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Rare disease

Familial haemophagocytic lymphohistiocytosis: two case reports

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Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a life threatening inflammatory syndrome, which presents a highly stimulated but ineffective immune response with severe hypercytokinaemia. HLH, primary or secondary, is characterised by prolonged fever and hepatosplenomegaly associated with pancytopenia, hypertriglyceridaemia and hypofibrinogenaemia. However, the hallmark of HLH is impaired or absent function of natural killer cells and cytotoxic T lymphocytes. HLH presents major diagnostic difficulties, since it may have an incomplete and/or late onset and with many conditions leading to the same clinical picture. When untreated, it is fatal in all primary cases and in a high percentage of acquired cases. Awareness of the clinical picture and diagnostic criteria is thus important to start life saving treatment. We describe two cases of primary HLH, with significant differences in their clinical presentation and evolution.

Background

Haemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory condition, with uncontrolled proliferation of activated lymphocytes and histiocytes secreting high amounts of inflammatory cytokines. However, this is an ineffective immune response, since there is an impaired function of lymphocytes.[1] HLH occurs in association with a variety of conditions (genetic or acquired) leading to the same inflammatory phenotype. Whether primary or secondary, it is characterised by prolonged fever and hepatosplenomegaly associated with pancytopenia, hypertriglyceridaemia and hypofibrinogenaemia.[2] Increased concentrations of cytokines and impaired or absent function of natural killer cells (NK) and cytotoxic T lymphocytes are biological markers of HLH.

The non-specific signs and symptoms, with multiorgan involvement and sometimes with an incomplete and/or late onset, make HLH a disease with major diagnostic and therapeutic difficulties. Diagnostic and therapeutic guidelines, based on common clinical, laboratory and histopathological findings, were presented by the HLH Study Group of the Histiocyte Society (revised in 2004). Altogether five of the eight criteria (fever, splenomegaly, cytopenias, hypertriglyceridaemia and/or hypofibrinogenaemia, haemophagocytosis, low/absent NK-activity, hyperferritinaemia and high concentrations of sIL-2r) must be fulfilled, although patients with a molecular diagnosis consistent with HLH do not need to fulfil the criteria.[3] HLH is a life threatening disease, and without effective treatment and supportive care, patients usually have a rapidly lethal course. Immunotherapy based treatment can achieve remission; however, haematopoietic stem cell transplantation (HSCT) has been established as the only curative therapy for primary HLH.[1] This highlights the importance of early diagnosis, with awareness of the clinical symptoms and diagnostic criteria.

Case presentation

Case 1

A 17-month-old girl, with no significant personal or familial medical history (non-consanguineous parents), presented to the emergency department with a 7 day low grade fever without accompanying

symptoms. The clinical and laboratory evaluation revealed hepatosplenomegaly and severe bicytopenia (anaemia and thrombocytopenia), which rapidly (day 10) evolved to pancytopenia with various episodes of febrile neutropenia. On day 39, the first severe episode of autoimmune haemolysis occurred, associated with hypovolaemic shock, splenic enlargement and acute respiratory distress syndrome (ARDS). On day 44, five criteria (fever, organomegaly, cytopenia, hypofibrinogenaemia and high ferritin concentrations) for HLH were finally present, leading to the HLH-2004 diagnostic and therapeutic approach.

Case 2

An 8-month-old girl, with no significant personal or familial medical history (non-consanguineous parents), presented to the emergency department with a 2 week low grade fever without accompanying symptoms. The clinical and laboratory evaluation revealed hepatosplenomegaly, severe pancytopenia, hypofibrinogenaemia and hypertriglyceridaemia. After admission, protocol for febrile neutropenia and transfusion support were started. On day 16, five criteria (fever, splenomegaly, cytopenia, hypofibrinogenaemia/hypertriglyceridaemia and high ferritin concentrations) for HLH were fulfilled, leading to the HLH-2004 diagnostic and therapeutic approach.

Investigations

Case 1

PCR for herpesvirus 6 was positive, but there was no serological confirmation of acute infection (IgM negative, IgG positive). Other viral and bacterial infections (Epstein–Barr virus (EBV), cytomegalovirus (CMV), parvovirus B19; herpes simplex virus I/II; HIV 1/2; adenovirus, enterovirus and leishmania) were excluded either by serology or polymerase chain reaction (PCR).

The first (day 10) histologic evaluation for neoplastic disease revealed: myelogram with normal morphology, cytogenetic and immunophenotypic analysis and myelofibrosis on bone marrow biopsy, and four of eight criteria for HLH. Repeated evaluation (day 44) confirmed the diagnosis with five of eight criteria: fever, splenomegaly, cytopenia (haemoglobin 2.4 g/dl, platelets 8000/μl, neutrophil count 300/mm^3); hypofibrinogenaemia (100 mg/dl); hypertriglyceridaemia (fasting triglycerides 408 mg/dl) and elevated ferritin (2720 ng/ml). Direct Coombs test was strongly positive. Bone marrow biopsy and myelogram were repeated (day 45), both showing haemophagocytosis but without myelofibrosis. Cerebrospinal fluid analysis was normal. Further study for primary HLH revealed: elevated sCD25 (31.944 U/ml), abnormal natural killer (NK) cell cytotoxicity (<10 lytic units), with normal degranulation of these cells. Genetic analysis for *PRF1*, *MUNC-13D* and *STX-11* mutations were negative (Karolinska Hospital, Stockholm).

Case 2

DNA from parvovirus B19 was found in the bone marrow aspirates through PCR; however, there was no serological confirmation of acute infection (IgM negative, IgG positive). Other viral and bacterial infections (EBV, CMV, herpes simplex virus 6, HIV 1/2, adenovirus, enterovirus, leishmania and *Mycobacterium tuberculosis*) were excluded either by serology, PCR or cultural assays. Initial (day 2) bone marrow (myelogram and bone biopsy) analysis excluded malignancy. On day 16, laboratory evaluation confirmed the diagnosis, revealing five of eight criteria for HLH: fever, splenomegaly, cytopenia (haemoglobin 8.4 g/dl, platelets 6000/μl, neutrophil count 100/mm^3), hypofibrinogenaemia (136 mg/dl), hypertriglyceridaemia (fasting triglycerides 355 mg/dl) and elevated ferritin (2683 ng/ml). Repeated (day 10) bone marrow biopsy and myelogram showed rare haemophagocytosis. Cerebrospinal fluid analysis was normal. Further study for primary HLH revealed: elevated sCD25 (>20 000 U/ml), abnormal NK cell cytotoxicity and degranulation. Genetic analysis revealed double heterozygosity for c-Munc 13-4 17p25.1: Nonsense mutation exon 23, C.2212C>T, causing a premature stop codon, and splicing site mutation (exon/intron 5) C.388 + 5G>A, causing mRNA framing shift. This last mutation was not previously described and subsequent studies are being performed (Karolinska Hospital, Stockholm).

Differential diagnosis

Infections, rheumatologic disorders or malignancy were excluded on both cases.

Treatment

Case 1

Due to febrile neutropenia, various courses of broad spectrum antibiotics and antifungal treatment were implemented. Following acute haemolysis with hypovolaemic shock and ARDS, therapy with immunoglobulin, corticosteroids and mechanical ventilation was necessary. On day 44, immunosuppressive therapy was initiated according to the HLH2004 protocol. Due to reactivation of HLH (third week), intensification therapy was instituted. On the 22nd week of specific therapy, haematopoietic stem cell transplantation from an HLA identical donor (brother, after normal functional study) with co-infusion of mesenchymatous cells was done. Preparation regimen for HSCT was done with busulfan and cyclophosphamide, and graft-versus-host disease (GVHD) prophylaxis with ciclosporin and methotrexate (Portuguese Institute of Oncology, Lisbon).

Case 2

Due to febrile neutropenia, broad spectrum antibiotics and antifungal treatment were implemented. Transfusion support and granulocyte colony stimulating factor (G-CSF) were started. On day 17, immunosuppressive therapy was initiated according to the HLH-2004 protocol. At the end of initial therapy (8 weeks), clinical remission was achieved. During the sixth week of continuation therapy (daily ciclosporin, weekly alternating dexamethasone and etoposide cycles) laboratory remission was obtained: normal blood cell counts (haemoglobin 10.2 g/dl, platelets 376 000/μl, neutrophil count 3000/mm^3), fibrinogen (387 mg/dl); fasting triglycerides (248 mg/dl), and ferritin (265 ng/ml). Haematopoietic stem cell transplantation was not yet performed, although an HLA identical donor was recently found.

Outcome and follow-up

Case 1

Ten days following HSCT, FISH XY on blood smear revealed 96% donor cells. Presently, 18 months after HSCT, clinical and laboratory remission persists.

Case 2

Currently, after 18 weeks of continuation therapy, with clinical and laboratory criteria of total remission, the patient is undergoing the preparation regimen for HSCT from a non-related donor (9/10 histocompatibility) with co-infusion of mesenchymal cells from the father (Portuguese Institute of Oncology, Lisbon).

Discussion

The description of these two cases, with different clinical and therapeutic outcomes, intends to reinforce the concept of HLH as an important diagnostic consideration in cases of fever of unknown origin[4] as well as a possible cause of multiorgan failure syndrome,[5] as it has been recently described.

Familial haemophagocytic lymphohistiocytosis (FHLH) is a group of genetically determined diseases, with an estimated incidence of 1:50 000 live births.[6] Most cases (85%) occur within the first year of age, with 70% occurring before 6 months; however, late onset cases have also been described.[1]

As an autosomal recessive disease, it is more frequent in ethnic groups where consanguineous marriages are common,[2] but despite its name, family history is often negative. Both our cases occurred in early infancy (the first after the first year) and in non-consanguineous families, with no past positive medical history.

Currently, there are four known forms of FHLH, three with causative genetic defects identified: mutations in the genes encoding for perforin (*PRF1*), *MUNC13-4*, and syntaxin 11 (*STX-11*). All of these proteins are involved in cellular cytotoxicity mediated by NK and T cells.[1] These mutations interrupt the exocytotic process of polarisation, docking, priming, and fusion in NK/cytotoxic T cells, leading to defective cytotoxicity and subsequently HLH.[7] Genetic analysis of children with primary HLH reveals a

frequency of mutations around 30% to PRF, 20% to UNC3D and 10% to STX11, with approximately 40% of the patients not having a known genetic defect.[7] According to the literature, the double heterozygosity for MUNC 13-4 identified in the second case had not been previously described.

Also, a rare finding in the first case was myelofibrosis on bone marrow biopsy and autoimmune haemolytic anaemia (AIHA), both previously described in association with HLH.[8–10] Myelofibrosis in childhood may be primary or secondary to infections, drugs, toxins, autoimmune conditions, malignancies and trauma. However, it is most often associated with haematologic malignancies. The underlying mechanisms of bone marrow fibrosis are not fully understood, but evidence suggests that it is mediated through numerous cytokines and growth factors. Thus, the development of reversible (with immunosuppressive therapy) myelofibrosis in HLH (as it happened in our case) is conceivable in the setting of a hyperinflammatory state.[8] In our case, myelofibrosis may be a primary effect of HLH, or secondary to a precipitating infectious agent such as HSV6 or autoimmunity. The cytokine overproduction in HLH might also be responsible for AIHA, since the mononuclear phagocytic system participates in the destruction of opsonised erythrocytes.[10]

Due to non-specific symptoms and signs, the diagnosis of HLH is difficult, and although the initial clinical presentation is highly variable, prolonged fever (up to 100%) and hepatosplenomegaly (30–90%) are the most frequent signs.[4,11] In these two cases, these signs were present from the onset of the disease. The main differential diagnosis is a normal infection in an immune competent patient, but it is the severity and progression of symptoms that are important for differentiation.[2] When a patient presents with prolonged fever unresponsive to antibiotics, hepatosplenomegaly and cytopenias, HLH should be considered. There is evidence that some patients do not meet all the diagnostic criteria and that many patients do so only late in the course of the disease, as in case 1, with five of eight criteria presenting only 44 days after the onset of disease. Furthermore, patients with a molecular diagnosis consistent with HLH do not need to fulfil the diagnosis criteria to start adequate therapy.[3]

FHLH is a fatal disease with a median survival of <2 months after diagnosis if untreated; mortality occurs mainly as a result of haemorrhage or opportunistic infections,[12] but is also due to multiorgan failure.

The immediate aim in treatment is to suppress severe hyperinflammation, using drugs that neutralise the functions of activated macrophages/histiocytes and T cells.[13] Current treatment includes chemotherapeutic (etoposide) regimens in association with dexamethasone and ciclosporin A.[3] The second aim is to remove the infectious stimulus for the ongoing activation of cytotoxic cells; however, appropriate antimicrobial treatment will only sometimes modify the course of the disease. The ultimate aim is stem cell transplantation to correct the defective immune system by providing normally functioning cells. At present, HSCT is the only curative treatment, and partial chimerism appears to be sufficient to prevent reactivation of HLH in most cases.[1] The follow-up study of HSCT in children treated with protocol HLH-94 revealed that marrow transplantation using matched related or unrelated donors offers a similar long term disease-free outcome (approximately 70% at 3 years). However, the success of HSCT depends on the extent of control of HLH before transplantation.[1,13] Despite reactivation of HLH on the third week of protocol HLH-04, HSCT from a matched sibling was performed successfully in our first case.

The clinical outcome in HLH patients often depends on how fast and accurately the diagnosis is established. Therefore awareness of the clinical symptoms and diagnostic criteria is crucial to start appropriate therapy, which has changed the prognosis from uniformly fatal to a cure rate of >50%.[2]

Learning points

- In cases of prolonged fever unresponsive to antibiotics, hepatosplenomegaly and cytopenias, haemophagocytic lymphohistiocytosis (HLH) should be considered.
- HLH might present as multiple organ dysfunction syndrome.
- It is important that paediatricians and paediatric intensivists know about the diagnostic criteria and possible clinical presentations of HLH so that treatment is promptly initiated
- Haematopoietic stem cell transplantation is the only curative treatment.

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Footnotes

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