Hemophagocytic Lymphohistiocytosis in Adults

Meghan Campo, MD[b], Nancy Berliner, MD[a,*]

KEYWORDS

• Hemophagocytic lymphohistiocytosis • Adults
• Acquired hemophagocytic lymphohistiocytosis • Treatment • Diagnosis

KEY POINTS

- Acquired hemophagocytic lymphohistiocytosis (HLH), though seen in the pediatric population, is the more common form of HLH in adults, often triggered by an underlying infection, malignancy, or rheumatologic condition.
- Acquired HLH is a highly morbid condition; if left untreated, patients survive for only a few months because of progressive multisystem organ failure.
- The treatment paradigm of adult HLH is largely based on the pediatric, HLH-1994 protocol. Further work is needed to refine the diagnostic criteria and treatment algorithm for the adult population.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal syndrome of pathologic immune dysregulation characterized by clinical signs and symptoms of extreme inflammation. The pathology of the condition centers on the activation and proliferation of uncontrolled macrophages and lymphocytes, culminating in an unrelenting cytokine storm and subsequent tissue infiltration and multiorgan system failure.

HLH can occur as a genetic or sporadic disorder and, though seen as an inherited condition affecting primarily a pediatric population, can occur at any age and be encountered in association with a variety of underlying diseases. Genetic HLH occurs in familial forms (fHLH), in which HLH is the primary and only manifestation, and in association with immune deficiencies such as Chédiak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome, whereby secondary HLH occurs sporadically and is often a terminal phase of the disease. Acquired HLH,

[a] Division of Hematology, Brigham and Women's Hospital, Harvard Medical School, Mid-Campus 3, 75 Francis Street, Boston, MA 02115, USA; [b] Dana Farber Cancer Institue, Boston, MA, USA
* Corresponding author.
E-mail address: nberliner@partners.org

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though seen in the pediatric population, is the more common form of HLH in adults and is often triggered by an underlying infection, malignancy, or rheumatologic condition (Box 1). Clinically the syndrome, whether genetic or acquired, is characterized by fever, hepatosplenomegaly, cytopenias, and the finding of activated macrophages in hematopoietic organs, often resulting in multiorgan system failure and death. Therapy centers on the suppression of this hyperinflammatory state, focusing on the destruction of cytotoxic T lymphocytes and macrophages with cytotoxic, immunosuppressive therapy and treatment of any existing HLH triggers.

ACQUIRED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Acquired HLH can present at any age, although it is more typically encountered in the adult population with a mean age at diagnosis of 48 to 50 years old.[1,2] It is associated with a wide variety of conditions including infection, malignancy, autoimmune disorders, and immunosuppression. These entities have been linked to the development of HLH in the literature; however, there are also case reports of lesser described triggers including medications, pregnancy, and post-hematologic and solid organ transplantation.

The clinical presentation of acquired HLH is similar to the familial form, and the diagnostic criteria remain the same. However, as the criteria for diagnosis were developed in the context of pediatric patients, there is considerable interest in adapting the diagnostic criteria to improve the diagnosis of HLH in adults. Genetic testing in these patients reveals a subset that displays heterozygous mutations and polymorphisms in the known fHLH genes (Table 1). In one study of adult patients who met the criteria for HLH, missense and splice-site sequence variants in *PRF1*, *MUNC13-4*, and *STXBP2* were present in 14% of patients, and the A91V-PRF1 genotype was found in 4.8%.[3] Hypomorphic alleles for fHLH genes are implicated in approximately 15% of acquired HLH. However, to date there are no data to indicate whether the prognosis of patients who possess these defects differs from those in whom such polymorphisms are not identified.[3]

Box 1
Conditions associated with HLH

Genetic

1. Familial
   - Known genetic defects: *PRF1*, *MUNC13-4*, *STX1*, *STXBP2*
   - Unknown genetic defects
2. Immune deficiency syndromes
   - Chédiak-Higashi syndrome, Griscelli syndrome, X-linked lymphoproliferative syndrome: *LYST*, *RAB27α*

Acquired

1. Infections
   - Viral, bacterial, fungal
2. Malignancy
3. Autoimmune conditions
4. Others: posttransplantation, pregnancy, drug-induced

Table 1
HLH subtypes and their known genetic defects

HLH Subtype	Genetic Defect	Resulting Defect
FHL1	9q21.3-locus 6	Unknown
FHL2	*PRF1*	Vesicle content
FHL3	*UNC13D*	Defective cytolytic granule exocytosis
FHL4	*STX18B*	Defective intracellular transport
FHL5	*UNC18B*	Defective membrane fusion

Data from Tothova Z, Berliner N. Hemophagocytic syndrome and critical illness: new insights into diagnosis and management. J Intensive Care Med 2014 Jan 8. [Epub ahead of print].

Infection

Viral infection, either as a primary infection or reactivation in an immunosuppressed host, is a frequent trigger of acquired HLH. In a large study of 96 adult patients from Taiwan with HLH, 30 were associated with infection.[4] The most common types of infection were viral (41%), mycobacterial (23%), bacterial (23%), and fungal (13%). The Epstein-Barr virus (EBV) is the most common viral pathogen linked to the development of HLH. EBV is postulated to cause a clonal proliferation and hyperactivation of EBV-infected T cells in patients with EBV-associated HLH. Other viral pathogens linked to the disorder include cytomegalovirus, parvovirus, herpes simplex virus, norovirus, varicella zoster virus, measles virus, human herpes virus 8, H1N1 influenza virus, and human immunodeficiency virus (HIV). In one retrospective analysis of 162 patients with HLH, approximately 25% were found to have an infectious trigger, with approximately half of these cases thought to be secondary to HIV.[2] Although less commonly reported, HLH may also occur in the setting of infections caused by bacteria (*Mycobacterium tuberculosis*, *Ricksettsia*, *Escherichia coli*), parasites (*Leishmania*), and fungi (*Histoplasma*).

Malignancy

The development of HLH in individuals with an underlying malignancy has been clearly described. The hematologic malignancies, specifically lymphoma, are the most common cause of malignancy-associated HLH. Among lymphomas, T-cell lymphoproliferative disorders, such as anaplastic large cell lymphoma and natural killer (NK) cell lymphoma, are the most frequently linked to HLH. A recent survey of adult patients with HLH reported that more than half (52%) were associated with malignancies. Of these cases, approximately 59% were associated with T-cell lymphoma and 19% were linked to diffuse large B-cell lymphoma.[5] Data are limited as to whether the malignancy itself is causative of HLH or whether the malignancy places the patient at increased risk of infection that ultimately triggers the syndrome.

Autoimmune Conditions, Macrophage Activation Syndrome

Several autoimmune conditions are known precipitants of HLH including systemic lupus erythematosus (SLE), mixed connective tissue disorder, dermatomyositis, systemic sclerosis, and Kikuchi disease. HLH may develop at any time during the course of a rheumatologic disorder, on presentation, during therapy, or at time of flare.[6] The specific term macrophage activation syndrome (MAS) is typically used when a hemophagocytic syndrome develops in children with juvenile idiopathic arthritis and other rheumatologic conditions, but it has also been documented as a syndrome in adults, the limited data for which suggest that it is seen most frequently in association with

adult-onset Still disease, SLE, and various vasculitic syndromes. The primary clinical manifestations of adult-onset MAS are identical to those in pediatric patients and include fever, lymphadenopathy, hepatosplenomegaly, and liver function test (LFT) derangements. In addition to similar clinical manifestations, MAS and HLH also share genetic similarities. Polymorphisms and heterozygous mutations in *PRF1* and *UNC13D* have been identified in MAS patients, most of whom also have decreased NK function, elevated soluble CD25 (sCD25), and elevated soluble CD163 (sCD163).[7]

Diagnosis

The diagnosis of acquired HLH, especially in adults, is often difficult, and may frequently not be considered or confirmed before a patient's death. The primary problem is the lack of a specific disease marker, as the clinical picture is often nonspecific and mimics alternative infectious or malignant conditions. Many of the initial, nonspecific tests that are helpful in evaluating HLH (complete blood count, coagulation studies, and LFTs) are completed in the evaluation of an unexplained febrile illness. Additional markers, including serum ferritin, triglycerides, and screening immunologic studies, are ordered when suspicion for HLH mounts.

Although the significance of the results remains to be determined, the author recommends that mutation analysis be requested for all adult cases of confirmed or suspected HLH at some time during their course, with analysis of the known fHLH mutations (*PRF1*, *UNC13D*, *STX11*, and *UNC18B*), as a subset will possess heterozygous mutations and polymorphisms in the known fHLH genes. That said, negative results will be found in most of the adult population. As the presence or absence of a mutation does not alter treatment, appropriate therapy should not be delayed while awaiting results, and in fact testing need not be done at the time of initial evaluation. However, the presence of an fHLH mutation may provide guidance in decisions regarding ongoing therapy or transplantation for patients who achieve remission with initial HLH therapy. It must be stressed that the clinical importance of finding hypomorphic fHLH alleles remains to be established in the adult population, but whether such mutations predict a course that is different from that in patients without mutations should become clearer as the disease becomes better recognized and testing becomes more universal. The Histiocyte Society developed a set of diagnostic criteria in 1994 to help clinicians identify pediatric patients with both familial and acquired HLH on clinical and laboratory grounds. These criteria were later refined in 2004 (**Box 2**) to include decreased NK-cell function and elevated sCD25 or serum-soluble interleukin-2 receptor (sIL-2R) levels. It should be noted that although these recently added markers (NK function, sIL-2R) are helpful in establishing a diagnosis, testing often requires sending samples to specialized laboratories, and these results are not always available to help with a timely diagnosis. It should also be recognized that these criteria were developed for the diagnosis of pediatric patients and may not be best suited to making the diagnosis of HLH in adults.

Clinical Manifestations

Adult HLH often presents as a febrile illness with multiorgan involvement that mimics common viral and bacterial infections. Patients typically present with high, prolonged fever and findings on physical examination of hepatomegaly, splenomegaly, and lymphadenopathy. Laboratory evaluation reveals the presence of LFT abnormalities, elevated ferritin, and cytopenias, most commonly anemia and thrombocytopenia. With few exceptions, the clinical manifestations are similar regardless of whether an underlying genetic defect is present and identified.

Box 2
Diagnostic criteria for the diagnosis of HLH

The diagnosis of HLH can be established if A or B is fulfilled

A. A molecular diagnosis consistent with HLH
   - Pathologic mutations of *PRF1*, *UNC13D*, *STXBP1*, *RAB27A*, *STX11*, *SH2D1A*, or *XIAP*

B. Five of the following clinical criteria
   - Fever
   - Splenomegaly
   - Peripheral cytopenias (affecting at least 2 of 3 cell lineages)
   - Hypertriglyceridemia (fasting, >3 mmol/L) and/or hypofibrinogenemia (<1.5 g/dL)
   - Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
   - Ferritin greater than 500 μg/L
   - Low or absent natural killer cell activity
   - Increased soluble CD25 concentration (α chain of soluble interleukin-2 receptor) greater than 2400 U/mL

Data from Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31.

Neurologic Manifestations

Neurologic manifestations are variable in presentation, and include focal neurologic deficits, seizure, encephalopathy, coma, and sensory and motor peripheral neuropathy resulting from myelin destruction by macrophages.[7] Approximately one-third of all patients with HLH will develop some degree of neurologic dysfunction during the course of their disease. The variability in presentation is similar to that found in laboratory and imaging findings, which makes the diagnosis of central nervous system (CNS) involvement difficult. In children with HLH, approximately 50% will have abnormalities of the cerebrospinal fluid (CSF), with most demonstrating a pleocytosis.[8] MRI of the brain of these same patients may show discrete lesions, leptomeningeal enhancement, and hypodense or necrotic areas, or may be completely normal.[9] However, in adult patients these laboratory and imaging findings are thought to be much less prevalent and have been restricted to case reports.[10] Regardless of the exact clinical manifestation in both the pediatric and adult population, the presence of neurologic involvement is thought to be a poor prognostic marker.[8,11]

Dermatologic Manifestations

Patients with adult HLH may have a wide array of cutaneous findings including generalized erythroderma, generalized maculopapular rash, petechiae, and purpura. Biopsies have shown that rashes may correlate with lymphocytic infiltration and frank hemophagocytosis. Close attention should be paid to those with subcutaneous panniculitic–like nodules attributable to the association with an underlying T-cell lymphoma.[1] These variable dermatologic manifestations are thought to be rare, although dermatologists have suggested that maculopapular rashes are fairly common.[12,13]

Laboratory Findings

Characteristic laboratory findings in all patients with HLH include liver function abnormalities, elevated ferritin, coagulopathy, hypertriglyceridemia, and cytopenias affecting

at least 2 lineages in the peripheral blood. These abnormalities are thought to be driven in large part by the hypercytokinemia that pervades this disorder.

Elevated ferritin

Ferritin has proved to be a valuable diagnostic and prognostic marker in cases of pediatric HLH. In pediatric populations, a ferritin greater than 10,000 mg/dL is 90% sensitive and 96% specific for a diagnosis of HLH.[14] However, although virtually all adults with HLH meet the diagnostic criteria of a ferritin count greater than 500 mg/dL, the sensitivity and specificity of this marker in the adult population is much less impressive. A study examining the correlation between HLH and hyperferritinemia in adult hospitalized patients with extremely high ferritin levels (>50,000 mg/dL) was recently reported. The specificity of the ferritin level was low in this group of adults, with a confirmed HLH diagnosed in only 19 of 111 individuals. Extreme elevations of ferritin were more typically seen with hepatocellular insult, renal failure, infections, and hematologic malignancies.[15] Consequently, although the negative predictive value of a normal serum ferritin is high, there is no level of ferritin that has high positive predictive value in diagnosing HLH.

Hemophagocytosis

Hemophagocytosis is defined by phagocytosis by histiocytes of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues. In the pediatric literature the reported incidence of hemophagocytosis detected on biopsy ranges from 25% to 100%.[7] This phenomenon, though semantically linked to HLH, is neither sensitive nor specific for the diagnosis, and is considered one of the less important diagnostic criteria even in cases of fHLH. More frequently, hemophagocytosis is induced by more common events such as infection, autoimmune conditions, and blood transfusions.[7]

In HLH, histologic examination of any involved organs may show infiltration by histiocytes and lymphocytes, with hemophagocytosis.[11,16] Evidence of hemophagocytosis at any biopsy site fulfills diagnostic criteria; however, bone marrow aspiration[11] is often the diagnostic modality of choice. Spleen biopsy has inherent complications, and liver biopsy is often uninformative because it often reveals a hepatitis-like lymphocytic infiltration rather than frank hemophagocytosis. Repeat bone marrow biopsy is often needed, as in most cases hemophagocytosis may not be observed in the initial bone marrow aspirate but will become evident on follow-up evaluation.

Liver function abnormality and coagulopathy

Though not part of the HLH-2004 diagnostic criteria, liver inflammation is almost always evident in adult patients with newly diagnosed HLH. Abnormalities range from mild transaminitis or cholestasis to fulminant hepatic failure. The prevalence of hepatic dysfunction is so high that normal LFTs should bring into question the diagnosis of HLH. Liver biopsy, if performed, is likely to show infiltration of lymphocytes into the portal tracts similar to that seen in chronic persistent hepatitis.[16] Bleeding complications are common in this condition and are seen in up to 60% of patients.[1] Hemorrhage may reflect a variety of factors, including coagulopathy from liver dysfunction, thrombocytopenia from bone marrow failure, or platelet function defects associated with an underlying genetic defect in platelet granules.[7]

Soluble CD163

CD163, a receptor for hemoglobin-haptoglobin complexes and a marker of macrophage activation, is of growing interest. Although increased plasma levels of sCD163 are seen in malignancy, autoimmune conditions, and infection, levels are

considerably higher in patients with HLH.[17] Though not specific for this disorder, in combination with additional clinical and laboratory findings suggestive of HLH, it can assist clinicians in establishing a diagnosis.

Depressed natural killer function

Demonstration of very low NK function can support a diagnosis of HLH. NK-cell activity can be measured by several modalities, including the ^{51}Cr release assay. In this assay, chromium-labeled NK cells are stimulated to degranulate. Release of the radionuclide is expected to be reduced or absent in HLH. The reported sensitivity of these tests approaches 100%. One study looking at 13 patients with adult HLH noted lower NK-cell activity in patients with confirmed HLH compared with controls.[18] However, studies demonstrate that even in genetically confirmed cases of fHLH, NK function may be normal, suggesting that preserved NK function does not preclude the diagnosis.[17,19] Furthermore, in most studies of adult HLH the NK function is seldom tested. For example, in the 62 patients who met the HLH-2004 diagnostic criteria in one study, only 5 had NK function tested, 3 of whom (60%) had depressed or absent NK function.[5]

Elevated serum-soluble interleukin-2 receptor

Measurement of the α chain of the soluble interleukin (IL)-2 receptor (sCD25), reflecting the degree of activation of T cells, can aid in confirming a diagnosis of HLH. Although recent studies have illustrated that levels of sIL-2Rα vary with age, very high levels are almost never seen outside HLH (Fill ASH, Weitzman ASH). Of note, recent studies have investigated sIL-2R/ferritin ratio as a marker to diagnose lymphoma-associated hemophagocytic syndrome (LAHS), which is a major subtype of adult-onset HLH. One study found that the mean sIL-2R levels were significantly higher in the LAHS group, whereas the ferritin levels were higher in the benign disease–associated HLH group. Consequently, the mean serum sIL-2R/ferritin ratio of patients with LAHS was markedly higher than that of patients with benign disease–associated HLH, thus demonstrating that the serum sIL-2R/ferritin ratio is a useful marker for diagnosing LAHS.[20]

Prognosis

The pediatric HLH-94 protocol yielded important early insights into HLH prognosis in children. In that study, the presence of elevated ferritin (>2000 μg/L), elevated bilirubin, and abnormal CSF findings correlated with increased mortality. Work is under way to identify prognostic factors in adult HLH, and although there has been no large scale prospective analysis there are several published retrospective case reviews. In adult HLH, prognosis seems to be negatively affected by the presence of underlying malignancy, certain laboratory abnormalities, and diagnosis at an older age.[21] Malignancy-associated HLH, specifically in the setting of T-cell lymphoma, fares poorly when compared with those cases driven by infectious or rheumatologic conditions,[5] with case series noting a median overall survival of 1 month versus 46 months for those with nonmalignant HLH.[22] In EBV-associated HLH, a high viral DNA load is associated with poor outcomes. Other laboratory findings including hypoalbuminemia, thrombocytopenia, and hyperferritinemia (>50,000 μg/L) have been shown to correlate with increased mortality in adult patients.[5,22,23]

Treatment

Acquired HLH is a highly morbid condition, and if left untreated patients survive for only a few months owing to progressive multisystem organ failure, with overall mortality ranging from to 41% to 75%.[1,24] However, those patients with confirmed

infectious or autoimmune triggers tend to have better outcomes, with mortality ranging from 8% to 24%.[25] Because of the high morbidity and mortality of the disorder, an aggressive therapeutic approach with rapid treatment of HLH is necessary, and therapy should not be delayed while awaiting molecular studies or other ancillary tests such as sCD25. In general, treatment entails the suppression of an overactive immune system and, in cases where a trigger is identified, focused therapy on the underlying cause. The current treatment of adult or acquired HLH is based on the pediatric HLH-94/-2004 protocols.

The first international treatment protocol for HLH, primarily designed to treat pediatric disease, was initiated by the Histiocyte Society in 1994.[26] This regimen entails an 8-week induction course of dexamethasone, etoposide, and intrathecal methotrexate. The principal goal of induction therapy is to suppress the overwhelming inflammatory process that drives HLH. Patients who complete the 8-week induction course and recover normal immune function and have no identified HLH-associated gene defects may stop therapy. If disease worsens during induction therapy while etoposide and dexamethasone are being tapered, indicated by progressive laboratory or clinical derangements, the doses can be escalated to full dose. Those who require additional therapy because of persistent disease are transitioned to continuation therapy, which in pediatrics is usually viewed as a bridge to hematopoietic cell transplantation (HCT). Continuation according to HLH-94 consists of pulses of dexamethasone and etoposide with the addition of cyclosporine in patients who are hemodynamically stable and have adequate liver and kidney function. In current practice, tacrolimus is often substituted for cyclosporine in adults, as it leads to less nephrotoxicity. Continuation therapy followed by HCT is recommended in pediatric patients with refractory disease and those with a high risk of relapse, including those with CNS involvement, persistent NK-cell dysfunction, documented homozygous or compound heterozygous HLH gene mutations, recurrent or progressive disease despite intensive therapy, and hematologic malignancy that cannot be cured otherwise.[7] The therapeutic indications for stem cell transplantation remain to be established for adults, but it is usually recommended for those who relapse or fail to achieve remission. It is also usually recommended for those who are found to have fHLH-related mutations (usually posited to be hypomorphic alleles), despite the lack of evidence that the latter group have a higher risk of recurrence.

The same group responsible for the HLH-94 protocol refined their treatment paradigm in 2004. The HLH-2004 protocol includes cyclosporine in the induction regimen and additionally adds hydrocortisone to intrathecal methotrexate for treatment of CNS disease.[27] The results of the treatment changes in the HLH-2004 protocol are not yet known. Without the final interpretation of HLH-2004 available, the risks and benefits of adding cyclosporine to the induction phase remain unconfirmed, and most clinicians continue to treat according to the protocol set forth by HLH-94.

Refractory/Recurrent Disease

After completion of induction therapy, a subset of patients demonstrates persistent disease or relapse shortly thereafter, and salvage therapy becomes necessary. In the pediatric literature, relapse typically occurs within a year of the initial acute illness, and these patients are more likely to harbor an HLH gene mutation than their counterparts who maintain remission.[7] Patients, both pediatric and adult, who have initially achieved disease remission with the HLH-94 protocol are often retreated with the same regimen. Studies have looked at the incorporation of alternative agents to etoposide and dexamethasone, such as alemtuzumab. A monoclonal antibody to the CD52 protein expressed on the surface of mature T cells and possibly NK cells,

alemtuzumab has been administered in patients with refractory disease. In a study of 22 pediatric and adult patients treated with alemtuzumab, a partial response was seen in 86%, and 77% were able to ultimately undergo HCT.[28]

Treatment of Specific Populations

Treatment of the clinically stable patient

Patients who are stable and have an identifiable condition responsible for triggering HLH, such as an underlying infection, may respond to treatment of the triggering condition alone. However, deterioration during the search for, or therapy for, the underlying condition is an indication to start HLH-specific therapy immediately.

Infectious trigger

Infections are a major trigger for adult HLH, and appropriately targeted antimicrobial and antiviral therapy is a cornerstone of management. Patients who are clinically stable and respond within a few days to treatment of an identified infection (bacterial, viral, fungal) may be able to avoid HLH-specific chemotherapy. However, initiation of HLH-specific therapy for severely ill patients should not be delayed while awaiting resolution of an identified infection.

Specifically for EBV-triggered cases of HLH, etoposide is a crucial therapeutic agent that must be added before disease response is achieved. The importance of etoposide is demonstrated in one large Japanese series involving patients with EBV HLH where survival was significantly improved if etoposide was initiated early and if at least 4 doses of etoposide were administered.[25] Rituximab has also demonstrated therapeutic benefit in EBV HLH as an adjunct to anti-HLH therapy. EBV largely resides in B lymphocytes, which can be rapidly depleted using the monoclonal antibody directed against the CD20 antigen on B lymphocytes. Depletion of B cells, which serve as a reservoir for EBV, is thought to improve survival by not only eradicating an HLH reservoir but also preventing relapse. The efficacy of rituximab in the treatment of HLH was investigated in 42 patients who were treated with rituximab-containing regimens. These patients, on average, received 3 rituximab infusions at a median dose of 375 mg/m^2, along with steroids, etoposide, and/or cyclosporine. Overall the therapy was well tolerated and resulted in clinical improvements in 43% of the patients, with most demonstrating reduced EBV viral loads.[29] However, as EBV also infects non–B-cell populations (T and NK cells) in patients with HLH, monotherapy with rituximab is not thought to be effective in eradicating HLH, and therefore must be used in concert with additional agents such as etoposide and dexamethasone.

Rheumatologic trigger

Treatment of a patient with an underlying rheumatologic condition centers on successful management of the underlying rheumatologic entity, which typically involves high-dose immunosuppressive agents. In cases of MAS, high-dose immunosuppression is the initial treatment of choice. However, in cases proven to be steroid refractory, cyclosporine has been found to be effective.[30] In addition to immunosuppression, investigators are studying the effects of several monoclonal antibodies in the treatment of MAS. Recent studies of patients with adult-onset Still disease complicated by MAS have evaluated the efficacy of the IL-1 receptor antagonist anakinra and the IL-6 receptor tocilizumab.[31,32] Although small case reports have been promising, there is concern that the inhibition of a single cytokine by a biological response modifier may be of limited efficacy for the treatment of the cytokine storm that is present in MAS. Confirmation of the efficacy of these agents awaits larger trials.

Oncologic trigger

For patients with disease thought to be driven by a hematologic malignancy, recommendations are made to treat with HLH-specific therapy, followed by appropriate chemotherapy for the malignancy with the caveat that HCT is often required.

FUTURE DIRECTIONS

HLH, though once considered a predominantly pediatric condition, is increasingly recognized in the adult population. Like its pediatric counterpart, adult HLH is a highly morbid condition that is almost universally fatal if unrecognized or untreated. At present there is little evidence to guide the evaluation, diagnosis, and treatment of HLH in the adult population. Further work is needed to discover clinically useful markers of the disease that can refine the current diagnostic criteria. With regard to treatment, further elucidation of genetic alterations and predisposing medical conditions linked to HLH should increase the understanding of the underlying pathogenesis, and lead to the development and implementation of more disease-specific therapies and improved outcomes in adults with HLH.

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