CASE REPORT

Hemophagocytic syndrome with atypical presentation in an adolescent

Marta Valente Pinto,^{1,2} Isabel Esteves,^{2,3} Yenan Bryceson,⁴ Anabela Ferrão^{1,2,5}¹Centro Hospitalar Lisboa Norte, Hospital Santa Maria, Lisboa, Portugal²Department of Pediatrics, Lisbon Academic Medical Center, Lisboa, Portugal³Paediatric Infectiology Unit, Immunodeficiencies Center, Lisboa, Portugal⁴Center for Infectious Medicine, Karolinska Institutet, Stockholm, Sweden⁵Paediatric Hematology Unit, Lisboa, Portugal**Correspondence to**Dr Marta Valente Pinto,
martamvalente@gmail.com**SUMMARY**

A 14-year-old adolescent presented with a prolonged fever, abnormal liver function, anaemia, thrombocytopenia, but a good general status. Diagnosis of hemophagocytic lymphohistiocytosis (HLH) was suspected, in spite of the initial indolent course. Secondary causes were excluded, but no specific mutation indicative of primary HLH was found. The patient started with specific therapy, but progressed with reactivations and later with persistently active disease. Haematopoietic stem cell transplantation was not successful and the adolescent died 7 months after diagnosis.

BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal immune dysregulatory disorder affecting predominantly infants and children.¹ The clinical presentation of HLH is generally acute, with the sudden onset of a high and unremitting fever.^{2–3} Familial HLH cases usually present in the first years of life, but cases in adolescents and young adults have also been reported.^{4–5}

This case is important because it highlights the severity and potentially fatal nature of HLH, particularly this atypical late onset form. It also enhances the importance of maintaining a high level of suspicion of HLH not only in critical patients, but also in the investigation of prolonged fever, cytopenias, unexplained liver failure and elevated inflammatory markers. Atypical forms are more prone to delayed diagnosis. Consequently, a delay in starting an effective treatment may compromise the patient's outcome.

CASE PRESENTATION

A 14-year-old caucasian girl was referred to the pediatric hematology unit with prolonged fever (1 month duration), abnormal liver function, anaemia and thrombocytopenia.

She had no relevant medical history and no relevant family history.

Four months prior to admission she was suffering from nausea, weight loss, myalgias and jaundice and hepatitis according to the biochemical evaluation. She developed high fever 3 months after the first manifestations and was admitted in a local institution for diagnostic work-up. She developed anaemia and thrombocytopenia and was referred to the pediatric hematology unit for follow-up.

On admission she had a good general status, but she was pale and had an enlarged liver and a set of laboratory tests were performed.

INVESTIGATIONS

Laboratory tests revealed: haemoglobin 8.5 g/dL, leucocytes 7920/mm³ with 67% polymorphonuclear neutrophils, platelets 102 000 × 10⁶/mm³, sedimentation rate 68 mm/s; negative antinuclear, antimitochondrial, antismooth muscle, anti-double-stranded DNA, anti-liver kidney microsomal, anti-neutrophil cytoplasmic, myeloperoxidase anticytoplasmic antibodies; normal screening coagulation tests; aspartate transaminase (AST) 278 U/L, alanine transaminase (ALT) 254 U/L, γ -glutamyl transferase 72 U/L, alkaline phosphatase 212 U/L, total bilirubin 0.72 mg/dL, lactic dehydrogenase 1183 U/L, triglycerides 347 mg/dL, ferritin 1922 ng/mL, normal kidney function tests, total proteins 7.7 g/dL with hypergammaglobulinemia 2.42 g/dL (31% of total proteins); normal blood smear.

Blood cultures for bacteria, mycobacteria and fungus were negative. Serologies for hepatitis A, hepatitis B, hepatitis C, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus 1, human herpes virus 6, Parvovirus B19, *Toxoplasma*, *Salmonella*, Lyme disease, *Leptospira*, *Brucella*, *Leishmania*, *Bartonella*, *Ehrlichia* and *Coxiella burnetii* were negative. Immunological study of autoimmune lymphoproliferative syndrome and metabolic studies were normal.

Bone marrow cytology showed unspecific alterations, namely, 14% of dysmorphic lymphoid cells. Slightly enlarged liver and spleen were found by abdominal ultrasound. Abdominal and pelvic CT showed slight homogenous liver enlargement and moderate splenomegaly. No abnormalities were found in the chest X-ray and echocardiogram and brain MRI.

On day 34 a liver biopsy was performed that was complicated by severe intra-abdominal haemorrhage, hypovolaemic shock and acute kidney lesion. She stayed 6 days in the intensive care unit when the fever recurred. Liver biopsy showed some Kupffer cells with erythrophagocytosis.

Immunological tests revealed soluble cluster (sCD25) level 1003 pg/mL (normal range 186–2768), highly reduced natural killer (NK) cell activity, flow cytometric analysis of perforin expression with reduced fluorescence. Specifically, the patient displayed overall normal lymphocyte numbers, albeit low NK cell counts (5 cells/ μ L). NK cell-mediated cytotoxicity was pathologically low in the

To cite: Valente Pinto M, Esteves I, Bryceson Y, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-200929

patient. NK cell degranulation and intracellular expression of perforin was within normal range in patients. Sequencing of the coding region and splice-sites of PRF1, STX11, UNC13D and STXBP2 did not identify any disease-causing mutations. Both cytotoxic lymphocyte activity studies and the genetic study were performed at the Center of Infectious Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden, as previously described.⁶

DIFFERENTIAL DIAGNOSIS

The first challenge in HLH is early recognition, since other conditions share the same symptomatic pattern.

The standard definition of HLH, according to the HLH-2004 study group, requires that at least five of the following clinical criteria are met: fever, splenomegaly, peripheral cytopaenias of 2 or 3 lineages, hypertriglyceridaemia/hypofibrinogenaemia, no evidence of malignancy, elevated ferritin ($>500 \mu\text{g/L}$), elevated sCD25 (interleukin-2 (IL-2) receptor $\geq 2400 \text{ U/mL}$), low or absent NK cell activity and histological evidence of hemophagocytosis in bone marrow, lymph nodes or spleen. A molecular diagnosis consistent with HLH may also be sufficient for the diagnosis.³

Our patient completed five of the defined criteria (fever, splenomegaly, hypertriglyceridaemia, elevated ferritin and low NK cell activity), and the diagnosis was established.

Defining the type of HLH can be difficult, despite the advances in molecular diagnosis. In this case, autoimmune disease, malignancies and infectious conditions were excluded during a 7-month investigation. Although the major gene defects described in familial HLH were excluded, the highly severe and persistently active disease suggested a primary cause.

TREATMENT

The patient received specific therapy according to the HLH-2004 protocol with dexamethasone, etoposide, cyclosporine A and prophylactic cotrimoxazole, itraconazole and immunoglobulin once every 4 weeks.³ A good partial response was initially observed with no fever, regression of hepatosplenomegaly, decreasing levels of ferritin (from 4000 to 1640 mg/L), triglycerides (from 400 to 80 mg/dL) and liver enzymes (AST from 240 to 40 U/L and ALT from 309 to 86 U/L). However, the patient had persistent anaemia requiring blood transfusions and thrombocytopaenia with several episodes of mucosal haemorrhage and need of platelet transfusions.

OUTCOME AND FOLLOW-UP

The patient had two reactivations of disease in the next 3 months, at weeks 6 and 8 of initial therapy of HLH-2004 protocol. Treatment included high-spectrum antibiotics, antifungal therapy and intensification of immunosuppressive treatment. There was a partial response, but rapid deterioration at the second episode led to a persistently active disease. She had two HLA-identical siblings with normal NK cell activity and received haematopoietic stem cell transplantation (HSCT) but deceased 1 month after transplant.

DISCUSSION

HLH is a hyperinflammatory condition caused by a highly stimulated, but ineffective immune response.^{7–8} Primary HLH is caused by a defect of the perforin-mediated cytotoxic activity of NK cells and CD8 T cells, leading to a hyperactivation and hyperproliferation of cytotoxic T cells and a hypercytokinaemia, with progressive organ dysfunction.^{1–2, 8–9}

The clinical presentation of HLH is generally acute, with the sudden onset of a high and unremitting fever. Splenomegaly is the second most common clinical finding and can be associated with hepatomegaly, lymphadenopathies, jaundice and central nervous system symptoms including confusion, seizures and focal deficits. A maculopapular skin rash and abdominal distension have also been described.² Commonly HLH is divided into primary or genetic HLH in addition to secondary HLH.^{1–5, 10} Genetic HLH is an autosomal recessive or X-linked disease and could be divided in two subgroups: familial HLH (FHL) and in association with other immune deficiencies, most commonly Chédiak-Higashi syndrome and Griscelli syndrome or X-linked lymphoproliferative syndrome.

Secondary or acquired forms of HLH occur in association with infections, usually viral (EBV, CMV and HIV), autoimmune diseases (macrophage activation syndrome in the systemic onset juvenile idiopathic arthritis and systemic lupus erythematosus), malignant diseases (lymphomas or leukemias), immune deficiencies (eg, after organ transplantation) or metabolic conditions (lysine protein intolerance and multiple sulfatase deficiency). Both sporadic and familial cases are often precipitated by acute infections.^{5–9}

The incidence of FHL is approximately 0.12–1 case/100 000 children/year, although this number is considered to be underestimated.¹¹ Until today five forms of FHL have been described, together with four genes (PFR1, UNC13D, STX1 and STXBP2), contributing to more than 90% of all FHL cases.^{7–9, 12} Despite the term 'familial', the recessive nature of this disease leads in the majority of the cases to an absence of positive family history. Usually FHL presents in the first 2 years of life, but cases in adolescents and adults have been reported.⁴ The atypical form of FHL is defined by presentation beyond 2 years of age and survival without HSCT until at least 6 years of age.⁴ The mechanism underlying the atypical cases is not yet defined, as well as the functional and biochemical abnormalities during the asymptomatic phase.¹³

The diagnosis of HLH is based on clinical, laboratory and histopathological findings, as described above.^{3–8} In the atypical or late form of FHL, the NK cell degranulation study is reliable, showing a reduced or absent NK cell cytotoxicity that is partially restored (to a level above 10%) after addition of IL-2.

Current treatment of this condition is based on the HLH-2004 protocol and consists in etoposide, dexamethasone, cyclosporine A and in patients with evidence of central nervous system involvement, intrathecal therapy with methotrexate and steroids.^{3–14} In patients with persistent or reactivated forms of disease, subsequent HSCT is recommended and could cure this condition.^{3–15, 16}

Learning points

- ▶ Hemophagocytic lymphohistiocytosis can affect paediatric patients at any age and a high level of suspicion is fundamental for early diagnosis, particularly in adolescent patients.
- ▶ Primary HLH (hemophagocytic lymphohistiocytosis) must be considered in adolescents after a secondary aetiology is ruled out, even in the absence of family history.
- ▶ Atypical forms of HLH may have an indolent course and the diagnosis must be considered in the presence of prolonged fever, cytopaenias and liver failure.
- ▶ The delay in the beginning of an effective treatment could affect the patient outcome and the disease could be fatal.

Contributors All the authors participated in the conception, design, acquisition of the data or analysis and interpretation of the data; drafting the article and the revision of the final version before submission.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Risma K, Jordan MB. Hemophagocytic lymphohistiocytosis updates and evolving concepts. *Curr Opin Pediatr* 2012;24:9–15.
- 2 Jabado N, McCusker C, Saint Basile G. Pediatric hemophagocytic syndromes: a diagnostic and therapeutic challenge. *Allergy Asthma Clin Immunol* 2005;1:142–60.
- 3 Henter JL, Horne A, Aricó M, *et al.* HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124–31.
- 4 Rohr J, Beutel K, Maul-Pavlic A, *et al.* Atypical familial hemophagocytic lymphohistiocytosis due to mutation in UNCC13D and STXBP2 overlaps with primary immunodeficiency disease. *Hematologica* 2010;95:2080–7.
- 5 Janka G, zur Stadt U. Familial and acquired hemophagocytic lymphohistiocytosis. *Hematology Am Soc Hematol Educ Program* 2005:82–8.
- 6 Chiang SC, Theorell J, Entesarian M, *et al.* Comparison of primary human cytotoxic T-cell and natural killer cell responses reveal similar molecular requirements for lytic granule exocytosis but differences in cytokine production. *Blood* 2013;122:1345–56.
- 7 Weitzman S. Approach to hemophagocytic syndromes. *Hematology Am Soc Hematol Educ Program* 2011;2011:178–83.
- 8 Tang YM, Xu XJ. Advances in hemophagocytic lymphohistiocytosis: pathogenesis, early diagnosis/differential diagnosis and treatment. *ScientificWorldJournal* 2011;11:697–708.
- 9 Bode SF, Lehmborg K, Maul-Pavlic A, *et al.* Recent advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis. *Arthritis Res Ther* 2012;14:213.
- 10 Canna SW, Behrens EM. Not all hemophagocytes are created equally: appreciating the heterogeneity of the hemophagocytic syndromes. *Curr Opin Rheumatol* 2012;24:113–18.
- 11 Henter JL, Elinder G, Söder O, *et al.* Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. *Acta Paediatr Scand* 1991;80:428–35.
- 12 Cetica V, Pende D, Griffiths GM, *et al.* Molecular basis of familial lymphohistiocytosis. *Haematologica* 2010;95:538–41.
- 13 Busiello R, Adriani M, Locatelli F, *et al.* Atypical features of familial hemophagocytic lymphohistiocytosis. *Blood* 2004;103:4610–12.
- 14 Jordan MB, Allen CE, Weitzman S, *et al.* How do I treat hemophagocytic lymphohistiocytosis. *Blood* 2011;118:4041–52.
- 15 Ouachée-Chardin M, Elie C, de Saint Basile G, *et al.* Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis—a single center report of 48 patients. *Pediatrics* 2006;117:e743–50.
- 16 Marsh RA, Jordan MB, Filipovich AH. Reduced intensity conditioning haematopoietic cell transplantation for haemophagocytic lymphohistiocytosis: an important step forward. *Br J Haematol* 2011;154:556–63.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow