CASE REPORT

Haemophagocytic lymphohistiocytosis presenting as liver failure following Epstein-Barr and prior hepatitis A infections

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is associated with high mortality even after prompt diagnosis. We present a young man with HLH triggered by two common viral diseases, infectious mononucleosis and hepatitis A. This patient presented with fever, rapidly progressive liver failure, anasarca and cholestasis, followed by anaemia and neutropenia. His carbohydrate antigen 19-9 reached over 9000 U/mL. Initial bone marrow and liver biopsies did not show histological features of malignancy or HLH. The patient was finally diagnosed and treated almost 1 year after the initial symptoms started, and had an excellent response with etoposide and dexamethasone. This case is unusual because it was triggered following mononucleosis in a patient with positive total antibodies against hepatitis A, with rapidly developing liver failure, and also because the patient's response was excellent despite the delay in treatment. It underscores the importance of suspecting HLH when severe systemic illness develops after a viral infection, even in the absence of clear histological features.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome that can be familial (F-HLH) or acquired; infections, autoimmune diseases, malignancy or immune suppression are the most common triggers of the acquired form.[1] Patients usually present with fever, cytopenia, hepatomegaly and splenomegaly. Laboratory findings include elevated ferritin, triglycerides transaminases and soluble interleukin-2 (IL-2) receptor levels. Fibrinogen and albumin are low and natural killer (NK) cells, although normal in numbers, have measurable impaired function. Bone marrow biopsy may not show haemophagocytosis during the initial stages of the disease. Liver biopsy usually shows a hepatitis-like periportal infiltrate of lymphocytes and histiocytes that can cause obstructive jaundice.[1 2] Patients treated following the current guidelines have a 50–60% probability of prolonged survival.[3 4]

We present a case in which the patient had daily fever, liver failure, anasarca, elevated ferritin and high levels of carbohydrate antigen 19-9 (CA 19-9) lasting for 1 year before a final diagnosis was made and therapy was started.

CASE PRESENTATION

A 23-year-old African-American man presented to The University of Texas MD Anderson Cancer Center on November 2010 for evaluation of persistent fever, anaemia, neutropenia, anasarca and weight loss. The patient had been generally healthy, other than being overweight, until October 2009 when he developed fever and submandibular lymphadenopathy; he was diagnosed with infectious mononucleosis based on high levels of Epstein-Barr virus (EBV) IgM in his blood. Within a few days he started to experience daily fever up to 40°C (104°F) and progressive weight loss. These symptoms persisted with no improvement and were thought to be secondary to his mononucleosis. In January 2010, the patient became jaundiced and was diagnosed with hepatitis A virus (HAV) infection, on the basis of abnormal liver function tests and apparently, from the patient's report, a positive test for HAV. During the following months, his liver function progressively deteriorated with elevated transaminases and alkaline phosphatase levels, and extremely low albumin. The patient continued to have daily fever peaks without a clear circadian pattern, and rapidly developed severe anasarca. In the months prior to his presentation at MD Anderson, he developed anaemia and neutropenia. He underwent extensive diagnostic evaluation for infectious disease which only showed antibodies against EBV and HAV consistent with previous infections. A bone marrow biopsy was performed which did not show malignancy.

At presentation to MD Anderson in November 2010, the patient appeared acutely ill, with severe anasarca. He presented with continuing daily fever, severe fatigue and malaise and occasional abdominal pain in the right-upper quadrant. He had not experienced arthritis, arthralgia, myalgia, alopecia, rash or skin abnormalities, Raynaud's phenomenon, sicca symptoms, haematuria and shortness of breath, cough or haemoptysis. The patient had been obese, and had lost weight at the beginning of his illness, but regained some after he developed peripheral oedema and anasarca. His medical history was unremarkable, other than the recent infections with EBV and possibly HAV. He did not have a family history of autoimmune disease, periodic fever or haematological malignancies. There was no history of unusual or chronic infectious disease in his immediate family. The patient had a younger brother who was healthy and had not

experienced similar symptoms. He had been attending business school until his health status deteriorated to the point he had to abandon his studies. He did not have a history of alcoholism, smoking or drug abuse, no recent travels or exposure to visibly sick people.

INVESTIGATIONS

On physical examination, the patient looked chronically ill and pale; his heart rate was 123 bpm; blood pressure, 120/80 mm Hg; temperature, 35.9°C (96.62°F); weight, 152 kg. He had severe anasarca, no lymphadenopathy or palpable hepatomegaly or splenomegaly.

Laboratory tests showed: albumin, 1.6 g/dL; total bilirubin, 0.8 mg/dL; alanine aminotransferase, 154 IU/L; aspartate aminotransferase, 383 IU/L; alkaline phosphatase, 309 IU/L. White cell count, 2.8×10^9/L; haemoglobin, 9.1 g/dL; platelet count, 117×10^9/L; prothrombin time, 20.3 s; partial thromboplastin time, 36.6 s; international normalised ratio, 1.69; d-dimer, 3.99 µg/mL, fibrinogen, 66 mg/dL; erythrocyte sedimentation rate, 62 mm/h; high sensitivity C reactive protein, 19.70 mg/L; lactate dehydrogenase, 2005 IU/L; ferritin, 5928 ng/mL; EBV PCR, undetectable. All autoimmune testing were negative, except a positive anticardiolipin antibody IgG, 34.7 GPL. Total HAV antibodies were positive and HAV IgM was negative, suggestive of prior infection. The patient was initially seen by us 9 months after the diagnosis of HAV had been made. Hepatitis B, C and HIV serologies were negative.

A positron emission tomographic/CT (PET/CT) scan demonstrated heterogeneous liver uptake without a focal metabolic or anatomic abnormality and absence of avid lymphadenopathy. MRI and CT of the abdomen showed gallstones, splenomegaly, hepatomegaly with diffuse heterogeneous density on an enlarged liver, no focal abnormalities on liver or pancreas and massive subcutaneous oedema.

The initial bone marrow biopsy was sent to our institution for evaluation. Histology showed a normocellular (50%) bone marrow with adequate trilineage haematopoiesis and mild megakaryocytic hyperplasia. No morphological evidence of myelodysplastic syndrome, myeloproliferative neoplasm or HLH was observed. Flow cytometry showed decreased granulocyte expression of CD10 and no clonal B cells or aberrant T cell antigen expression.

A transjugular liver biopsy was performed, which showed an atypical T cell lymphoid infiltrate associated with multifocal non-zonal necrosis and macrovesicular steatosis involving 40% of hepatocytes and septal fibrosis. The lymphocyte infiltrate was predominantly composed of cytotoxic T cells (CD3+, CD5+, CD4+ and granzyme+), with very few CD8+ T cells, NK cells (CD56+), or B cells (CD20). No T cell restriction by T cell receptors β and γ or light chain restriction by λ and κ were observed with in situ hybridisation. No distinct monoclonal TCR γ chain gene rearrangement was detected. The pathologist's interpretation was that the findings could represent chronic hepatitis, persistent HAV infection or a drug reaction, but that a T cell lymphoma could not be entirely discarded.

The patient was started on 60 mg of daily oral prednisone, and while his fever and fatigue improved, his laboratory parameters continued to deteriorate, with a ferritin of 23 609 µg/mL, high sensitivity C reactive protein 83.90 mg/L, D-dimer >20.0 µg/mL, IL-2 receptor (sIL-2r) >6500 U/mL and CA 19-9 3296 U/mL. A second liver biopsy was performed, which showed prominent lobular activity with more than 2–3 foci per lobule, lymphocytes and plasma cells, and hepatocellular necrosis. Hepatocytes showed reactive changes in the form of ballooning degeneration and minimal macrovesicular steatosis. Sinusoids were dilated with prominent Kupffer cells. The portal area showed relatively mild inflammation without evidence of damage to intralobular bile ducts or portal veins. No significant cholestasis, viral inclusions or malignancy were observed. Immunostains showed that the infiltrating lymphocytes did not have an aberrant immunophenotype. The pathologist suggested that the changes were compatible with chronic hepatitis secondary to autoimmune disease or toxin-related injury.

In May 2011, the patient clinical status deteriorated with increased fever, malaise and fatigue and he was admitted under a presumptive diagnosis of HLH or lymphoma. At admission laboratory findings included: CA 19-9 9613 U/mL, ferritin 16 798 ng/mL, albumin 1.6 g/dL; triglycerides, 184 mg/dL and high sensitivity C reactive protein 70.60 mg/L. A bone marrow biopsy was performed, which showed a cellular marrow (60%) with trilineage haematopoiesis, a single small focus of necrosis and a mild increase in plasma cells with no morphological evidence of lymphoma. Immunohistochemistry was negative for malignancy. Therapy for HLH was initiated at admission. The tissue specimen of the liver biopsy previously performed outside our institution was requested and reviewed. Histology showed haemophagocytosis by Kupffer cells (figure 1).

TREATMENT

The patient was not responsive to the initial treatment with oral prednisone alone and therapy for HLH was initiated before a histological diagnosis of HLH was confirmed. Current guidelines recommend initiating treatment as soon as a clinical diagnosis is made,[5 6] even in the absence of histological confirmation. The patient was treated with dexamethasone and etoposide following the HLH-2004 recommendations and suggested therapy for EBV-HLH.[2 3 6–8] The patient had no nervous system manifestations and his spinal fluid did not show increased histiocytes or haemophagocytosis, so intrathecal therapy with methotrexate was not recommended.[1–3 9]

OUTCOME AND FOLLOW-UP

The patient completed therapy in December 2011, and is not receiving any medications. His anasarca significantly improved with loss of 24 kg. Current laboratory results show albumin, 4.3 g/dL; alanine aminotransferase, 33 IU/L; aspartate aminotransferase, 33 IU/L; alkaline phosphatase, 102 IU/L; total bilirubin, 1.0 mg/dL; white blood cells, 3.6×10^9/L; haemoglobin, 13.9 g/dL; platelets 143×10^9/L; CA 19-9 35.9 U/mL; ferritin,

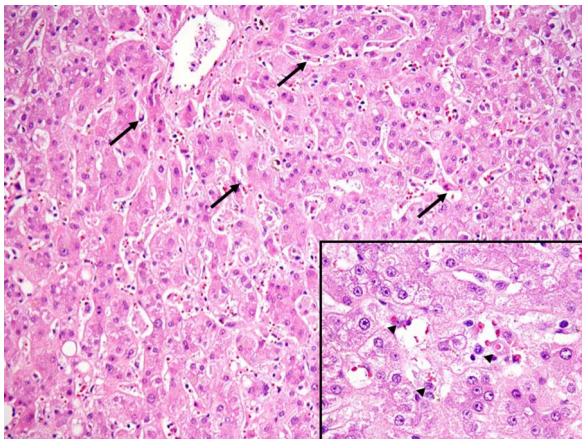

Figure 1 Liver histology showing haemophagocytosis.

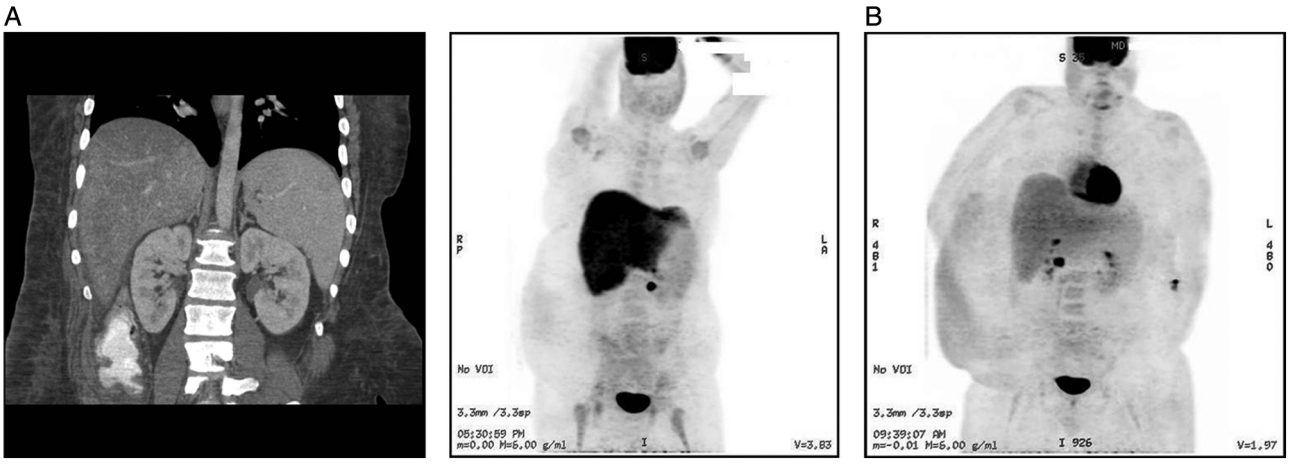

Figure 2 Positron emission tomographic/CT scan (A) prior to therapy and (B) after therapy.

530 µg/mL and triglycerides 250 mg/dL. A PET/CT scan demonstrated a decrease in the previously detected diffuse hepatic hypermetabolic activity (figure 2A,B).

DISCUSSION

Hyperinflammation caused by an excessive activation and proliferation of T cells and macrophages is the main cause of organ damage and death in patients with HLH.[1 2 4 9] Acquired HLH is the most commonly observed form of the disease in adults and children,[10] with infections, particularly viral infections,[5 11–14] malignancy,[15] autoimmune diseases[16] and acquired immunodeficiency conditions[17 18] as the most commonly described causes. The pathogenesis of the acquired form of disease is not as well understood as that of F-HLH, and the heterogeneity of its initial symptoms can make it difficult to reach a prompt diagnosis. Patients usually present with persistent fever that does not respond to antibiotics, signs of liver involvement, encephalopathy and coagulation disorders.[1 2 5 9 10] Hepatomegaly and splenomegaly are common. Laboratory abnormalities include cytopenia or pancytopenia, hyperferritinaemia, hypertriglyceridaemia, hyperbilirrubinaemia, hypoalbuminaemia, elevated transaminases and hypofibrinogenaemia. The main immunological findings are increased sIL-2 receptor levels and impaired NK cell function.[1 2 10] The pathological confirmation of haemophagocytosis in bone marrow, liver or lymph node biopsies, although ideal, is not always present in the early stages of the disease. Repeated biopsies may be necessary to detect haemophagocytosis. Therapy should not be delayed in cases of strong clinical suspicion but absent pathological confirmation. The 2004 guidelines for diagnosis include fever, splenomegaly, cytopenia in at least two of the three blood cell lineages, hypertriglyceridaemia and or hypofibrinogenaemia and haemophagocytosis in the bone marrow, spleen or lymph nodes. New criteria have been added including low or absent NK-cell activity, hyperferritinaemia and high levels of sIL-2r (box 1). Five of the eight criteria must be fulfilled, except for patients with genetic or molecular diagnosis of HLH.[8]

We did not conduct genetic studies to rule out a mutation in our patient because of his rapid response to treatment which is not common in the familial form of the disease; however, if his disease reactivated genetic testing would be indicated to rule out F-HLH.[1 2 4 6 19] Various genetic mutations can cause F-HLH including mutations in genes encoding perforin (F-HLH2), MUNC13-4 (F-HLH3), syntaxin-11 (F-HLH4) and MUNC18-2 (F-HLH5). These proteins are involved in the pore formation, vesicle priming and vesicle transport and fusion at the immunological synapse between cytotoxic cells and their targets. Mutations in lysosomal transport (LYST or Chediak-Higashi), RAS-associated protein 27A (Griscelli 2) and adaptor protein 3 B1 subunit (Hermansky-Pudlak2) can also cause F-HLH. X linked lymphoproliferative syndrome, X linked severe combined immunodeficiency and X linked hypogammaglobulinaemia have also been associated with F-HLH. Although F-HLH usually occurs during childhood, it has also been reported in adults.[1 6 19]

The HLH-2004 protocol for treatment includes dexamethasone and etoposide, an antimonocytic and antihistiocytic agent. Monocytes and histiocytes are thought to control antigen load via elimination of infected antigen-presenting cells. Cyclosporine A which suppresses cytotoxic T lymphocyte and macrophage activity has also been recommended. Intrathecal methotrexate is used when the patient has central nervous system involvement. For patients with F-HLH or recurrent disease, haematopoietic stem cell transplant with reduced-intensity conditioning therapy, has become the standard

Box 1 Diagnostic criteria for acquired haemophagocytic lymphohistiocytosis

- Fever
- Splenomegaly
- Cytopenia ≥2 cell lines
- Haemoglobin <9.0 g/dL
- Platelets $<100\times10^9$/L
- Neutrophils $<1\times10^9$/L
- Hypertriglyceridaemia and/or hypofibrinogenaemia
- Fasting triglycerides ≥265 mg/dL
- Fibrinogen <150 mg/dL
- Ferritin ≥500 ng/mL
- sIL-2r ≥2400 U/mL
- Decreased or absent NK-cell activity
- Haemophagocytosis in bone marrow, CSF or lymph nodes

Supportive evidence: CNS symptoms, CSF with moderate pleocytosis and/or elevated protein, elevated transaminases, bilirubin, LDH.

sIL-2r, soluble IL-2 receptor; NK cell, natural killer cell; CNS, central nervous system; CSF, cerebrospinal fluid; LDH, lactate dehydrogenase.

of care.[1–4 8 19] The survival of patients with HLH has improved. The mortality of HLH associated with rheumatological disease or infection is between 8% and 24%.[7] Delay in diagnosis, high ferritin levels, low albumin and multiorgan involvement are associated with poor prognosis.[19–21]

Our case is unique from several perspectives. First, it is surprising that our patient survived for a year without therapy, since diagnosis delay is a known determinant of worse prognosis.[1 2 19] Second, this patient originally developed lingering mononucleosis symptoms, but his HLH appears to have been triggered by a subsequent infection with HAV. While there are previous reports of HLH after EBV or HAV infection, to our knowledge, this is the first case reporting prior close occurrence of both infections. EBV infection has been the most commonly reported viral trigger for acquired HLH and the clinical characteristics vary from mild-to-severe; for its diagnosis, the patient must fulfil the HLH diagnostic criteria described in box 1. Antiviral therapy, intravenous immunoglobulin, rituximab and alemtuzumab have been used for patients who relapse, with haematopoietic stem cell transplantation if other therapies fail.[7 13 22] There have also been a few reported cases of HLH after HAV infection. These patients received steroids and supportive care.[14 23 24] The third unique characteristic to this case is the marked elevation of CA 19-9. To our knowledge, one case report described elevation of CA 19-9 and CA 125 in a patient with disseminated tuberculosis and secondary HLH, but the levels were not reported.[25] Elevated CA 19-9 levels have been reported in patients with cancer of the pancreas or the biliary tract, and also in patients with liver cirrhosis, and choledocholithiasis with acute cholangitis,[25–27] but are not considered as a feature of HLH. Further research should evaluate whether CA 19-9 might be a useful marker of HLH course in patients with liver involvement.

Our case demonstrates the difficulties in diagnosing HLH in patients without clear histology. It also highlights the possible synergistic effect of two viral infections in the development of this disease, and the potential value of CA 19-9 as a marker of disease activity in patients with liver disease. Fortunately, our patient responded very well to therapy despite the delay in diagnosis.

Learning points

- Acquired haemophagocytic lymphohistiocytosis (HLH) can present in heterogeneous ways. When evaluating an adult for prolonged fever and severe systemic illness, HLH should be in the differential diagnosis, particularly after a viral illness.
- HLH can present with hepatitis as its predominant feature. Carbohydrate antigen 19-9 might be a useful biomarker in these cases.
- Therapy should not be delayed in the absence of histological confirmation if there is high suspicion of HLH on the basis of clinical presentation.

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Competing interests None.

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