Neonatal Hemochromatosis: A Case Report

Prapun Aanpreung, M.D.*, Piyavadee Leksrisakul, M.D., Paisal Parichatikanond, M.D.****

**Department of Pediatrics, **Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Neonatal hemochromatosis (NH) is a rare disease causing severe liver failure in neonate. Gestational alloimmune liver disease was recently proposed as an etiology. We present a unique case of a male infant with severe cholestasis soon after birth. Preliminary diagnosis of NH was made by detecting high serum ferritin level along with demonstrating iron deposition in hepatic tissues by magnetic resonance imaging (MRI). Despite being treated with blood exchange transfusions, antioxidant and chelating agents when NH was diagnosed around 2 months of age, he continued to have increasing bilirubin level and worsening coagulopathy. Eventually, he died from severe infection and liver failure at 5 months of age. His autopsy showed siderosis of liver and pancreas, which supported the diagnosis of NH. The specific treatments for NH should be initiated as early as possible once the diagnosis has been made, so that improved clinical outcome may be expected.

Keywords: Gestational alloimmune liver disease, siderosis, cirrhosis

Siriraj Med J 2015;67:187-191
E-journal: http://www.sirirajmedj.com

INTRODUCTION

Neonatal hemochromatosis (NH) is a rare disorder in the newborn consisting of severe liver disease and siderosis of liver and extrahepatic organs. Previously NH was described as an inborn error of iron metabolism, whereas NH is now recognized as a phenotype of severe fetal liver damage due to maternal alloimmune injury to liver.[1] NH should be suspected in all neonates with antenatal or postnatal signs of severe liver disease. The diagnosis of NH can be made by clinical, laboratory, and radiological findings along with excluding other causes of neonatal liver failure.

We describe a male infant with a diagnosis of NH who had severe cholestasis soon after birth and progressive cholestasis despite administration of NH specific treatment. Pathogenesis, recommended investigations and managements for this rare disease are reviewed.

CASE REPORT

A Thai male infant was a product of 36-year-old, G2 P2 mother. There was no history of parental consanguinity and no history of metabolic disorders or liver diseases in the family. His sibling was reported to have meconium aspiration syndrome. He was born full term at 38 weeks gestation via cesarean section due to previous C-section at outside hospital. His birth weight was 2,710 grams. Apgar scores were 7, 9 at 1 and 5 minutes, respectively. At 3 hours of life, he developed clinical jaundice. The rest of physical examination showed pallor and hepatosplenomegaly. Initial laboratory findings showed hematocrit 33% ,white blood cell count 30,460/mm^3 (manual differential counts showed N 52%, L 23%, atypical L 13%, band 9%, myelocyte 3%) and platelet count 66,000/mm^3, reticulocyte count

Correspondence to: Prapun Aanpreung
E-mail: prapun.aan@mahidol.ac.th
Received 9 December 2014
Revised 23 February 2015
Accepted 9 March 2015

22%, RBC indicies were anisocytosis 3+, microcytic 2+, polychromasia 3+ spherocyte 2+, coagulogram: prothrombin time (PT) 14.4 seconds, partial thromboplastin time (PTT) 41.6 seconds, international normalized ratio (INR) 1.25, and fibrinogen 247 mg/dl. Mother and patient's blood group were O Rh^+ and B Rh^+, respectively. Direct Coombs' test was positive 2+. Hemoglobin typing and G6 PD level were normal. TORCH titers were negative. At 24 hours of life, his microbilirubin level was 23 mg/dL and direct bilirubin level was 9 mg/dL therefore a total blood exchange transfusion was performed at outside hospital prior to transferring patient to our hospital. At our hospital which was day three of life, his pertinent physical findings were body weight of 2,760 gram, no pallor, marked jaundice, systolic murmur grade II/VI at left upper parasternal border, liver 3 cm below right costal margin (RCM) and spleen 2 cm below left costal margin (LCM). Additional laboratory data showed total/direct bilirubin 21.5/13.8 mg/dL, AST 46 U/L, ALT 19 U/L, ALP 146 U/L, GGT 29 U/L, albumin 3.1 g/dL and globulin 2 g/dL. Abdominal ultrasound demonstrated hepatosplenomegaly with bile sludge in gall bladder. A provisional diagnosis was BO incompatibility or red blood cell membrane defect which resulted in cholestasis and probable mechanism was an inspissated bile plug related to severe hemolysis. Therefore, he received treatments including phototherapy, red blood cell and platelet transfusion, antibiotics and administration of ursodeoxycholic acid which improved overall clinical status and he was discharged home at 14 days of age. Despite receiving treatment at out patient clinic with ursodeoxycholic acid and vitamin supplements, he remained having marked jaundice from cholestasis and worsening of liver function tests.

At 50 days of age, he was re-admitted to the hospital due to severe cholestasis. Physical examination showed marked jaundice, progressive enlargement of liver measured 7 cm below RCM and progressive enlargement of spleen measured 7 cm below LCM, and normal ophthalmic exam. Further investigations revealed total/direct bilirubin 32/25 mg/dL, AST 382 U/L, ALT 154 U/L, GGT 38 U/L, albumin 3.5 g/dL, globulin 1.1 g/dL, ammonia 63 μmol/L, ferritin 11,893 ng/mL, transferrin 150 mg/dL, serum alpha-fetoprotein 73,733 ng/mL, normal plasma amino acids and negative urine succinylacetone. At this point, neonatal hemochromatosis was considered as a developing diagnosis. A MRI of abdomen showed decreased T2 signal intensity of hepatic parenchyma suggesting an evidence of iron deposit in the liver, but this finding was not found in the heart or pancreas. Therefore, exchange transfusion was initiated in order to remove possible maternal alloantibodies along with administering vitamin E (25 IU/kg/day), deferoxamine (30 mg/kg/day, IV), N-acetylcysteine (100 mg/kg, IV) and prostaglandin E1.

Despite the treatments above, he continued to have worsening bilirubin level and coagulopathy. Subsequently, he was listed for liver transplantation. Unfortunately, he had several episodes of severe infection including *Staphylococcus aureus, Enterobacter cloacae* and *Candida albican* septicemia. He died at 5 months of age due to severe sepsis, infectious associated hemophagocytic syndrome, and severe liver failure. The summaries of follow-up laboratory investigations have been shown in Table 1.

Postmortem examination showed enlarged liver with bile staining. The liver architecture was distorted due to parenchymal collapse, pronounced fibrous tissue, and ductular reaction (Fig1A). Some preserved hepatocytes showed giant cell and pseudoacinar transformation with cholestasis (Fig1B). Iron deposition was noted in hepatocytes (Fig 2A). Pancreas showed autolytic change and intracellular iron deposition (Fig 2B).

DISCUSSION

We report an infant with a diagnosis of NH which resisted to medical management. Initial presentations, which were found soon after birth included hyperbilrubinemia , anemia, thrombocytopenia, and positive direct Coombs' test. The preliminary diagnoses were BO incompatibility and cholestasis from the inspissated bile plug syndrome. Later in the course with progressive cholestasis and hepatosplenomegaly, the possible causes of neonatal liver failure were CMV infection, tyrosinemia, galactosemia, familial hemo-

TABLE 1. The summaries of laboratory investigations.

Day	D1*	D3**	D22	D50	D60***	D90	D120 #	D150 §
TB (mg/dL)	20	21.5	9.7	32.4	53	31.7	53.9	67.3
DB (mg/dL)	9.2	13.8	7.3	21.1	40.7	24	34	38.3
SGOT (U/L)		46	145	382	1594	830	1003	463
SGPT (U/L)		19	120	154	448	255	292	196
Alb (g/dL)		3.1	3.5	3.5	3.9	3.7	3.5	3.6
Glo (g/dL)		2	1.9	1.1	0.7	1.3	1.4	2.4
NH_3 (µmol/L)				63			104	
Hct (%)	33	35			40.3	25.3		
WBC (mm^3)	30,406	17,890			9,610	8,170		
Platelet (mm^3)	66,000	82,000			85,000	15,3000		
PT (sec)	14.5				14.2	13.7	16.6	39
PTT (sec)	41.6				37.8	41.5	45.2	106
Ferritin (ng/mL)				11,893	43,885	10,307	3,759	16,337
Triglyceride (mg/dL)				588				102

*Total blood exchange, **Post blood exchange, ***Total blood exchange, antioxidant agents and chelator, # Stop antioxidant agents and chelator, § Dead

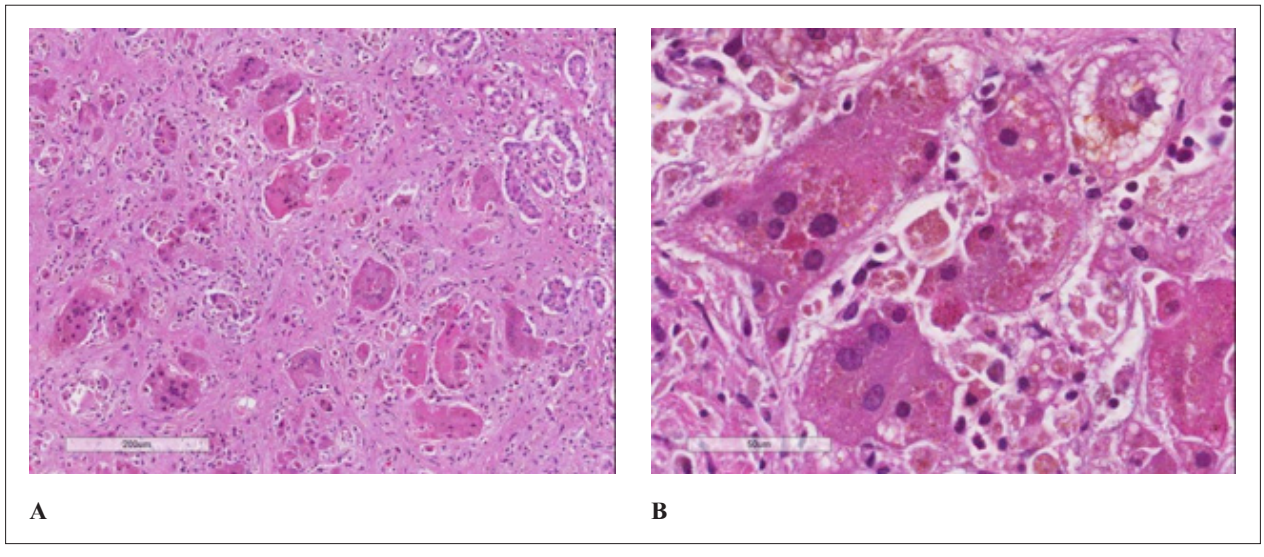

Fig 1. A. H&E stained slide showed hepatic parenchyma which was replaced by pronounced fibrous tissue, multinucleated giant hepatocytes and ductular reaction. (original magnification x 100). **B.** Intracellular coarse golden brown granules (siderosis; iron deposition) were present in multinucleated giant hepatocytes. (original magnification X 400)

phagocytic syndrome and NH. The investigations which supported diagnosis of NH, were very high level of ferritin and demonstration of iron deposition in the liver from MRI along with excluding other diseases. The absence of iron deposit in the heart and pancreas from the MRI cannot exclude NH, because MRI can demonstrate abnormal iron deposit in hepatic and extrahepatic tissues in about two-thirds of cases.[1] Despite specific treatment for NH including total blood exchange transfusion, antioxidant drug administration and chelator administration were done, this patient still developed progressive liver failure, which could be from delayed recognition of NH that resulted in delayed initiation of specific treatment. Intravenous immunoglobulin was not considered to be used at that time due to lack of suggestive data. Our managements did not work effectively,

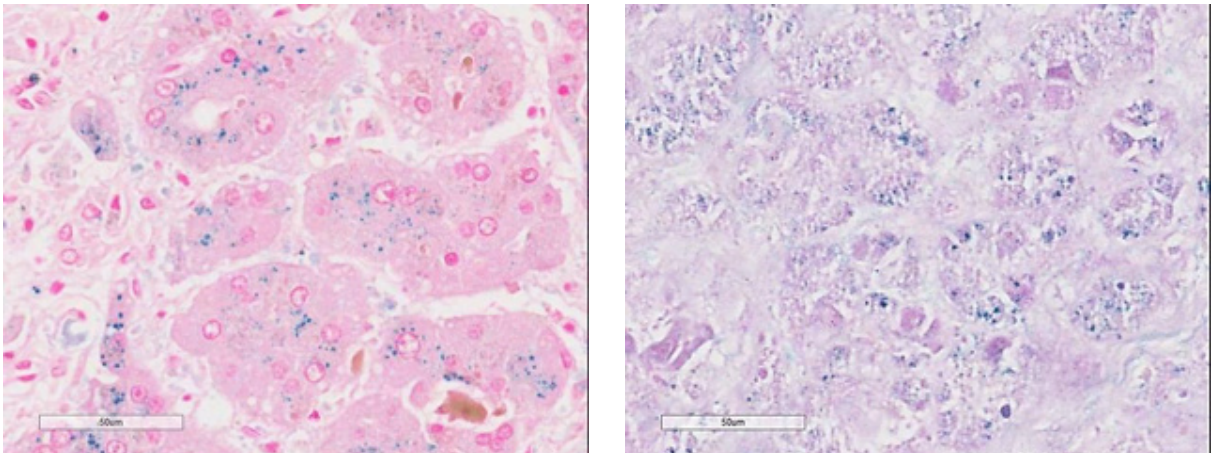

Fig 2. A. Perl's Prussian blue stain showed iron deposition in multinucleated giant hepatocytes. Cholestasis was noted. (original magnification X 400). **B.** Perl's Prussian blue stain showed iron deposition in pancreatic parenchyma. (original magnification X 400)

possibly due to delayed diagnosis. Unfortunately, he died from severe liver failure and severe infections. The autopsy demonstrated deposit of iron in liver and pancreas, which strengthened the final diagnosis of neonatal hemochromatosis.

Currently, the gestational alloimmune liver disease (GALD) is proposed to be the etiology of nearly all cases of NH.[1] GALD is also the basis of other maternal alloimmune diseases such as rhesus hydropsfetalis, ABO incompatibility hemolysis, and alloimmune thrombocytopenia in the newborn baby.[2] The principle of GALD involves exposure of a mother to a fetal hepatocyte antigen which results in sensitization and production of specific immunoglobulin of the IgG class. The maternal IgG antibody is actively transported across the placenta to the fetus from about the 12th week of gestation to activate fetal complement that leads to the formation of membrane attack complex, resulting in liver cell injury.[3] The destruction of liver cells in NH is very severe and cause cirrhosis in nearly all cases. In addition, there are deposits of iron in the liver and extrahepatic organs such as pancreas, myocardium, thyroid, and the mucosal minor salivary glands of the oronasopharynx.[4] The spleen, lymph nodes, and bone marrow contain scanty quantities of stainable iron. However, GALD can be diagnosed in the absence of hepatic and extrahepatic siderosis.[5] Siderosis of hepatic and extrahepatic organs in the fetus is the result of hepatic damage[6]. Generally, the liver controls placental iron flux by producing hepcidin as a regulatory feedback molecule. The liver injury cannot produce adequate hepcidin to appropriately regulate placental iron flux. It results in iron overload in the fetus. The main cause of liver injury is from maternal IgG antibody to hepatocytes rather than iron overload.[6] Having BO incompatibility, thrombocytopenia and liver failure in our patient supported GALD as a hypothesis. Onset of the presentation usually starts in utero. Therefore, clinical manifestations of liver disease are generally apparent within hours of birth, such as severe jaundice, hepatosplenomegaly and ascites.

The presence of high serum ferritin level and deposition of iron in liver support the diagnosis of NH, but iron deposit in hepatic tissue also can be found in bile acid synthetic defect, neonatal lupus, echovirus infection, mitochondrial disease and tyrosinemia.[7] Therefore, the diagnosis of NH needs a demonstration of iron deposition in extrahepatic organs, which could be done by oral mucosa biopsy or by MRI.[8] Both investigations are positive in about two-thirds of NH cases.

Specific medical treatment for NH should be initiated as early as possible after the diagnosis is made. Although spontaneous remission has been reported in few cases, most infants do not survive without treatment. Previously, medical treatment for NH included antioxidant agents and chelator

which yielded poor success.[9] Survival rates following this treatment have been reported to be 10 to 20%. High dose IVIG may be considered in the initial course of the disease in order to treat the pathogenesis NH resulting from GALD. If the infant does not show significant clinical improvement, then exchange transfusion should be performed and followed by a second dose of IVIG in order to remove and counteract maternal IgG antibody.[1] A patient who does not respond to this specific treatment option is indicated for liver transplantation. The risk for recurrence in subsequent offspring of an affected woman is very high though prevention of recurrent severe NH by gestational treatment using IVIG has been potent.[10]

In conclusion, neonatal hemochromatosis has proven to be the one of the maternal alloimmune diseases, which needs blood exchange transfusion and high dose of IVIG to remove and counteract maternal IgG antibody. Although this disease is rare, it should be taken into account in all cases of liver failure in the neonatal period. Early diagnosis and proper managements may help to improve the survival rate.

REFERENCES

1. Whitington PF. Gestational alloimmune liver disease and neonatal hemochromatosis. Semin Liver Dis. 2012 Nov;32 (4): 325-32.
2. Whitington PF, Malladi P.Neonatal hemochromatosis: is it an alloimmune disease? J Pediatr Gastroenterol Nutr. 2005 May;40(5):544-9.
3. Pan X, Kelly S, Melin-Aldana H, Malladi P, Whitington PF. Novel mechanism of fetal hepatocyte injury in con genital alloimmune hepatitis involves the terminal complement cascade. Hepatology. 2010 Jun;51(6):2061-8.
4. Knisely AS, O'Shea PA, Stocks JF, Dimmick JE. Oropharyngeal and upper respiratory tract mucosal-gland siderosis in neonatal hemochromatosis: an approach to biopsy diagnosis. J Pediatr 1988 Nov;113(5): 871-4.
5. Whitington PF, Pan X, Kelly S, Melin-Aldana H, Malladi P. Gestational alloimmune liver disease in cases of fetal death. J Pediatr. 2011 Oct;159(4):612-6.
6. Bonilla S, Prozialeck JD, Malladi P, Pan X, Yu S, Melin-Aldana H, et al. Neonatal iron overload and tissue siderosis due to gestational alloimmune liver disease. J Hepatol. 2012 Jun;56(6):1351-5.
7. Knisely AS. Iron and pediatric liver disease. Semin Liver Dis. 1994 Aug;14(3):229-35.
8. Hayes AM, Jaramillo D, Levy HL, Knisely AS. Neonatal hemochromatosis: diagnosis with MR imaging. Am J Roentgenol. 1992 Sep;159(3): 623-5.
9. Flynn DM, Mohan N, McKiernan P,Beath S, Buckels J, Mayer D, et al. Progress in treatment and outcome for children with neonatal haemochromatosis. Arch Dis Child Fetal Neonatal Ed. 2003 Mar;88(2): F124-7.
10. Whitington PF, Kelly S. Outcome of pregnancies at risk for neonatal hemochromatosis is improved by treatment with high-dose intravenous immunoglobulin. Pediatrics. 2008 Jun;121(6): e1615-21.