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REVIEW

Hemophagocytic lymphohistiocytosis and primary immune deficiency disorders

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is characterized by uncontrolled immune activation and is traditionally associated with inherited gene defects or acquired causes. In addition to abnormalities in cytotoxic granules and lysosomes, various primary immune deficiency disorders (PID) have been identified among patients suffering from HLH. Our purpose was twofold: to better characterize and detail the association between PID and HLH.

We found that HLH occurs infrequently among patients with PID, particularly those suffering from abnormalities that impair T cell function. The prognosis of patients suffering from PID and HLH is poor, emphasizing the need for rapid clinical and genetic diagnosis of the PID as well as initiation of appropriate management of the HLH, including allogeneic hematopoietic stem cell transplantations.

The association of HLH and PID implicates abnormal T cell function as an important factor in HLH development. It also suggests that the partition of HLH into genetic versus acquired forms might be misleading.

Abbreviations: BTK, Bruton tyrosine kinase; CGD, chronic granulomatous disease; CMC, chronic mucocutaneous candidiasis; γc, γ-common; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; ITK, IL2-inducible T cell kinase; NK, natural killer; PID, primary immune deficiency disorders; PNP, purine nucleoside phosphorylase; SAP, signaling lymphocyte activation molecule (SLAM)-associated protein; SCID, severe combined immunodeficiency; WAS, Wiskott–Aldrich syndrome; XIAP, X-linked inhibitor of apoptosis protein; XLA, X-linked agammaglobulinemia; XLP, X-linked lymphoproliferative syndrome

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1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life threatening disorder characterized by uncontrolled immune activation, particularly of macrophages, as well as overproduction of cytokines such as interferon-γ, IL-6 and IL-10 [1,2]. These cytokines contribute to the typical clinical and laboratory features commonly observed among patients including prolonged fever, hematological cytopenias, liver failure, seizures and abnormal natural killer (NK) cell function (Table 1). Additional laboratory tests, including soluble CD25, and CD168 as well as the surface expression of CD107 on NK and cytotoxic T cells (marker of granule-mediated cytotoxicity integrity) can assist in rapidly diagnosing some patients with HLH [3]. Traditionally, affected patients have been categorized as suffering from a genetic (also known as the familial/primary) form or an acquired (also known as the secondary) form [4,5]. Patients in the genetic form have an identifiable genetic defect and often, albeit not invariably, present at young age or have additional affected family members. In contrast, among patients in the acquired form there are often precipitating factors such as infections, autoimmunity diseases, malignancies, metabolic abnormalities or immune modulating medications, but no known affected family members or inherited defects in susceptibility genes [6]. Establishing the diagnosis of HLH and assigning the patient to the correct group has significant management implications. Treating the precipitating factors and suppressing the exaggerated immune activation can help many patients with the acquired form of HLH, while urgent allogeneic hematopoietic stem cell transplantation (HSCT) is often indicated for those suffering from the genetic form [7,8].

Since the seminal description of mutations in the PERFORIN as a cause for the familial form of HLH [9], defects in additional molecules important for cytotoxic granules and lysosomes have been identified among patients with genetic HLH. These discoveries have emphasized the role of NK cells in the development of HLH. In recent years, there have also been reports of patients suffering from HLH who had a variety of primary immune deficiency disorders (PID), particularly T cell deficiencies; however a comprehensive review of this association is lacking. We used the terms hemophagocytic, lymphohistiocytosis, HLH, macrophage activating syndrome, MAS, immune deficiency, primary, T cells, B cells, individually and in combination to probe the English medical literature (PubMed and Google Scholar) for the all descriptions of HLH among patients with PID. We found that HLH is reported infrequently among patients with PID, particularly those suffering from abnormal T cells (Table 2). This association implicates abnormal T cell function as an important factor in the development of HLH. It also suggests that the partition of HLH into genetic versus acquired forms might be misleading as patients with presumably acquired HLH might be suffering from PID and thus require a different management approach.

Table 1 HLH diagnostic guidelines.

Clinical criteria
1. Fever (>38.5 °C)
2. Splenomegaly
Laboratory criteria
3. Cytopenia (affecting >2 of 3 lineages in peripheral blood)
4. Hypertriglyceridemia (fasting > 265 mg/dL) or hypofibrinogenemia (<150 mg/dL).
5. Low or absent NK cells activity
6. Hyperferritinemia (>500 μg/L)
7. Increased levels of sCD25 (>2400 U/mL)
Histopathological criteria
8. Hemophagocytosis in the bone marrow, spleen or lymph nodes with no evidence of malignancy

The diagnosis HLH can be established if: 1. Five out of the eight criteria are fulfilled, or 2. A molecular defect consistent with HLH is demonstrated.

2. Primary immune deficiency disorders associated with HLH

2.1. Isolated granule-mediated cytotoxic dysfunction of T cells and NK cells

Identification of mutations in the PERFORIN gene among patients with the genetic form of HLH (familial HLH type 2) significantly advanced the understanding of the pathogenesis of this condition [9]. Patients' lymphocytes demonstrate defective cytotoxic activity, thereby emphasizing the crucial role of granule mediated cytotoxicity of NK and T cells in down-regulating the immune response.