocytic hyperplasia and haemophagocytosis [80]. Even when MAS is recognized, up to 58.2% of patients require mechanical ventilation and 53.6% require inotropic support, highlighting the importance of early recognition and prompt treatment [81].

Fever or pyrexia of unknown origin is the cardinal sign of HLH, and is almost always present in children and adults, with primary/familial or secondary HLH/MAS. A transition from the spiking or quotidian fever, classic of sJIA/AOSD flare, to a persistent, non-remitting fever heralds the onset of MAS in this scenario, at which point other clinical and laboratory features of MAS become evident [17, 82]. Persistent fever in unwell adults without an attributable cause, or worsening fever in patients with treated infection, should prompt investigation for sHLH.

Neurological dysfunction is a poor prognostic marker and is often a consequence of established sHLH, although it can occur early in the disease course. A range of CNS clinical symptoms and signs can develop in sHLH, from subtle changes in mood and personality, to seizures, limb weakness, cranial nerve palsy, reduced conscious level and coma [83, 84].

The most common renal manifestation is acute kidney injury, which may be present in up to 62%, of whom 59% require renal replacement therapy, and approximately one-third of the patients who survive have chronic kidney disease at 6 months [85].

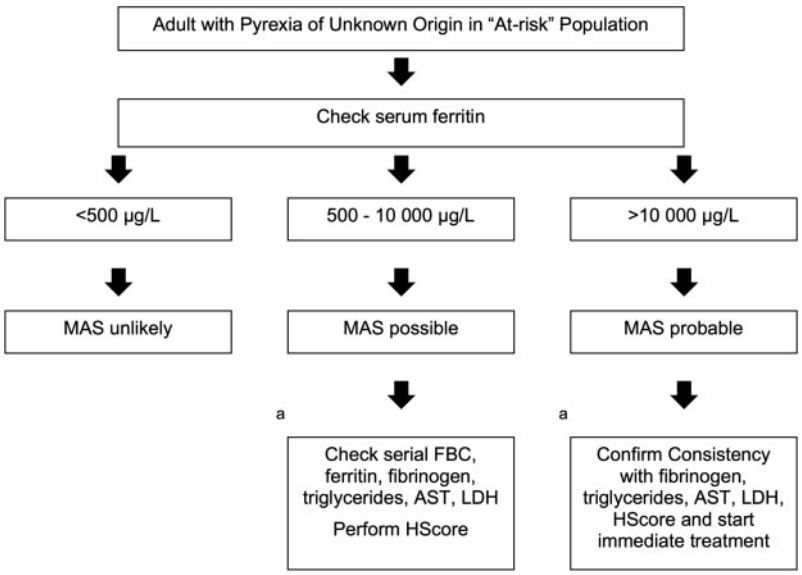
Pulmonary involvement is found in approximately half of patients with sHLH and may manifest as acute respiratory distress requiring mechanical ventilation. It is a poor prognostic indicator, and more common in severe sHLH requiring critical care admission compared with those requiring only ward-based care [86].

TABLE 2 Selected MAS/HLH classification criteria currently in use

	Primary HLH	Secondary HLH and MAS	
	HLH-2004, Henter *et al.* [77]	HScore, Fardet *et al.* [78, 79]	PRINTO criteria, Ravelli *et al.* [17]
Target population	Primary HLH	Adults	sJIA
Clinical features			
Fever	+	<38.4 (0), 38.4–39.4 (33), >39.4 (49)	+
Hepatomegaly		Neither (0), either hepatomegaly	
Splenomegaly	+	or splenomegaly (23), both (38)+	
Immunosuppression		No (0), yes (18)	
Lab criteria			
Cytopaenia in more than two lineages	Either: haemoglobin <90 g/l, platelets <100 × 10^9/l, neutrophils <1 × 10^9/l	One lineage (0), two lineages (24), three lineages (34)	
Platelets			⩽181 × 10^9/l
Ferritin, ng/ml	⩾500	<2000 (0), 2000–6000 (35), >6000 (50)	>684
Hypertriglyceridaemia, mmol/L	⩾3	<1.5 (0), 1.5–4 (44), >4 (64)	>1.76
Hypofibrinogenaemia, g/l	⩽1.5	>2.5 (0), <2.5 (30)	⩽3.6
Liver function tests, IU/l		AST <30 (0), >30 (19)	AST >48
Low/absent NK cell activity	+		
Soluble CD25, U/ml	⩾2400		
Haemophagocytosis	+	No (0), yes (35)	+
Fulfillment of criteria	Molecular diagnosis consistent with primary HLH or five or more of eight criteria	Produces a probability outcome. Scores >169 are 93% sensitive and 86% specific for HLH	Febrile patient with known or suspected sJIA, ferritin >684 ng/ml and two or more additional items

HScore calculator (for percentage probability of secondary HLH) is available at http://saintantoine.aphp.fr/score/ [78]. PRINTO: Paediatric Rheumatology International Trials Organization; HLH: haemophagocytic lymphohistiocystosis; AST: aspartate transaminase; sJIA: systemic-onset JIA; MAS: macrophage activation syndrome.

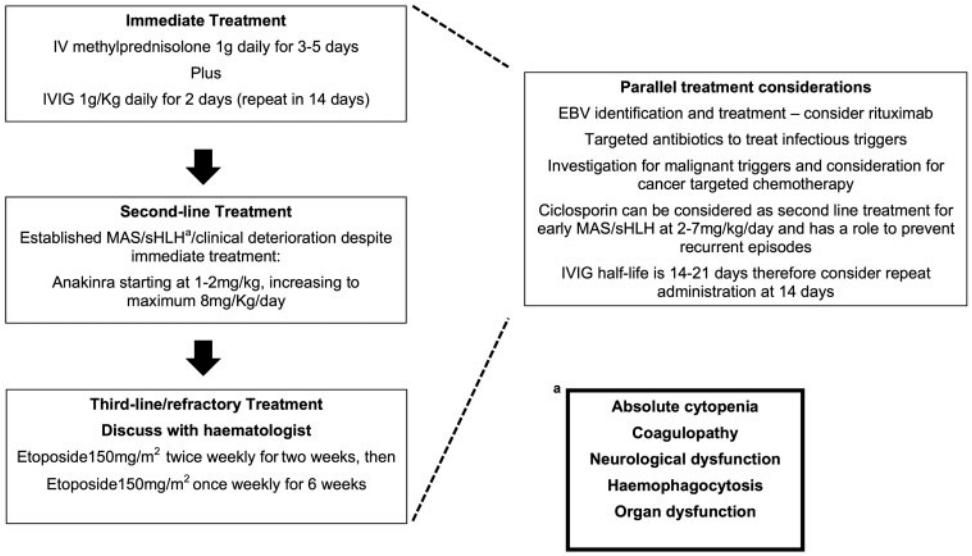
FIG. 3 Diagnostic algorithm for MAS/sHLH in adults



[a]Where underlying cause in not known, investigative approach includes imaging/bone marrow biopsy for malignancy, thorough infectious screen and targeted viral serology dependent on epidemiological risk for exposure to various pathogens (EBV serology and EBV DNA is recommended in all patients). MAS: macrophage activation syndrome; sHLH: secondary haemophagocytic lymphocytosis; FBC: full blood count; AST: aspartate transaminase; LDH: lactate dehydrogenase.

Hyperferrinaemia is a key laboratory feature, which is critical in the identification of HLH. In a single centre retrospective review of serum ferritin, levels >10 000 µg/l were 96% specific and 90% sensitive for HLH [39, 87]. Serum ferritin is closely related to disease activity, and both maximum serum ferritin levels during sHLH, and a fall of <50% after treatment are associated with a higher mortality [88–90]. Furthermore, serial ferritin measurement is

Fig. 4 Recommended treatment protocol for adults with MAS/sHLH



MAS: macrophage activation syndrome; sHLH: secondary haemophagocytic lymphocytosis.

useful to monitor response to treatment, as a fall to baseline is observed with successful treatment, and rebounds in recurrence [91].

Two recent multi-national collaborative studies in sJIA identified serum ferritin as the most dynamic marker of change in MAS, by assessing serum ferritin before and after the development of MAS, which increased by 556 and 889% before and at diagnosis of MAS, respectively. Other parameters showing a >50% change before and at development of MAS were platelet count, liver transaminases, lactate dehydrogenase, triglycerides and D-dimer. CRP increases and ESR falls in most patients [39, 92]. Similar patterns are observed in adult sHLH.

Hypofibrinoginaemia may be a consequence of the procoagulant activity of inflammatory cytokine TNFα or a consequence of accelerated degradation of fibrinogen, and leads to a paradoxical fall in ESR [18, 93]. A combination of inappropriate thrombocytopaenia and hypofibrinogenaemia may result in haemorrhagic manifestations in severe HLH, especially in critically ill populations, including petechiae, ecchymosis, purpura, gastrointestinal bleeding and disseminated intravascular coagulation [39, 94]. Liver dysfunction resembles chronic active hepatitis and results in transaminitis and hypertriglyceridaemia [95–98].

It is recognized that haemophagocytosis is a late feature of HLH [75, 99], and does not correlate as well as fever or serum ferritin with clinical diagnosis of sHLH [100]. Therefore haemophagocytosis is not considered essential for clinical diagnosis enabling fulfillment of classification criteria for HLH in the absence of haemophagocytosis, and permits earlier identification and treatment [17]. Conversely, haemophagocytosis on bone marrow aspirate done to investigate cytopaenia may be the first feature of investigations prompting a consideration of sHLH. Close coordination with haematology colleagues enables prompt diagnosis and treatment.

Specific serum markers of HLH activity include soluble CD25 and soluble CD163, which are both upregulated in HLH, and reflect levels of T cell activation and overall degree of haemophagocytosis, respectively [101, 102]. However, due to the lack of widespread availability and use of the test, it has not contributed to current classification criteria in sJIA-associated MAS or adult sHLH [17].

Fardet *et al*. developed the HScore [78], integrating nine key clinical and laboratory features of HLH, available for use by clinicians to produce a probability score for sHLH (Table 2). The study population included patients with sHLH associated with malignancies, autoimmunity and infection, and has shown excellent discriminatory performance [79]. A subsequent study of patients in Turkey (46.7% AOSD, 33.3% sJIA, 20% SLE) found that the HScore outperformed the HLH-2004 criteria, but a higher cut-off of 190.5 performed better, with a sensitivity of 96.7% and specificity of 98.4%, reflecting the heterogeneity of HLH populations [103].

In summary, there is no single diagnostic feature of MAS/sHLH, but the patterns of laboratory values (in particular highly elevated ferritin levels and relative or absolute cytopaenias) in febrile patients are key, as are the clinical context and associated clinical features. Features indicating that MAS/sHLH has become established include signs of neurological dysfunction, absolute cytopaenias, hypofibrinogenaemia (and thereby low ESR), haemophagocytosis and organ dysfunction (Fig. 4).

Prognosis

In all causes of sHLH in adults the overall morality is significant at 41%, and ranges from 5 to 39% in autoimmune

disease-associated MAS [50–52, 61, 63, 104]. Maximum serum ferritin level has been associated with mortality, whereas a rapid rate of fall in serum ferritin by >50% after treatment is associated with a decreased mortality [87, 89, 105–108]. In patients managed in an intensive treatment unit setting, death occurs in approximately half, with increased risk in those in whom there is shock at admission and severe thrombocytopaenia [81]. Older age at onset and increased comorbidity is associated with increased mortality independent of whether disease is triggered by malignancy or another cause [63, 106, 109, 110]. In EBV-associated HLH, 30-day mortality is associated with neutropenia, hypoalbuminaemia, hyperbilirubinaemia and serum lactate dehydrogenase levels [111].

Malignancy-associated HLH mortality rates are abysmal, with overall mortality rates between 42 and 88% in adults [63, 112, 113]. In a 73 patient cohort of malignancy-associated HLH median survival was 1.13 months and 30-day survival was 27.4% [114]. In a nationwide Japanese survey, 5-year survival in HLH in all age groups with malignancy-triggered sHLH was <15% [115]. Concomitant viral infection in malignancy-triggered sHLH is associated with increased mortality [116].

Treatment

There are no validated treatment protocols for sHLH in adults, where treatment regimes have been informed by retrospective case series and case reports, and extrapolated from treatment guidelines and protocols in other disease contexts including fHLH and sJIA-associated MAS. A lack of agreement in nomenclature and classification, the rarity of the condition, and the heterogeneity of triggering factors and underlying conditions all form barriers to prospective research.

Henter *et al*. developed treatment guidelines for patients with fHLH in 1994 [117], using combination chemotherapy (etoposide, dexamethasone, CSA, plus intrathecal MTX for progressive CNS involvement), ultimately leading to the curative treatment of haemopoietic stem cell transplant, which corrects the underlying genetic defect of cytolysis. These guidelines were later updated in 2004 to include CSA use upfront, recognizing that early aggressive strategies may prevent deaths, which appeared to occur in the first month as a result of active HLH when using the 1994 protocol [77].

In MAS/sHLH, remission is achieved by a combination immunosuppression in an approach extrapolated from the fHLH evidence-based treatment protocols in which corticosteroids are the cornerstone of treatment [6, 9, 40, 118–120]. Early use of high-dose steroids may be successful alone, but over half of reported adult cases are steroid resistant [51].

In contrast to fHLH, patients have rarely undergone haemopoietic stem cell transplant as a result of severe sJIA with MAS [27]. Recent worldwide collaborative approaches to characterize MAS in sJIA and guidelines specific to sJIA have provided clarity for clinicians managing MAS in this patient group where early use of anakinra is advocated. Such evidence and emerging work reviewed here in sHLH emphasize the need for early, aggressive immunosuppressive treatment in MAS/sHLH to treat hypercytokinaemia in addition to treatment of any trigger (e.g. infection or inflammation) to prevent multi-organ failure and death.

In the authors' experience, immediate treatment of sHLH with intravenous methylprednisolone 1 g daily for 3–5 days plus IVIG 1 g/kg for 2 days (consider repeating at 14 days due to half-life of 14–21 days [121]) is given as first-line treatment. If there are features of established HLH or signs of clinical deterioration despite immediate treatment, anakinra as second-line treatment should not be delayed (see Fig. 4). Referral to haematology is recommended to consider etoposide use in refractory cases. Parallel treatment considerations include the identification and eradication of EBV with rituximab treatment and aggressive and targeted antibiotic treatment to address infectious triggers. Investigation for a malignant trigger should be considered, especially where no obvious cause for MAS/sHLH is identified, and subsequent cancer-directed chemotherapy as required. Ciclosporin may also have a role in preventing relapse. The treatment approach is summarized in Fig. 4 and the literature underpinning this approach is further outlined below.

In malignancy-associated HLH, it is not clear whether primarily a cancer-directed treatment or an HLH-directed treatment is more effective. The current consensus recommendations for treatment from a malignancy-associated HLH standpoint are that every case must be evaluated on its individual characteristics, to determine which treatment approach will give most benefit [67]. In contrast to malignancy-associated HLH, the treatment approach is somewhat clearer for patients with MAS, where there is considerable overlap between the immunosuppressive treatment directed towards MAS and that directed towards treatment of the underlying immune condition. It is important to re-iterate however, that treatment of the underlying immune condition trigger may not be sufficient, and the hyperinflammatory, hypercytokinaemic process needs treatment in its own right.

Historically, CSA has been the most frequently used second-line treatment. Dramatic responses have been achieved with CSA in combination with corticosteroids, using doses of 2–7 mg/kg/day [9, 40, 122–126]. Neurotoxicity has been associated with ciclosporin use and reported in children treated for fHLH and in EBV-triggered sHLH [127, 128]. The neurological manifestations can be diverse, however posterior reversible encephalopathy syndrome is well recognized [48, 127]. Differentiation between worsening sHLH with CNS involvement and ciclosporin neurotoxicity may require withdrawal of ciclosporin and a break in effective treatment. The authors recommend switching treatment to anakinra to prevent delay in effective treatment if this occurs.

Individual case reports have reported successful use of IVIG in corticosteroid refractory MAS [120, 129], and has also been successfully used in children with EBV-triggered sHLH [130, 131] and in adult populations with sHLH [85, 132]. In comparison with other treatments,

adverse events are usually mild and transient and do not include myelosuppression, making it an acceptable treatment choice for clinicians [133, 134].

There is a paucity of data for etoposide use specifically in sHLH and MAS, aside from individual case reports [48, 135]. However, etoposide use is well established in fHLH protocols [77], and early use in this context, in children with EBV-triggered sHLH and in adults with sHLH, is associated with a favourable outcome [110, 136, 137]. It may be more important in EBV-triggered sHLH as not only does etoposide lead to apoptosis of activated CTLs and macrophages, but it also inhibits EBV DNA synthesis [138]. It is therefore important to consider, especially as we know that in up to one-third of patients, MAS/sHLH may have been triggered by infection, of which EBV is the most common [39, 63]. The principal limitations to its use have been cases of fatal myelosuppression and opportunistic infection. Patients with liver dysfunction may be at higher risk as etoposide is metabolized in the liver, and dose adjustment is needed [117, 139–141].

A Chinese prospective, uncontrolled study treated 63 patients with combination chemotherapy called the DEP regime, consisting of doxorubicin, etoposide and methylprednisolone, in patients with refractory HLH. The cohort included 22 patients with EBV-HLH, 29 with lymphoma-associated haemophagocytosis, 4 with FHL and 4 cases where the cause of HLH was unclear. This led to complete response in 27% and partial response in 49.2%, and no response in 23% [142].

In MAS associated with sJIA evidence supports the early use of IL-1 blockade with anakinra, which may be adopted in the adult MAS population in the future [10, 11, 143]. Anakinra has been shown to be effective in treatment of MAS in cases where corticosteroids, IVIG, ciclosporin and etoposide have failed to control disease [12, 23] and has been successfully used in combination with corticosteroids alone [144, 145]. It is encouraging that anakinra use is associated with improved outcome in patients with sepsis and features of MAS, giving a favourable signal for safe use in the context of sHLH even when triggered by infection [146]. It is important to highlight that doses of 100 mg four times daily of anakinra have been needed to achieve remission in refractory cases of MAS, highlighting that initial doses of 1–2 mg/kg may not be sufficient [147].

Three studies of IL-1 blockade with anakinra, canakinumab and rilonacept in patients with sJIA reported cases of MAS, indicating IL-1 blockade is not sufficient to prevent MAS. In these cases, addition of corticosteroid, ciclosporin and/or anakinra was required to treat patients with MAS [48, 148, 149].

In patients receiving tocilizumab MAS has also been reported. In these cases, tocilizumab does not increase the risk of MAS development, but may mask the clinical presentation of MAS with lower ferritin levels, reduced frequency of hepatomegaly and normal CRP [3, 46, 150].

Rituximab may also have a role in conjunction with other therapies, and has been demonstrated to reduce EBV viral load, serum ferritin levels and overall clinical outcome in patients with EBV-driven HLH [151].

Conclusion

sHLH in adults has a broad range of triggers including infection, malignancy and autoimmunity. Rheumatologists must be aware of the possibility of sHLH and MAS in ‘at-risk’ populations residing in hospital under the care of different hospital specialties. MAS should be considered as a possible differential diagnosis in all patients with sJIA, AOSD or SLE with pyrexia or inflammation of unknown origin.

Morbidity and mortality are high, and early identification is important to enable early and aggressive treatment with combination immunosuppression and treatment of co-triggers to achieve remission. The recent developments of the HScore and classification criteria for MAS in patients with sJIA have provided practical tools that clinicians can use to identify MAS/sHLH and provide lifesaving treatment.

Recent evidence showing excellent, safe clinical responses to anakinra in MAS associated with sJIA has highlighted its use as a next generation treatment option in management of sHLH, which can be successfully used in adult populations.

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