Hemophagocytic Lymphohistiocytosis: an update to diagnosis and management

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Hemophagocytosis may accompany many conditions such as infections, malignancies and metabolic disorders, however hemophagocytic lymphohistiocytosis (HLH) is the clinical syndrome of an overstimulated but ineffective immune response associated with hypercytokinemia [1]. Killing of the infected cells or cancer cells are achieved with the help of the cytotoxic T lymphocytes and natural killer (NK) cells in a normal functioning immune system. There are secretory lysosomes inside these cytotoxic T lymphocytes and NK cells which contain perforin and granzymes. Perforin is a tetrameric protein which can produce pores on the lipid bilayer of the membrane of the target cell, whereas granzymes are serine proteases which trigger apoptosis of the target cell by initiation of caspase cascade after taken inside throughout the pores produced by the aid of perforins [2,3]. In patients with HLH, there occurs a defect in killing of the pathogens or cancer cells due to an underlying inherited defect in cytotoxicity in genetic forms of the disease, ending up with not only inability to kill the target cell, but also a hypercytokinemia and activation of macrophages. Histopathological evaluation reveals tissue infiltration by macrophages, hemophagocytosis and lymphohistiocytic infiltration. Moreover, serum cytokines such as IFN-γ, IL-6, IL-10, IL-12, IL-6 and TNF-α are highly elevated in addition to markers of immune activation such as soluble CD8, CD25 and CD163 [3,4].

Classification

Hemophagocytic lymphohistiocytosis is classified into two major groups as genetic (primary) and acquired (secondary):

1. Genetic (primary) HLH

This group includes the autosomal recessive, familial HLH cases, in addition to HLH associated to immune deficiency syndromes such as Griscelli syndrome, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome and X-linked lymphoproliferative syndrome [4,5]. Familial HLH is a rare disease and the incidence in Sweden has been reported to be 1 in 50,000 births [5]; however the disease is higher in countries with higher rates of consanguineous marriages and higher birth rates, such as Turkey.

Familial HLH cases are diagnosed before one year of age in 70-80% of the cases [6,7]; however there are occasional patients who have been reported to have onset of manifestations as late as adolescence or event during adulthood [8,9]. The molecular spectrum of genetic causes of HLH are summarized in Table 1. The genes involved in familial HLH (FHL) forms are responsible from the cytotoxic granule exocytosis and function. The molecular defects of patients with HLH associated with primary immune-deficiencies are also related to granule exocytosis pathways, explaining the bleeding tendency, albinism and immune deficiency state of these patients related to granule exocytosis defects.
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2. Acquired (secondary) HLH

Acquired forms of HLH are more common than genetic forms. Secondary HLH has been initially described related to viral infections following organ transplantations and was formerly described as virus-associated HLH [10]; however in latter times bacterial, fungal and protozoal agents have been shown to be causative pathogens, as well. Among the common infections causing secondary HLH, Epstein-Barr virus (EBV), cytomegalovirus (CMV), Leishmania, influenza viruses are the prominent causatives [1,3,5]. Sepsis/systemic inflammatory response syndrome (SIRS) share many common clinical findings and HLH may accompany severe sepsis cases in which the control of the infectious trigger is not easily achieved. In addition to infection-associated HLH, HLH may develop secondary to malig
nancies, autoinflammatory/autoimmune diseases and metabolic disorders [5,12-16]. Sepsis/systemic juvenile idiopathic arthritis, systemic lupus erythematosus, Kawasaki disease and this type of secondary HLH developing due to an underlying autoinflammatory/autoimmune disease is usually termed as macrophage activation syndrome (MAS). Macrophage activation syndrome usually develops during the early or active phase of these disorders.

Clinical symptoms, laboratory findings and diagnostic criteria

Histiocyte Society proposed a guideline, namely HLH-2004 criteria, for diagnosis of patients with primary and secondary HLH (Table 2) [18]. If a patient has a known molecular defect, the diagnosis of primary HLH is established. However, for patients without a known positive molecular defect, the diagnosis of either primary or secondary HLH could be established with the presence of at least five of the eight diagnostic criteria, including fever, bi- or pancytopenia, splenomegaly, hypertriglyceridemia or hypolipoproteinemia, hyperferritinemia, elevated sCD25 (sIL-2 receptor), low NK cell activity and occasional hemophagocytosis might be seen in biopsy samples obtained from bone marrow (Figure 1) [19]. The genetic diversity in familial HLH is examined in Table 3, and the other possible and common laboratory findings are listed in Table 4.

Table 1. The molecular spectrum of genetic causes of HLH

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHL1</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>FHL2</td>
<td>PRF1</td>
<td>9q21.3-q22</td>
<td>Perforin</td>
</tr>
<tr>
<td>FHL3</td>
<td>UNC13D</td>
<td>17q21.3</td>
<td>Munc13-4</td>
</tr>
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<td>STX11</td>
<td>6q24</td>
<td>Syntaxin11</td>
</tr>
<tr>
<td>FHL5</td>
<td>STXBP2</td>
<td>19p13</td>
<td>Munc18-2</td>
</tr>
<tr>
<td>GSD2</td>
<td>RAB27A</td>
<td>15q21</td>
<td>RAB27A</td>
</tr>
<tr>
<td>CHS</td>
<td>LYST</td>
<td>1q21-q22</td>
<td>LYST</td>
</tr>
<tr>
<td>HPS2</td>
<td>A002B3</td>
<td>5q14.1</td>
<td>AP-3</td>
</tr>
<tr>
<td>XLP-1</td>
<td>SIGD1A</td>
<td>9q25</td>
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</tr>
<tr>
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<td>XIA1</td>
<td>9q25</td>
<td>XIA</td>
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</tbody>
</table>
STX11 gene has 2 exons [3]. Although, initially hepatocytes are reported solely among patients of Turkish/Kurdish ethnicity, there are reports from other populations [3]. STX11 encodes a SNARE protein syntaxin, which is important in intracellular vesicular trafficking [29].

A more recently defined gene responsible in the development of familial HLH cases is STXBP2 and was found to be responsible from 20% of familial cases [30]. Patients with STXBP2 gene mutations may have some additional findings such as gastrointestinal symptoms, including chronic diarrhea, gastrointestinal reflux in addition to bleeding diathesis [3,30].

Genetic remarks in some of the secondary HLH cases

It is of interest why some of the patients with an underlying metabolic disease develop secondary HLH, whereas others do not. It has been previously reported that carrying a heterozygous A91V mutation of PRF1 gene has been reported to be 2.8 times more common among patients with secondary HLH compared to healthy controls [31]. In familial HLH, there are reports of macrophage activation syndrome recurrence among patients with rheumatological disorders who are carriers for HLH mutations [32,33].

Primary HLH disease is characterized by high mortality rates unless hematopoetic stem cell transplantation (HSCT) has been established. However, the patients who have no suitable donor are treated with HLH-2004 protocol, which includes etoposide, dexamestethone, cyclosporine A. The patients with CNS involvement receive intrathecal methotrexate. The results of HLH-2004 protocol have not been published yet and the patient recruitment has finished [5]. However, the results of the previous study protocol, namely HLH-94 has been reported to have a 5-year survival rate of 54% [34]. The HLH-94 and HLH-2004 protocols differ in terms of the presence of cyclosporine A in the first 8 weeks of HLH-2004 protocol. The patients who have a donor for HSCT have been reported to have better transplant outcomes if they were transplanted after achievement of remission in disease activation criteria after initiation of HLH-94 [34]. There is one report from a single-center that reported 55% survival with treatment against anti-thymocyte globulin (ATG) and methylprednisolone with subsequent HSCT [35]. Patients who are refractory to standard treatment of either HLH-94 or HLH-2004 have been reported to be treated with alemtuzumab (anti-CD52) prior to HSCT with 64% partial response, 77% survival until HSCT [36]. The ultimate curative treatment is HSCT in patients with familial HLH. This type of treatment is donor-dependent. The survival rates after HSCT have been reported as 53-71% with myeloablative conditioning regimens including busulfan, cyclophosphamide, etoposide and ATG [5,37-39].

Secondary HLH

The association of HLH to an infection increases the mortality significantly and usually it is mandatory to control hyperinflammation concomitant to the treatment of the triggering infection. Among triggers of HLH, the worst prognosis is seen among the EBV related HLH group. In a series of 78 patients with EBV related HLH from Japan survival rate has been reported as 75% for 45 months of follow-up. During treatment of these patients 85% required addition of etoposide [40]. Addition of aciclovir to treatment of EBV related HLH usually has no additional impact. In EBV related HLH, the patients who received no etoposide within 4 weeks of diagnosis of HLH have been reported to have 14 times more mortality rate compared to those who have received etoposide [41]. In a recent study, addition of rituximab (anti-CD20) to standard treatment has been reported to induce decrease in EBV viral load and serum ferritin levels in all half of the patients with EBV related HLH [42]. However, in patients with EBV related HLH, it is not uncommon for EBV to infect T cells, as well in contrast to classical EBV infection which has propensity to infect specifically B cells [43], which might be the situation in refractory patients.

Leishmania donovani may also trigger HLH in addition to mimicking HLH with the presentation of fever, splenomegaly and cytopenias. Administration of liposomal amphotericin B is the treatment of choice [44].

In patients with HLH accompanying sepsis, the standard treatment approach is antibiotics and supportive treatment; however a course of corticosteroids and/or intravenous immunoglobulin may be suggested to control the hyperinflammation and hypercytokinemia in patients who do not improve with antibiotics and supportive measures and prog- ress to organ failures. However, cytotoxic treatment with etoposide may not be beneficial an de may have deleterious effects on the already impaired immunity in patients with HLH.

Patients with MAS may be treated with pulse corticosteroid treatment with or without the addition of cyclosporine A [5]. Plasma exchange may be used in patients who do not respond to standard treatments of primary or secondary HLH [45].

In patients with an underlying metabolic disease that triggered HLH, the correction of the metabolic defect is usually adequate to control HLH mani- festations [46].

Patients who were initiated HLH-94 or HLH-2004 treatment protocols when a differentiation of primary or secondary HLH could not be established, are usually suggested to have cessation at 8th week of treatment protocol, if the HLH diagnostic criteria have remitted. On the other hand, patients with primary HLH should continue HLH-94 or HLH-2004 protocols up to HSCT. Patients who were initiated these protocols with a diagnosis of secondary HLH may cease treatment whenever the diagnostic criteria remits. Patients whose primary or secondary HLH discrimination could not be done with absolute clarity are suggested to have cessation of treatment at 8th weeks if the disease activity criteria have remitted. During the follow-up of these patients, if relapse of HLH occurs after cessation of HLH specific treatment, pa- tients are usually considered as primary HLH and treated accordingly [1,5,6].

In conclusion, although the diagnostic criteria of HLH are well established, it is sometimes challenging to differ between primary and secondary HLH cases. Additionally, both conditions have high mor- tality rates.
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Turker M, Guler E, Ertem M, Albayrak M, Patiroglu T, Cetica V, Pende D, Griffiths GM, Aricò M.


