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Review Article

Adult Secondary Hemophagocytic Lymphohistiocytosis: A Mini-Review on Recent Developments

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Abstract

Hemophagocytic Lymphohistiocytosis, also known as HLH, is a group of disorders classified as a type of cytokine release syndrome triggering an abnormal activation of lymphocytes. First described in a pediatric case with viral trigger in 1979, the key features of this syndrome include rapid progression with high mortality and impaired immunity. Many different etiological triggers have been described since the initial case. The syndrome can have profound impacts on all body systems which is explored to some extent within this text. Several agents have been tried in the treatment of this condition, particularly with respect to sustained remission and mortality benefits overall. This review seeks to outline clinical presentation and prognostic factors of HLH as well as recent advances in clinical treatment. Trials are discussed from literature review outlining prognostic markers as well as a discussion of tried therapies, recent advances and emerging agents of interest. Significant progress has been made in recent years although this remains a very complex and challenging disease to treat and mortality also remains high.

Keywords: Hlh; Hemophagocytic; Lymphohistiocytosis; Review; Treatment; Developments

Introduction

Hemophagocytic Lymphohistiocytosis, also called the Hemophagocytic Syndrome (Here after referred to as HLH) is a cytokine release syndrome with a variety of triggers leading to an abnormal proliferation of activated lymphocytes and histiocytes. This results in uncontrolled inflammation in a variety of organ systems manifesting with various symptoms. This syndrome was first described by Risdall, et al in 1979 in a case with a viral etiology as the suspected trigger [1]. Hallmark clinical features include fever, cytopenias resulting in impaired immunity, with a typically rapid clinical progression tending towards high mortality rates [2]. This article is not meant as a comprehensive review of the topic but will seek to outline the clinical features and general prognostic factors of HLH and to bring a spotlight to recent advances in our understanding of this clinical syndrome and its treatment.

Background

As previously mentioned, this is a typically rapidly progressive syndrome with high mortality and thus earlier diagnosis and effective treatment is crucial towards improving survival. In the original study, 19 patients were reported with similar symptoms and a viral trigger suspected, the most common of which being the herpesviridae. Other studies have also been conducted citing infection as likely the most common trigger [2]. The signs and symptoms reported in this landmark study included fever and other constitutional symptoms, with peripheral cytopenia and other laboratory abnormalities particularly liver function including coagulation. Additionally, hepatosplenomegaly, lymphadenopathy and pulmonary infiltrates can be seen. Another common factor was immune dysfunction, particularly cell-mediated given the underlying process [1]. Many of these features were later factored into the HLH-94 and then the HLH-2004 diagnostic criteria that followed. A summarization of these criteria can be seen in Table 1 [4].

Some aspects of this diagnostic criteria have been called into question recently. A retrospective study performed last year following 1055 patients noted HLH was positively identified as the diagnosis in only 50% of these cases as the level approached 900 [6]. Another retrospective analysis by the same group was performed to assess the performance of the soluble interleukin-2 receptor (sIL-2r, CD25). This study included 132 adult patients of which 65 were within criteria for the diagnosis of secondary HLH. The non-HLH group were primarily diagnosed with hematologic malignancy, autoimmune disease and sepsis. When utilizing the standard range cutoff for this marker per the 2004 criteria sensitivity was decent but specificity was very low and as such in comparing the two groups HLH was weakly correlated [7].

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While the disease initially was seen primarily in the pediatric population, there has been growing focus on adult cases in recent years. It is possible the condition was simply underdiagnosed or was described as a different syndrome (e.g. the macrophage activation syndrome in chronic Rheumatoid Arthritis patients). The disease as mentioned is capable of manifesting in susceptible individuals as a result of almost any major insult. One author of this article previously worked with another research group and published a case series of 5 different adult patients with varying triggers to the illness. Two of these patients expired during their initial hospitalization. Three cases included different infectious triggers. One such case was thought to be triggered by Still's disease, and another which was initially suspected to be triggered by amoxicillin ended up having underlying acute lymphocytic leukemia which was masked by the HLH [5].

Clinical Trends & Prognostic Factors

There are multiple retrospective analyses of this syndrome including case series as noted above as well as retrospective analysis of larger cohorts of cases. One such analysis of 47 cases out of China was described in the literature. This study followed patients for a total of 4 years with average age of onset at 46 years of age and an almost 1:1 gender distribution with slightly larger numbers in the female cases. Mortality was analyzed as well as the heaviest contributing factors from the study which revealed hemorrhage, thrombocytopenia, and pleural effusion were amongst the highest mortality risk in these patients who developed such symptoms independently of other factors [1]. Also of note, the study concluded that infectious triggers were the most common, occurring in just over half the cohort. The only malignancies reported were leukemia and lymphoma, the least common two triggers of this study.

Prior to this, guidelines were developed by a group including one of the members of the HLH-2004 research group which sought to draw attention to malignancy as a trigger of HLH. Among their recommendations and consensus statements, full consensus was reached in declaring that malignancy can be either a primary trigger or the HLH can occur in the setting of immune suppression therapy. They also found that malignancy triggered HLH occurred most frequently in cases of Lymphoma, particularly Hodgkin's & DLBCL [3]. Likelihood of finding an underlying malignancy also increased with age and during chemotherapy was most likely the result of an infectious trigger. They also noted that in the event of HLH during treatment postponing further cycles would be of benefit unless their malignancy relapsed.

Other potential markers of prognosis continue to be explored for this clinical syndrome. This recently included a very interesting article regarding patients with thyroid dysfunction resulting in low T3 levels. They studies 111 patients with HLH, of which low T3 was found in 75% of their cohort. The patients were followed for 1 year. During median follow-up a 3-fold higher rate of mortality was observed in the low T3 group as opposed to the euthyroid group [8]. This is the only such study that was found in the literature for this review.

Advances in Treatment

This condition has had difficulties with undergoing proper clinical trials to optimize therapy owing to the low numbers of active cases and the high early mortality rates. As such, no clear guidelines for the treatment of HLH currently exist for adult patients. Various therapeutic options have been tried, mostly with anecdotal results. Corticosteroids have been utilized in this manner. However, there was a study in 2003 of young adults with HLH triggered by the Epstein-Barr virus (EBV) and treated with Etoposide. Those who received the treatment within 4 weeks of diagnosis had a good prognosis [9]. Etoposide has since become a mainstay in the treatment of HLH.

Table 1: The HLH-2004 Diagnostic Criteria.

Clinical /Pathologic Features of HLH	
Fever	
Splenomegaly	
Cytopenias in at least 2 cell lines	
Hemoglobin	<9
Platelets	<100
Neutrophils	<1.0
Ferritin Level	>500
Fibrinogen Level	<1.5
Elevated IL-2r/CD25	>2400U/mL
Reduced NK cell activity	
OR	
Demonstrable Hemophagocytosis of the Bone Marrow or other Tissues	

Several case reports of other agents have been reported in the literature as well. One such report published in 2008 evaluated the use of anti-CD25 antibody daclizumab in the treatment of HLH in one adult patient. He was initially treated with steroids and immunosuppression with cyclosporine as was routinely done with many such cases at the time including those in this first author's case series [8]. Unfortunately, cyclosporine was discontinued due to renal dysfunction and hyperkalemia. Daclizumab was instituted in the treatment of this patient with good response [10]. There were no newer cases reported in the literature with this agent encountered in our search at the time of this article's writing.

Scientific studies have attempted to further explain the triggering cascade of events in hopes of finding better targets for curative treatment. One interesting study observed the inhibitory receptors on cytotoxic lymphocytes including NK cells were upregulated in adult patients with HLH. Cytotoxic T-cells in particular were noted to express greater levels of PD-1 and lower secretions of gamma interferon for example [11]. This observation is logical to such a process of proliferating lymphocytes and the proinflammatory state.

One such agent most recently has made major impacts on refractory disease in particular. That agent is ruloxitinib, a janus kinase ½ inhibitor which has shown promise in mouse models and there are now several case reports in human patients. The first of these was published in 2017 and involved a pediatric case of an 11 year old boy. Although the drug has been in trial for adult patients there was no such report of efficacy in pediatrics. The boy had a rapid decline and within the first 24hrs of administration of ruloxitinib the patient stabilized [12]. Another case reported last year involved a 38 year old woman who developed secondary HLH along with a diffuse rash on her upper extremities. She was subsequently diagnosed with an EBV infection. Hemophagocytosis was observed on bone marrow aspiration. She was given conventional therapy of steroids and etoposide followed by a trial of rituximab with no significant response. She also incidentally developed *Candida krusei* pneumonia. As a final attempt, ruloxitinib was given in five doses and responses were appreciated in her laboratory values but unfortunately she did expire [13].

Positive outcomes have also been reported in cases over the

last 3 years as well. One such case of a 24 year old female patient was tried initially with conventional therapy similar to the previous patient in this article. Unfortunately she continued to deteriorate and there was concern that she has refractory disease. She was to receive the unproven agent alemtuzumab as a final salvage attempt but it was not immediately available to her physicians. Based on preliminary data in the literature they chose to initiate ruloxitinib alongside her steroids. Within 48hrs there was significant clinical improvement. Alemtuzumab was then added on later [14]. The same authors treated a second case of secondary HLH in a 26yo female patient with acute Hepatitis C and Epstein-Barr virus infection encephalopathy. She was treated with intrathecal methotrexate along with conventional therapy with improvement. Once therapy was stopped she declined further and was transferred to a transplant center. Ruloxitinib was started. The patient's symptoms quickly improved and she was stabilized without the need for HSCT [14]. Such results illustrate great promise in this novel therapeutic agent.

Conclusion

There has been significant progress in the understanding and management of this potentially deadly clinical syndrome over the years. This review has sought to bring focus on the most recent advances in both our scientific understanding and diagnostic approaches to secondary HLH in the adult population as well as highlight areas where study is needed. We also have explored the condition's varying treatment options particularly with respect to ruloxitinib. While much more work is needed this agent in particular appears to have great promise in the treatment of HLH. Current challenges remain classifying the major triggers of such disease and to ensure prompt recognition and treatment thereby promoting maximal opportunities for survival in our patients.

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