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Review Article

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome: Review of the Literature

Chiara Gioia*

Department of Clinical, Anaesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

ABSTRACT

HLH is a life-threatening condition characterized by the uncontrolled activation of cytotoxic T lymphocytes, NK cells, and macrophages, resulting in an overproduction of pro-inflammatory cytokines. A primary and a secondary form are distinguished. Clinical manifestations include fever, splenomegaly, neurological changes, coagulopathy, hepatic dysfunction, cytopenia, hypertriglyceridemia, hyperferritinemia, and hemophagocytosis. In adults, therapy, although aggressive, is often unsuccessful. We previously reported a case of HLH related to EBV-infection and hematologic malignancies in a Burkina Faso 41-year-old man, presented acute onset of fever, fatigue, and weight loss. EBV-DNA load of more than 90000 copies/mL was found. Bone marrow aspirate showed hemophagocytosis while biopsy revealed a marrow localization of peripheral T lymphoma. High doses of glucocorticoids were immediately administered but the course was rapidly progressive until the patient died. HLH is a rare but usually fatal complication in adults of hematologic, autoimmune, and malignant diseases. Very early diagnosis and treatment are critical but not always sufficient to save patients.

Keywords: Hemophagocytic lymphohistiocytosis; Macrophage activation syndrome; Cytokine storm; T lymphoma; EBV-infection

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS) are life-threatening systemic hyperinflammatory syndromes characterized by fever, cytopenia, elevated ferritin, hepatitis, disseminated intravascular coagulopathy, and central nervous system inflammation. These conditions are characterized by a high risk of progression to multiple organ failure, shock, and often have fatal outcomes. Over the years, especially since the COVID pandemic, this condition has been variously referred to as HLH, MAS, "Cytokine Storm Syndrome (CSS)", "hyperinflammation", "hyperferritinemic sepsis-induced multiorgan dysfunction", or "SARS-CoV-2 associated multisystem inflammatory syndrome in children or adults" [1].

LITERATURE REVIEW

We previously reported an illustrative case of HLH related to EBV-infection and hematologic malignancies. We described a case of a 41-year-old man, with no apparent history of previous disease and an acute onset characterized by fever, fatigue and weight loss. The man was from Burkina Faso and had made trips to his home country in the previous five months. On admission, leukopenia, thrombocytopenia, increased creatinine and transaminases, LDH, and CRP with a normal ESR were found. The patient also presented with hypertriglyceridemia and hyperferritinemia. An infectious or autoimmune aetiology was ruled out. A total body CT scan showed bilateral pleural effusion and hilar mesenterial, abdominal, and paratracheal lymphadenopathy. Lymphoproliferative disease with HLH complication was therefore suspected. High doses of glucocorticoids were then administered. A cytologic analysis of the pleural effusion showed anaplastic lymphoma cells and bone marrow aspirate showed hemophagocytosis. An Epstein–Barr Virus (EBV) DNA load of more than 90000 copies/mL was found. Bone marrow biopsy showed a marrow localization of peripheral T lymphoma. The course was rapidly progressive until the patient died [2].

Correspondence to: Chiara Gioia, Department of Clinical, Anaesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy; Email: chiara.gioia@uniroma1.it

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HLH is characterized by the persistent activation of cytotoxic T lymphocytes and Natural Killer (NK) cells. The uncontrolled immune response is responsible for the production of pro-inflammatory cytokines and subsequent activation of macrophages, resulting in systemic inflammation. Hyperferritinemia is generally exploited as a biomarker, especially for the early identification of patients with a severe form of the disease. HLH is usually classified into primary or familial and secondary or reactive. Familial HLH (F-HLH) is typical in children and is caused by the presence of several genetic defects characterized by mutations or genetic variants that modulate cytolytic functions, lymphocyte survival, and inflammasome activation. Secondary or acquired HLH, which accounts for about 40 percent of total HLH cases, can result from the presence of neoplastic, infectious, or autoimmune disease. When HLH occurs in the context of a rheumatologic disease, it is often referred to MAS [3]. Clinically, HLH presents with fever, cytopenia, lymphadenopathy, hepatomegaly and splenomegaly, hepatic dysfunction, coagulopathy, hypertriglyceridemia, neurological dysfunction, and multiorgan failure. Laboratory data commonly consist of increased acute-phase reactants. However, both clinical manifestations and data obtained from laboratory investigations are often nonspecific. Therefore, diagnosis is a challenge for the physician. In the presence of elevated ferritin levels, the rapid exclusion of various possible causes, including hematologic, infectious, and hepatic diseases, is essential. The rapid recognition of secondary HLH is critical to start treatment as quickly as possible. A hallmark of HLH is the presence of hemophagocytosis in the bone marrow and lymphatic system. Diagnostic scoring systems such as HScore and HLH-2004 criteria are commonly used for diagnosis [4]. Treatment is directed at reducing the immune response with immunosuppressive or myelosuppressive therapies, which can sometimes even complicate the condition of patients with multiorgan failure at the time of diagnosis. In addition, the search for possible triggers and their appropriate management is crucial.

A literature review was conducted: Publications (reviews, original articles and case report series) from the period 2004-2024 were analysed. Research parameters were: “HLH”, “MAS”, “CSS” and “T lymphoma”.

DISCUSSION

HLH and MAS are life-threatening systemic hyperinflammatory syndromes characterized by fever, cytopenia, elevated ferritin, hepatitis, disseminated intravascular coagulopathy, and central nervous system inflammation. The pathophysiology of HLH is related to the inability of NK cells and CD8+ T cells to eliminate activated Antigen Presenting Cells (APC), due to the lack of perforin-dependent granule-mediated cytotoxicity. This leads to the prolonged activation of NK cells, CD8+ T cells, and macrophages, resulting in excessive cytokine secretion or “cytokine storm”. CSS embodies a broad spectrum of similar but not identical systemic hyperinflammatory states characterized by elevated levels of circulating cytokines and the hyperactivation of immune cells. These can be triggered by pathogens, including SARS-CoV-2, neoplastic diseases, and autoimmune and autoinflammatory conditions.

In 2022, the European Alliance of Association for Rheumatology (EULAR) defined systemic hyperinflammation as a state of excessive immune activation that could lead to HLH/MAS. In addition, three categories of factors contributing to the development of HLH/MAS have been defined: Genetic causes, predisposing conditions, and triggering factors such as infections and immunotherapy [5].

According to current knowledge, the first step in the pathogenesis of MAS would be a defect in the cytolytic activity of lymphocytes. Normally, cytotoxic cells are able to cause the apoptosis of hyperactivated cells, including macrophages and activated T cells. Such cells could then control the extent of the inflammatory response. A defect in this function may result in the overstimulation of the immune system, leading to multi-organ failure such as that observed in HLH. In addition, pro-inflammatory cytokines in the microenvironment, particularly Interleukin (IL)-6, have been shown to reduce the cytolytic function of NK cells. The inability of NK cells and CD8+ T lymphocytes to lyse activated APCs induces the amplification of the downstream pro-inflammatory cytokine cascade. The “cytokine storm” in turn causes macrophage activation, contributing to multiorgan dysfunction. Several cytokines, including Tumour Necrosis Factor (TNF), Interferon (IFN)-γ and numerous interleukins such as IL-1, IL-6, IL-18 have been implicated in this process. In addition, genetic mutations in cytolytic pathway genes associated with *fHLH*, such as *PRF1* and *UNC13D*, have been identified in a large subgroup of patients with MAS. These are responsible for defects in the synthesis of proteins responsible for the production and transport of cytotoxic granules, leading to the apoptosis of target cells. The role of macrophages in MAS has been widely recognized as these cells may be responsible for hemophagocytosis. On the other hand, macrophages also play a critical role in the regulation of the excessive immune response due to their functional plasticity in response to various stimuli in the inflammatory microenvironment. Hemophagocytosis occurs in more advanced stages and is found in approximately 60% of biopsies of patients with HLH/MAS. It has been shown that during disease progression, macrophages can switch from a pro to an anti-inflammatory phenotype, thus attempting to suppress the extremely hyperactive inflammatory state in patients with fulminant disease [6].

Because HLH is a hyperinflammatory syndrome, increased serum ferritin levels can be exploited as a very useful diagnostic marker, and hyperferritinemia is included among the clinical diagnostic criteria for HLH. Nevertheless, it has been found that HLH is not diagnosed in most critically ill adult patients [7], also because of the high degree of difficulty in interpreting elevated ferritin levels. However, three causes explain more than two thirds of cases of hyperferritinemia ≥ 5000 μg/L, such as infectious diseases, HLH and acute hepatitis. In adult critically ill patients without HLH, sepsis/septic shock, liver disease and hematologic neoplasms are thus the main factors associated with hyperferritinemia. Hyperferritinemia in liver disease may result from damaged liver cells, particularly hepatocytes, which contain

high amounts of iron and synthesize ferritin. Hyperferritinemia in sepsis is related to a pro-inflammatory state, with increases in IL-6, IL-18, IFNγ, and sCD163, a decrease in the IL-10/TNFα ratio, and the production of elevated levels of Reactive Oxygen Species (ROS), leading to the expression of ferritin as an antioxidative stress response and as an acute-phase reactant. Among hematologic diseases, T/NK cell lymphomas are characterized by the highest serum ferritin levels. Importantly, ferritin values generally correlate with the level of inflammation in neoplastic diseases and proliferation rates in T/NK cell lymphomas. Based on these considerations, HLH-2004 criteria should be applied in hyperferritemic patients to exclude HLH, especially in the context of liver disease, hematologic neoplasms, sepsis/septic shock. On the other hand, hematologic neoplasms may not only be the cause of hyperferritinemia but also the trigger in patients with HLH. The HLH-2004 diagnostic criteria have been shown to differentiate between HLH and non-HLH as causes of hyperferritinemia in critically ill adult patients with good sensitivity and specificity.

Neoplasm-associated HLH (M-HLH) is a rare type of HLH described in about 1% of adults with hematologic malignancies and characterizes 40–70% of all HLH cases in adults. M-HLH is most commonly found in association with lymphomas, mainly T-cell lymphomas, followed by diffuse large B-cell lymphoma and Hodgkin's lymphoma. Probably, in the case of lymphomas, the cytokine storm is related to persistent antigen stimulation and the hypersecretion of proinflammatory cytokines by neoplastic cells. The diagnosis of M-HLH can be challenging because many of the markers listed in the HLH-04 criteria (e.g., fever, splenomegaly, cytopenia, hemophagocytosis) may be abnormal in patients with hematologic malignancies. The prognosis of refractory M-HLH is inauspicious, and treatment options are mostly borrowed from studies of non-malignant HLH. Ruxolitinib, a Janus Kinase 1/2 (JAK1/2) inhibitor, has been shown to be effective in some forms of secondary HLH both as monotherapy and in combination with doxorubicin, etoposide and dexamethasone. In cases of refractory M-HLH that can achieve partial or complete response, allogeneic HSCT is strongly recommended [8]. Peripheral T-Cell Lymphoma (PTCL) is a rare disease, categorised in 2016 by the WHO as primary EBV-positive T-cell and NK-cell nodal lymphoma. This form of lymphoma occurs most commonly in elderly and/or immunodeficient patients. It lacks nasal involvement and is more often T-line rather than NK-line. Epidemiologically, a male predominance has been described and some cases may be associated with autoimmune diseases and/or immunosuppressive treatment. The median overall survival of EBV+ nodal disease is 2.5–8.0 months, significantly lower than that of NKTL (26–50 months) or PTCL (16–20 months) [9].

The treatment of patients with suspected HLH/MAS requires a careful evaluation of the risk–benefit ratio. Intensive care unit admission is necessary in about half of adults with HLH/MAS, requiring mechanical ventilation, vasopressor/inotropic therapy, and renal replacement therapy [10,11]. Because immuno-modulatory treatment has dramatically improved survival in most patients with HLH/MAS with features at a high risk of progression, empiric immunomodulation in the early stages, such as the use of Glucocorticoids (GCs), the recombinant IL-1 receptor antagonist (IL-1RA) anakinra, and/or the administration of Intravenous Immunoglobulin (IVIg), is strongly recommended. Regarding GC therapy, "pulsed" doses of intra-venous methylprednisolone are effective in forms associated with severe rheumatic and neuroinflammatory diseases, while dexamethasone is used because of its good penetration into the central nervous system. Anakinra appears to be a generally safe and effective treatment for many autoinflammatory and rheumatic disorders and, because of its rapid onset and short half-life, is preferred in rapidly evolving patients. B-cell depletion may be useful in some patients with EBV-HLH. The early initiation of chemotherapy-based treatment regimens with etoposide has been shown to be lifesaving for patients with primary HLH and severe EBV-HLH but not indicated for most non-EBV infections while its efficacy in neoplasm-associated HLH is currently unclear [12]. For patients with increased inflammation and/or worsening organ damage despite early immunomodulation, the escalation of treatment with higher doses of GC and/or alternative agents such as cyclosporine, rituximab, ruxolitinb, and emapalumab should be considered. Increasing evidence supports the involvement of the IFN γ pathway in HLH/MAS. To this end, ongoing clinical trials to test the safety and efficacy of agents such as ruxolitinib (NCT04551131), alemtuzumab (NCT02472054), tadekinig alfa (NCT03113760), emapalumab (NCT05001737), and MAS825 (NCT04641442) in different HLH/MAS settings are crucial.

CONCLUSION

HLH and MAS are life-threatening systemic hyperinflammatory syndromes with a high risk of progression to multiple organ failure, shock, and often death. Elevated serum ferritin levels are an important diagnostic and prognostic index. Very early diagnosis with the underlying cause and the timely initiation of immunosuppressive therapy is essential.

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