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Haemophagocytic lymphohisticytosis—an underrecognized hyperinflammatory syndrome

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Abstract

Haemophagocytic lymphohisticytosis (HLH) is a syndrome of uncontrolled, severe systemic inflammation (hyperinflammation) arising either from a genetic immune system defect [primary (pHLH)] or triggered as a complication of malignancy, infection, or rheumatologic disease [secondary (sHLH)]. Patients with HLH often have non-specific symptoms and become progressively and critically unwell, with fever, cytopenia and multi-organ failure. Untreated, HLH is almost universally fatal, but even when treated, mortality is high, particularly when HLH complicates malignancy. HLH is managed with immunosuppression, and this can seem difficult to justify in such unwell patients. This review aims to examine the diagnostic and treatment challenges posed by sHLH and to improve recognition among rheumatologists who, being expert in the management of multisystem diseases and in the use of immunosuppression, are ideally placed to deliver care and build an evidence base for better disease characterization and treatment.

Key words: haemophagocytic lymphohistiocytosis, hyperinflammation, immune suppression, interleukin 1, fever

SUPPLEMENT

Rheumatology key messages

- HLH is underrecognized, with high mortality, and should be considered in any unwell, febrile, cytopenic patient.
- HLH may be primary (genetic) or acquired, secondary, to infection, rheumatic disease, malignancy or autoinflammation.
- Current HLH diagnostic criteria have significant limitations, particularly in adults.

What is haemophagocytic lymphohisticytosis (HLH), and who is at risk?

HLH is a syndrome of severe, uncontrolled, self-perpetuating inflammation leading to a cytokine storm and multi-organ failure. The understanding of HLH is derived largely from the study of the genetic disease (primary HLH [pHLH]) in children [1], although the acquired, secondary (sHLH) form of the disease is increasingly recognized [2].

Most known mutations in pHLH lead to deficiencies in perforin-dependent lymphocyte cytotoxic function [3], with a lack of perforin function leading to dysregulated immune response to stimuli. Under normal circumstances, CD8 T cells and natural killer cells eventually lyse antigen-presenting cells via a perforin-dependent mechanism [4], limiting the amplification of immune cell activation and cytokine production. In HLH, this negative feedback loop fails. Animal models also suggest that the abnormal CD8 T cells themselves produce excess IFN-γ when stimulated by antigens, further propagating the exaggerated response. The result is uncontrolled activation of tissue histiocytes (macrophages), which in turn leads to haemophagocytosis (hence cytopaenia), invasion of tissues by macrophages and a hyperinflammatory cytokine storm [4], which if unchecked causes multi-organ failure, haemophagocytosis and death.

The division of HLH into primary and secondary forms may well be an oversimplification. An updated model considers the patient's innate tendency towards HLH to be on a continuum [5]. Patients with monogenic pHLH are most at risk of hyperinflammation and therefore present in infancy. Homozygotes with missense, rather than nonsense, mutations present later. Heterozygote patients appear to have a lower risk of developing the disease, but likely have a higher risk than that of the general population [6]. Other patients have a polygenic tendency to hyperinflammation, and under certain circumstances, such as infection, will go on to develop sHLH. A reason

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for considering both forms of HLH together is that the resulting inflammatory picture is very similar. Initial therapy in both contexts is also likely to be overlapping, but diagnosing genetic pHLH is critical, as these patients can be cured by successful bone marrow transplantation.

Diagnoses in which sHLH may be triggered include malignancy (usually haematological), rheumatologic disease, particularly adult-onset Still's disease and SLE [7, 8] and infection. Infection may be the only trigger or may act as an additional 'hit' in a patient already at risk. In patients with a malignancy such as lymphoma, a further trigger such as infection with EBV may induce the syndrome [9].

In people with rheumatologic disease, such as systemic JIA (sJIA), HLH is often termed macrophage activation syndrome (MAS). There are advantages and drawbacks to this approach. HLH in this context carries a better prognosis than with other causes of HLH especially malignancy (8% *vs* 80% mortality) [10]. There is a feeling that in sJIA, the features of HLH simply represent the more severe end of the activity spectrum of the underlying disease itself rather than a distinct entity [11]. There are also some differences in the cytokine profiles in sJIA patients with MAS compared with pHLH. For instance, IL-18 levels are higher in patients with MAS [12]. Conversely, having two separate names for what is, for all practical purposes, a single disease state may be unnecessarily complicating matters, causing further diagnostic confusion with ensuing deleterious effects on outcome.

HLH is a recognized complication of a number of immune deficiency states, including X-linked lymphoproliferative disease, Chediak–Higashi syndrome, common variable immunodeficiency, chronic granulomatous disease [13] and autoinflammatory disease [14]. The genesis of HLH in these conditions may be particularly related to an inability to clear antigen and therefore persistent stimulation of cytokine production.

Clinicians need to consider HLH in 'at-risk' groups such as those with rheumatologic disease, infections, or malignancy who are persistently febrile and cytopenic, and in whom treatment of the initial diagnosis is not effective.

Diagnosing HLH

HLH causes a constellation of non-specific findings, including persistent fever, altered mental state, rash, cytopenias affecting all cell lines (often with thrombocytopenia initially), elevated lactate dehydrogenase (LDH), hepatosplenomegaly, lymphadenopathy and transaminitis. Typically patients have hyperferritinaemia (highly elevated ferritin $>10\,000$ μg/l may be pathognomic of HLH in some contexts) with elevated triglycerides and decreasing fibrinogen [15]. However, often one or more of these abnormalities is not seen.

Key to early detection of HLH before the 'tipping point' into hyperinflammation is interpretation of patterns of results rather than absolute values and recognizing worrying trends (e.g. decreasing ESR in a patient with a known chronic disease).

The absence of haemophagocytosis on bone marrow can be falsely reassuring. The test is not 100% sensitive, and it may not be present in up to 30% of cases [10, 16] or only appear on repeat testing. Furthermore, haemophagocytosis on bone marrow, or in other tissues, is not binary, nor is it sufficient to make the diagnosis of HLH—some degree of haemophagocytosis can be present in the marrow of patients without HLH [17, 18]. Close collaboration with haematologists when managing HLH is therefore essential.

In the paediatric and adult populations, hyperferritinaemia is shown to be both sensitive and specific as a marker for HLH and MAS in 'at-risk' patients [19, 20] and a marker of response to treatment. Diagnostic algorithms have been developed utilizing ferritin, given its wide availability and low cost [2, 21]. Hyperferritinaemia is not specific for HLH in the adult population as a whole [22], being seen in a number of other conditions including renal failure, liver failure, and iron overload.

pHLH has an established set of diagnostic criteria—the Histiocyte Society's HLH-2004 criteria [23] [see Table 1]. These criteria have been extrapolated to the diagnosis of sHLH; however, there is concern that this leads to underrecognition. For instance, features well recognized in adults [such as elevated LDH and alanine aminotransferase (ALT)] are not included in the diagnostic criteria [10, 24], and some of the variables measured in the HLH-2004 criteria are not readily available in many hospitals.

The H-score, developed by Fardet *et al.* [17] [see Table 2], is the first diagnostic scoring system for sHLH to be validated in adults. It comprises nine criteria: three clinical (immunosuppression, fever, organomegaly), five laboratory [ferritin, triglyceride, aspartate transaminase (AST), fibrinogen, cytopenia] and one histological/cytological (haemophagocytosis on bone marrow). This gives a probability of HLH being present. The H-score has been shown to perform better than the HLH-2004 criteria

Table 1 HLH-2004 diagnostic guidelines. A diagnosis of HLH can be made if either of the following conditions are met: a molecular diagnosis consistent with HLH, or five of the following criteria:

HLH-2004 diagnostic criteria
Any five of:
Fever >7 days
Splenomegaly
Cytopenia—any two of:
Haemoglobin <9 g/dl
Platelets $<100 \times 10^9$/ml
Neutrophils $<1 \times 10^9$/ml
Hypetriglyceridaemia and/or hypofibrinoginaemia (fasting triglycerides $\geqslant 3$ mmol/l, fibrinogen $\leqslant 1.5$ g/l)
Low or absent natural killer cell activity
Ferritin >500 ng/ml
Soluble CD25 $\geqslant 2400$ U/ml
Haemophagocytosis in the bone marrow, spleen or lymph nodes
No evidence of malignancy

Table 2 The H score can be used to assess the likelihood of sHLH in a patient. For instance, a score of 200 gives a 90% chance of HLH. Adapted from Fardet *et al.* [17]

The components of the H score are
Fever
Organomegaly
Cytopenia
Ferritin (ng/ml)
Triglycerides (mmol/l)
Fibrinogen (g/l)
Haemophagocytosis in bone marrow
AST (IU/l)
Known underlying immunosuppression

H score			
Fever	<38.4 = 0	38.4–39.4 = 33	>39.4 = 49
Organomegaly	No organomegaly = 0	Splenomegaly or hepatomegaly = 23	Splenomegaly and hepatomegaly = 38
Cytopenia (Hb 9.2 g/dl and/or a leucocyte count of 5000/mm^3 and/or a platelet count of 110000/mm^3)	1 cell line = 0	2 cell lines = 24	3 cell lines = 34
Ferritin (ng/ml)	<2000 = 0	2000–6000 = 35	>6000 = 50
Triglycerides (mmol/l)	<1.5 = 0	1.5–4 = 44	>4 = 64
Fibrinogen (g/l)	>2.5 = 0	⩽2.5	
Haemophagocytosis in bone marrow	No = 0	Yes = 35	
AST (IU/l)	<30 = 0	⩾30 = 19	
Known underlying immunosuppression	No = 0	Yes = 18	

The scores for all components are summed to calculate the H score	
90	<1
100	1
110	3
120	5
130	9
140	16
150	25
160	40
170	54
180	70
190	80
200	88
210	93
220	96
230	98
240	99
250	>99

Hb: haemoglobin.

if used at presentation, with sensitivity of 90% and specificity of 79%.

In patients with systemic sJIA, a further set of classification criteria have been published. In this context, the bar for diagnosing MAS/HLH is much lower, given the well-recognized link between sJIA and sHLH: ferritin >684 ng/ml, inappropriately low/normal platelets and fibrinogen, and mildly elevated AST (Table 3) [25].

Some patients with sepsis are recognized to have features of HLH, so called macrophage activation-like syndrome [26]. The prevalence of this subgroup in the sepsis population has been found to be 3.7–4.3% [26], with

TABLE 3 Diagnostic criteria for MAS in the context of sJIA. Adapted from Ravelli *et al.* [25]

The criteria for diagnosing MAS in sJIA are a diagnosis of sJIA, a fever and
Ferritin >684 ng/ml
And any two of
Platelet count $\leqslant 181 \times 10^9$/l
AST >48 IU/l
Fibrinogen $\leqslant 360$ mg/dl
Triglycerides >156 mg/dl

MAS: macrophage activation syndrome.

mortality at approximately 66%. Serum ferritin >4420 ng/ml was associated with early mortality in this sepsis cohort [26], even disregarding analysis of the other H-score variables. Serum ferritin in excess of 4420 ng/ml may be a useful screening test for HLH or macrophage activation-like syndrome in the sepsis population.

As important as recognizing the presence of HLH is recognizing the trigger and/or driver. While treatment directed at the HLH process can improve outcome, definitive treatment should target the precipitant [27], and the superadded risk of an additional trigger, such as infection, needs to be excluded.

In patients in whom no trigger is found, the search for an underlying malignancy must be exhaustive. Haematological malignancy is the single most common cause of sHLH in the adult population [27]. Additionally, sHLH is disproportionately a feature of difficult-to-diagnose lymphomas, including intravascular lymphoma [10]. It is also worth noting that the genetic defects associated with deficient perforin function are also associated with the development of lymphoma [28]. Therefore, genetic testing should be considered in selected patients presenting with HLH due to lymphoma, particularly in younger patients.

In summary, available diagnostic criteria are useful, but given their limited validation, they should be used with some caution. Overreliance may lead to missed patients with features of HLH but not meeting the diagnostic criteria. There are instances where these patients may still benefit from HLH targeted therapy. For instance, in the rheumatologic cohort, HLH should be considered in patients with active, inflammatory disease whose ESR and platelets start to fall inappropriately [23].

Treatment

Treatment of pHLH is with immunosuppression, using dexamethasone, etoposide (VP-16), cyclosporin A and intrathecal methotrexate for CNS disease, aimed at controlling the acute episode of hyperinflammation and enabling the child to go forward to bone marrow transplant according to the HLH-2004 protocol [23]. There has been little consensus on how to treat sHLH with the exception of MAS complicating sJIA [25], and often elements of the HLH-2004 protocol are used. A recent evidence-based algorithm has been proposed [2] using IL-1 blockade with anakinra (Fig. 1), although this has not been validated or universally adopted. Importantly, the HLH-2004 protocol was written before the development and use of drugs such as anakinra.

Therapy can divided into those aimed at addressing the HLH process (using elements of HLH-2004 and other immunosuppressive approaches) and those directed towards the underlying disease trigger.

Immunosuppressive treatment of HLH

HLH targeted therapy aims to attenuate the immune system–mediated hyperinflammatory state. The drugs used aim to reduce the number of cells secreting pro-inflammatory cytokines or interfere with the cytokines themselves [2]. Use of these medications is limited by the risks of immune suppression. This is of particular concern in patients in whom the trigger for HLH is felt to be an infection. All patients however, regardless of the initial cause, are likely to be at risk of superadded infection. The authors manage HLH through dedicated multidisciplinary teams, and first-line therapies are glucocorticoids, IVIG, anakinra, and cyclosporin. Drugs used to treat HLH are listed in Table 4.

Dexamethasone is used in pHLH and in adult haematology practice, in part because of good brain penetrance [29]. In rheumatologic practice, there is a tendency to give pulsed intravenous methylprednisolone at the outset [2]. The life-threatening and sometimes fulminant nature of HLH limits the extent to which a steroid-sparing regimen can be considered.

Cyclosporin may be an attractive medication for adult treatment protocols, as it is effective in some of the rheumatologic diseases that trigger HLH. It is also a medication with a reasonable long-term safety profile (although not without side effects), demonstrated by its use as an immunosuppressive medication in a number of chronic diseases [30]. There have been some concerns about the risk of posterior reversible encephalopathy syndrome [31], particularly when given intravenously and at higher doses. However, the optimal timing for initiation relative to other medications is not confirmed, and may vary between different HLH drivers.

IVIG has a role in the treatment of HLH in adults. It has an impact on the HLH process and serves to reduce inflammation by several mechanisms, including reducing complement activation and cytokine inhibition [32, 33]. It may also have the additional benefit of counteracting some of the immune deficiency brought about by other drugs and the disease state. However, there are potential side effects of IVIG, but these are relatively rare [34]. The risk of anaphylaxis is likely mitigated by the concurrent use of steroids in HLH protocols.

Anakinra is a recombinant form of endogenous IL-1 receptor antagonist. It has been used successfully in the treatment of sJIA, which is well recognized as progressing to HLH (MAS) during acute disease flares [35]. The effectiveness of anakinra in sJIA forms part of the rationale for its more widespread use in sHLH. Further support for its

Fig. 1 Treatment algorithm for management of sHLH. Adapted from Carter *et al.* [4]

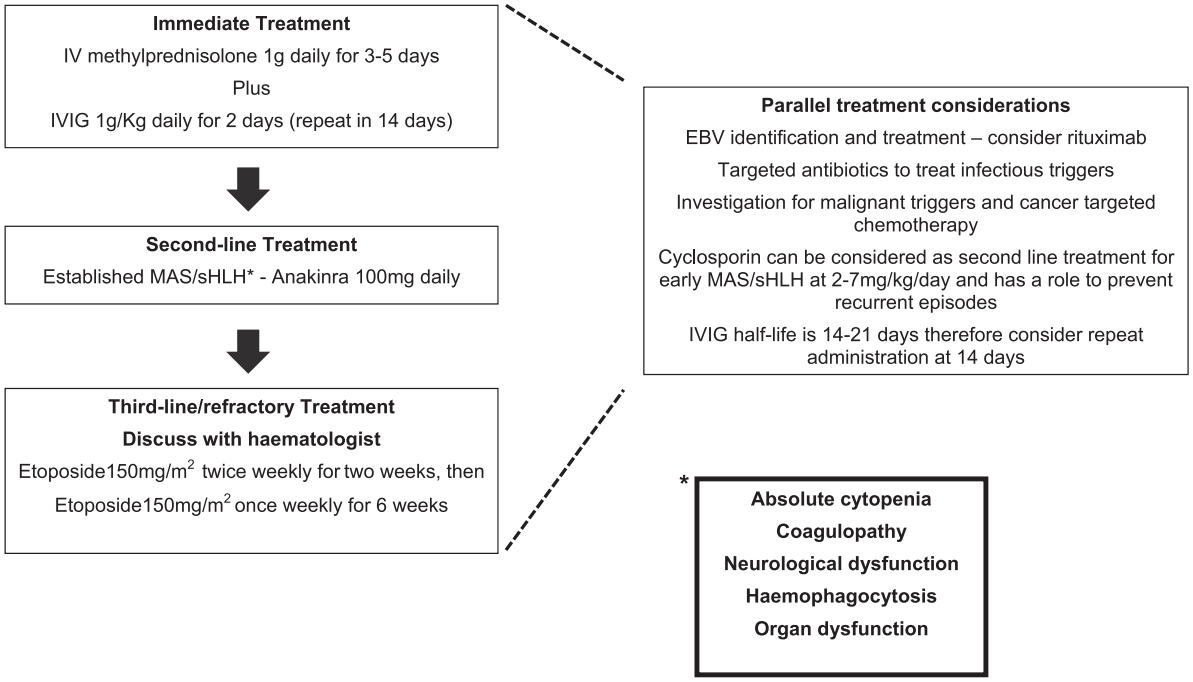

Table 4 Summary of medication used for HLH

Drug	Level of evidence (phase)	Side effects
Glucocorticoids (dexamethasone)	Prospective therapeutic study: HLH 1994/2004 (2b)	Infection, hyperglycaemia/metabolic derangement, impaired wound healing, osteoporosis, hypertension, psychiatric disturbance
Etoposide	Prospective therapeutic study: HLH 1994/2004 (2b)	Bone marrow suppression, infection, increased risk of malignancy (acute myeloid leukaemia), nausea and vomiting, alopecia
Cyclosporin	Prospective therapeutic study: HLH 1994/2004 (2b)	Infection, gum hypertrophy, kidney injury, liver injury, posterior reversible encephalopathy syndrome, nausea and vomiting, hypertension, hypercholesterolaemia
IVIG	Retrospective study of cases (4)	Infusion reactions, anaphylaxis, renal impairment, transfusion-related acute lung injury, thrombosis, arrhythmia
Anakinra	Retrospective study of cases (4)	Infection, leucopenia, thrombocytopaenia, hypercholesterolaemia, liver injury
Tocilizumab	Retrospective study of cases (4)	Infection, lipid derangement, leucopenia, conjunctivitis, cough/dyspnoea, abdominal pain, increased risk of gastrointestinal perforation + diverticulitis
Rituximab	Retrospective study of cases (4)	Infection, hypogammglobulinaemia, infusion reaction, anaphylaxis, progressive multifocal leucoencephalopathy, pancytopenia, hypertension, gastrointestinal upset
Mycophenolate mofetil	Individual case reports	Infection, pancytopenia, increased risk of malignancy, hyperglycaemia, hyperlipidaemia, hypercholesterolaemia, tremor, liver injury, renal impairment
Cyclophosphamide	individual case reports	Infection, increased risk of malignancy (depends on dose), bone marrow suppression, haemolytic uraemic syndrome, anaphylaxis, syndrome of inappropriate antidiuretic hormone secretion, liver injury, alopecia, cystitis, fever, impaired fertility (depends on dose)
Anti-IFN-γ (emapalumab)	Multicentre open-label trial (2)	Infection, hypertension, infusion reactions, fever, hypokalaemia

use comes from the mortality benefit in septic macrophage activation-like syndrome patients with HLH features. The original trial investigating the use of anakinra in the wider sepsis population did not yield positive results. Importantly, however, there was no increased mortality in the sepsis group treated with anakinra [26], suggesting the relative safety of the drug, even in patients with severe infection. There are multiple case reports/series describing successful use of anakinra in sHLH, with multiple triggers, but a dearth of high-quality evidence [36].

Etoposide in animal models has been shown to selectively kill activated T cells [37] and is used in pHLH to achieve remission before definitive treatment with bone marrow stem cell transplantation [5]. The indication for etoposide in adults with sHLH is not as clear. The side-effect profile is significant and may exacerbate cytopenia, complicating the assessment of treatment response [32]. Some mortality in treated patients is likely due to etoposide toxicity.

Tocilizumab is an IL-6 inhibitor. IL-6 levels are increased in HLH and there is interest in the therapeutic benefit of blockade [38], with use currently being trialled as well as current use in the HLH-like cytokine release syndromes seen with cancer immunotherapy, such as chimeric antigen receptor T cell therapy. However, tocilizumab has a tendency to promote infection [39], likely more than anakinra, potentially limiting its use in HLH. IL-6 attenuates the levels of CRP, preventing using this as a marker of both worsening inflammation and infection, a cause for further concern.

Rituximab has been used successfully in the treatment of HLH, primarily in the context of B cell lymphomas. Rituximab forms part of the treatment regimen for the underlying malignancy. In the case of active EBV infection, B cell depletion with rituximab has also been used with good effect [40], as B cells act as a reservoir for the virus. Rituximab has been used successfully in the treatment of HLH in the context of disease triggers that respond to rituximab therapy, such as SLE [41].

Mycophenolate mofetil is a well-recognized treatment for autoimmune disease, especially SLE. Patients with HLH complicating SLE have been successfully treated with regimens including mycophenolate when other combinations of medications have failed [42].

Cyclophosphamide has been used in the paediatric population, in the context of stem cell transplantation, for example, post-transplant in haplo-identical transplant [43]. Cyclophosphamide has also been used in the context of HLH triggered by immune-mediated inflammatory diseases such as SLE. Again in this context, it is likely that the treatment is targeting both the HLH and the triggering disease.

Anti-IFN-γ antibody therapy (emapalumab) has been used in children with pHLH, with positive results in patients refractory or intolerant to conventional therapy in one pilot study and with trials in adults under way. Promisingly, the treatment has been well tolerated, with few of the toxic side effects of more established regimens [44].

Treatment of an underlying malignancy highlights a particular issue in terms of side effects and treatment-related toxicity. Cytotoxic medications have the risk of further exacerbating the cytopenia already caused by the disease [10]. Patients are, almost by definition, already frail and critically unwell and will likely have a poor performance status. Chemotherapy given in this context may be associated with adverse outcomes.

Once disease control has been achieved, treatment should be tapered, but there is little consensus as to how to do this safely. It is logical to withdraw the most potentially harmful medications first, assuming there is no compelling evidence that one medication has proven more pivotal in achieving remission than others. The use of anakinra as long-term maintenance therapy in JIA would suggest it may potentially have a prolonged role in HLH. It is reasonable to keep patients on this for the medium to long term, until the treating clinicians are confident the risk of recurrence is acceptably low.

Once treatment has been tapered, it is necessary to monitor patients for recurrence of inflammation. The risk of recurrence depends on the cause/trigger—patients with genetic HLH almost always relapse without bone marrow transplant [1]. On the other hand, patients with infections or rheumatologic disease are less at risk once the trigger has been controlled. There is no established protocol in terms of blood monitoring for relapse; however, serum ferritin may be useful.

Illustrative cases

Patient 1

A 47-year-old man with a 6-month history of gradual weight loss and mild anaemia presented with a month's history of fever with intermittent hypotension. Blood work showed three-line cytopenia, elevated ferritin (2210 μg/l), elevated triglycerides (5 mmol/l) and normal fibrinogen. PET-CT demonstrated a bone lesion in the right femur. No lymphadenopathy was found. Bone marrow analysis did not show any significant haemophagocytosis, but the clinical picture was considered to be consistent with HLH. There were concerns about an underlying lymphoproliferative disease, so steroids were avoided for fear that they would obscure the diagnosis on subsequent biopsies. Treatment was started with anakinra and IVIG. He went on to have a biopsy of the bone lesion, which confirmed lymphoma. He was started on etoposide and then chemotherapy for the lymphoma, but died 1 week later.

Patient 2

A 23-year-old woman presented with intractable fever on the background of a 5-year history of adult-onset Still's disease. Her adult-onset Still's disease had proved difficult to control—she had failed methotrexate and azathioprine. Her blood tests 2 weeks earlier showed CRP 120 mg/l, ESR 86 mm/h and platelets 350×10^9/l. On this occasion, CRP was 150 mg/l, ESR 40 mm/h, platelets 120×10^9/l and ALT 112 IU/l. Ferritin was found to be 15 235 μg/l, with normal triglycerides but low fibrinogen

(1.3 g/l). The patient went on to have a bone marrow biopsy and treatment of HLH was commenced with pulsed methylprednisolone (1 g × 3), IVIG and anakinra. The patient responded quickly to treatment, with an improved clinical picture within 2 days and improved blood tests by day 3. Bone marrow results demonstrated significant haemophagocytosis. The patient was discharged home after 10 days on daily anakinra and a weaning dose of steroid.

Patient 3

A 72-year-old man who was normally completely fit and well presented with fever, malaise and intermittent confusion. Although no localizing signs of infection were identified, he was treated as presumed chest sepsis. He remained febrile, so the first-choice antibiotic meropenem was changed to tazocin. Over 5 days he became increasingly unwell and developed three-line cytopenia, but CRP decreased from 80 mg/l on admission to 42 mg/l. Opinions from haematology and infectious diseases were sought, but while waiting for these he collapsed on the ward and was admitted to the critical care unit. Ferritin was checked and was found to be 16 558 μg/l and a rheumatologic referral was made. The patient's wife gave additional history that he had had an episode of shingles 3 weeks prior to admission and had 'not been right since, with temperatures and confusion'. An H-score was calculated and showed a 95% probability of HLH and a diagnosis of sHLH induced by shingles was made. Treatment of sHLH was commenced with pulsed methylprednisolone (1 g × 3) and IVIG. Rapid improvement was made and therefore anakinra was not given. A bone marrow examination confirmed the presence of significant haemophagocytosis. The patient was transferred back to the ward and made a complete recovery.

Conclusion

What is the role of rheumatology and how to interface with other specialities?

The role of rheumatology in the management of patients with sHLH is dual. Patients may present with a confirmed rheumatologic disease, in which case they will need to advise on the management of the underlying condition in this acute setting. In patients without a confirmed underlying diagnosis, the question is asked whether an as yet undiagnosed rheumatologic disease is driving the process. In this situation, it will fall to the rheumatologists to give an opinion as to the likelihood of this based on the clinical and laboratory information available.

In the case of patients in whom underlying rheumatologic disease is excluded, rheumatologists still have a role. They have experience in managing patients with multisystem inflammatory disease and as such, are well placed to offer guidance on treatment and monitoring response. Familiarity with medications such as IL-1 inhibitors will often prove useful when tasked with administering them to critically ill patients in intensive care.

HLH is relatively rare and often difficult to diagnose. It can present to many different specialities. Treatment is challenging and mortality is high. For this reason, a multispeciality cooperative approach is required in order to achieve the best outcomes.

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