Liver failure with marked hyperferritinemia: 'Ironing out' the diagnosis

Susan E Natsheh MD FRCPC¹, Eve A Roberts MD FRCPC^{1,2}, Bo Ngan MD PhD FRCPC³, Peter Chait MD FRCPC⁴, Vicky Lee Ng MD FRCPC^{1,2}

SE Natsheh, EA Roberts, B Ngan, P Chait, VL Ng. Liver failure with marked hyperferritinemia: 'Ironing out' the diagnosis. *Can J Gastroenterol* 2001;15(8):537-540. Hemophagocytic lymphohistiocytosis (HLH) may manifest as neonatal liver failure characterized by hepatosplenomegaly, profound coagulopathy, ascites and hyperbilirubinemia. Marked hyperferritinemia may be present in these patients, mimicking perinatal hemochromatosis. Tissue specimens are critical in distinguishing these two diseases and in directing management. Clinical recognition and diagnosis of HLH can be difficult but are crucial for appropriate therapy and genetic counselling. Liver transplantation is absolutely contraindicated for patients with HLH but may be the only life-saving treatment modality for patients with perinatal hemochromatosis.

Key Words: Hemophagocytic lymphohistiocytosis; Hyperferritinemia; Neonatal iron storage disease; Neonatal liver failure; Perinatal hemochromatosis

Insuffisance hépatique et hyperferritinémie marquée : " Ferrer " le diagnostic d'épuisement ferrique

RÉSUMÉ : La lymphohistiocytose hémophagocytaire (LHH) peut se manifester par une insuffisance hépatique néonatale caractérisée par une hépatosplénomégalie, une coagulopathie profonde, de l'ascite et de l'hyperbilirubinémie. L'hyperferritinémie marquée peut être présente chez ces patients et donner l'impression d'une hémochromatose périnatale. Des spécimens tissulaires sont essentiels pour distinguer ces deux maladies et orienter le traitement. La reconnaissance et le diagnostic clinique de la LHH sont parfois difficiles mais essentiels pour administrer le traitement approprié et donner de bons conseils sur le plan génétique. La transplantation hépatique est absolument contre-indiquée chez les patients qui présentent une LHH et elle est parfois le seul traitement qui puisse sauver la vie des patients atteints d'hémochromatose périnatale.

The diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH) include clinical, laboratory and histopathological criteria (1). The clinical hallmarks of the disease – fever, cytopenia, hepatosplenomegaly, hypofibrinogenemia and/or hypertriglyceridemia – are somewhat

nonspecific; thus, accurate diagnosis may be difficult. A spectrum of hepatic manifestations has been described (1), but fulminant hepatic failure is often not recognized as a presentation of HLH (2). An elevated serum ferritin level is often seen in HLH, which may further confuse the diagnosis

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¹Department of Paediatrics, Division of Gastroenterology and Nutrition; ²Paediatric Academic Multi-Organ Transplant (PAMOT) Program;

³Department of Pathology; and ⁴Department of Radiology, The Hospital for Sick Children, Toronto, Ontario

Correspondence: Dr Vicky Lee Ng, Division of Gastroenterology and Nutrition, 555 University Avenue, Toronto, Ontario M5G 1X8.

Telephone 416-813-8757, fax 416-813-6531, e-mail vicky.ng@sickkids.on.ca

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Figure 1) Hepatic infiltrates of histiocytes with engulfed erythrophagocytes

with perinatal hemochromatosis (PH). Histopathological documentation of hemophagocytosis may be identified in various organs (1). Correct and prompt diagnosis is crucial for effective therapy and genetic counselling. HLH has a uniformly fatal course if untreated. Liver transplantation is absolutely contraindicated for patients with HLH (3) but may be the only life-saving treatment modality for patients with PH (4,5).

CASE PRESENTATION

A six-week-old African-American male infant was transferred from a community hospital for evaluation of persistent fever. He was the product of an uncomplicated pregnancy of nonconsanguineous parents of Jamaican ethnicity. There was no family history of liver disease, and he had a healthy seven-year-old half-sibling. He was delivered at term with a birth weight of 4.4 kg. He was exclusively breastfed and had been well until five weeks of age, when he developed a high fever (39°C axillary). A septic work-up revealed an *Escherichia coli* urinary tract infection, and appropriate intravenous antibiotics were administered. However, the fever persisted, and six days after initial presentation, the infant was transferred to the general pediatric service of The Hospital for Sick Children (Toronto, Ontario).

On admission to the hospital, the infant's weight was 5.92 kg (greater than the 95th percentile). He appeared active, nontoxic and nutritionally replete. He had no dysmorphic features and was not jaundiced. Moderate hepatosplenomegaly was present; there was no obvious ascites, peripheral edema or scrotal swelling. Initial laboratory results included: white blood cell count $9.2 \times 10^9/L$, hemoglobin 81 g/L (normal 90 to 135 g/L), platelets $52 \times 10^9/L$, partial thromboplastin time longer than 212 s, international normalized ratio 3.06, fibrinogen less than 0.35 g/L (normal 1.6 to 4 g/L), aspartate aminotransferase 1378 U/L (normal less than 110 U/L), alanine aminotransferase 293 U/L (normal less than 60 U/L), alkaline phosphatase 336 U/L (normal 175 to 600 U/L), gamma-glutamyl

transferase 153 U/L (normal less than 225 U/L), conjugated bilirubin 64 $\mu\text{mol/L}$ (normal less than 2 $\mu\text{mol/L}$), unconjugated bilirubin 0 $\mu\text{mol/L}$ (normal range 0 to 17 $\mu\text{mol/L}$), albumin 21 g/L (normal 32 to 48 g/L), ammonium 34 $\mu\text{mol/L}$ (normal less than 35 $\mu\text{mol/L}$), lactate 6 mmol/L (normal 0 to 2.4 mmol/L) and pyruvate 0.17 mmol/L (normal 0.03 to 0.08 mmol/L). The Gastroenterology service was consulted, and additional investigations revealed: alpha-fetoprotein 117,000 mg/L (normal 90 to 10,000 mg/L at one month of age), ferritin 31,098 $\mu\text{g/L}$ (normal 14 to 400 $\mu\text{g/L}$), triglycerides 1.25 mg/dL (normal 0.4 to 1.3 mg/dL), factor V 0.84 U/mL (normal 0.5 to 1.5 U/mL), factor VII 0.21 U/mL (normal 0.2 to 0.8 U/mL) and factor VIII 0.75 U/mL (normal 0.5 to 1.5 U/mL). Metabolic work-up ruled out tyrosinemia, galactosemia, bile acid synthetic defects and alpha-1 antitrypsin deficiency. Infectious studies, including hepatitis B and C, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, *Toxoplasma gondii*, human herpesvirus 6, echovirus, parvovirus and coxsackievirus, were negative. Hyperferritinemia suggested perinatal hemochromatosis, and the decision was made to start an abbreviated 'antioxidant cocktail' (vitamin E, selenium and N-acetylcysteine) (6). Deferoxamine and prostaglandin E, the other two components of this regimen, were deliberately withheld, because their potential toxicities outweighed their potential benefits with the information available at this point.

Ultrasonography with Doppler showed hepatosplenomegaly, absence of focal hepatic lesions, and patent portal and hepatic blood vessels. Magnetic resonance imaging (MRI) was remarkable for an enlarged spleen containing multiple nodular lesions; however, there was no abnormal iron deposition in the hepatic or extrahepatic organs.

Tissue biopsies were obtained to establish the diagnosis and appropriately direct further management (1). Bone marrow biopsy showed dyserythropoietic maturation. Infiltrates of macrophages or erythrophagocytosis were not seen. A transjugular liver biopsy specimen revealed multifocal hepatic lobular liver damage by extensive infiltrates of reactive erythrophagocytic lymphohistiocytic cells (Figure 1). Iron stains were negative. The diagnosis of HLH was confirmed.

The patient was transferred to the Haematology-Oncology service. He received an eight-week course of etoposide and tapering doses of dexamethasone; the patient experienced resolution of coagulopathy and cytopenia, and normalization of liver function tests. He has been assessed for bone marrow transplantation.

DISCUSSION

Although HLH is primarily a hematological disorder, infants with this disease may initially present to the pediatric gastroenterologist with liver failure. Variable hepatic manifestations have been described in HLH, ranging from mild synthetic dysfunction and jaundice to overt liver failure (1). Between 16% to 36% of HLH patients have some form of hepatic involvement (7). It is important to recognize HLH as a cause of neonatal liver failure, because prompt diagnosis and appropriate treatment may improve outcome (4,5,8).

Lymphocytic histiocytosis may be sporadic or hereditary. Familial hemophagocytic lymphohistiocytosis (FHL) is the familial occurrence of HLH and is an autosomal recessive disease of early infancy, with an estimated incidence of approximately one in 50,000 live births in Europe (8,9). HLH is the more applicable term for our patient, because it is a broader category encompassing all infants with or without history of parental consanguinity or other affected family members. An association with infection at presentation has been reported in approximately 51% of infants (8), particularly with viruses of the herpes group. The features of these patients with 'infection-associated' HLH do not significantly differ from those with FHL.

The clinical and laboratory diagnostic criteria for HLH outlined by the FHL Study Group of the Histiocyte Society include fever for longer than seven days, splenomegaly, cytopenia affecting two or more cell lines, hypofibrinogenemia and/or hypertriglyceridemia; histopathological criteria include documentation of hemophagocytosis in bone marrow, secondary lymphoid tissues and the spleen (1).

This patient's coagulopathy, hypoalbuminemia, hyperbilirubinemia, splenomegaly and hyperferritinemia led us to consider both HLH and PH as the etiology of his liver failure. However, his persistent fever, cytopenia and severe hypofibrinogenemia were less typical of PH. His MRI did not show evidence of hepatic or extrahepatic iron deposition. While MRI has been valuable in the estimation of hepatic iron concentration in adults with hemochromatosis, its value has not been as well realized in neonatal and/or perinatal hemochromatosis (10-12).

Information from liver specimens was critical in directing patient management and understanding the natural history of the patient's liver disease. The absence of hemophagocytic activity on initial bone marrow examination does not exclude this diagnosis, and serial biopsies may be required (1,8,13). Persistent coagulopathy prevented splenic biopsies, although the biopsies might have been necessary if the liver biopsy did not document the histopathological criteria.

Transjugular liver biopsy was essential not only for the diagnosis, but also for the emergency assessment for liver transplantation. Results from our institution indicate that transjugular liver biopsy can be performed safely at a centre with a skilled interventional radiologist and a well equipped angiography suite (14).

Recent insight into the pathogenesis of HLH was gained with the identification of defects in the perforin gene, located on chromosome 10q22. As a downregulator of lymphocyte cytotoxicity, perforin mediates cytotoxic activity of T cells and natural killer cells in vitro (15). This abnormality may explain the disorganization of the histiocytic system in these patients. Inevitably, future studies on perforin may provide insight on treatment and genetic counselling.

The estimated five-year survival for treated HLH patients is 21%. Chemotherapy alone results in a 10.1% survival rate, but survival increases to 66% with bone marrow transplantation (8). Liver transplantation is a con-

traindication for these patients (3), and indeed, poor outcomes and/or reoccurrence of disease in the graft have been documented in HLH patients who have been misdiagnosed and received transplants for PH (16,17).

Ferritin is the major iron storage protein found in nearly all cells of the body, but is particularly abundant in hepatocytes and in the macrophage system of the bone marrow (18). Serum levels may be increased in disorders affecting either system. The use of serum ferritin to diagnose PH has also been disputed (4,19). The mechanism of hyperferritinemia in HLH is likely multifactorial, and includes increased synthesis and secretion by activated macrophages, and increased release from damaged macrophages and hepatocytes. In his review of 14 patients with PH, Sigurdsson et al (4) reported serum ferritin values between 485 and 3300 ng/mL (normal range 10 to 282 ng/mL). Serum ferritin levels in three patients with HLH ranged widely from 803 ng/mL to 93,000 ng/mL (16,17). Despite our patient's critical clinical presentation, his highly elevated serum ferritin levels alerted us to the possibility of a diagnosis other than PH, and mandated ruling out the diagnosis of HLH before listing for liver transplantation.

In summary, HLH must be included in the differential diagnosis of neonatal liver failure. There is clinical overlap of HLH with PH. Elevated ferritin levels are not specific for PH, and fever and cytopenia should alert the clinician to another diagnosis. Histopathological documentation of hemophagocytosis is required to confirm the diagnosis of HLH. Bone marrow biopsy may be negative in the early stages of the disease, necessitating searches in other organs, including the liver. Prompt transfer to a tertiary care centre with a pediatric gastroenterologist is advised to provide timely diagnosis and direct management. Liver transplantation is not indicated for HLH and may delay institution of potentially life-saving chemotherapy.

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