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Neonatal Hemochromatosis
— Report of An Autopsy Case —

Yeon-Lim Suh, M.D., Shin Kwang Khang, M.D. and Kwang Nam Kim*, M.D .

Departments of Pathology, College of Medicine, Inje University Seoul Paik Hospital
Department of Pediatrics, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea*

A case of neonatal hemochromatosis in a 3 - hour - old male is described. He presented with hypotonia, mild jaundice, and respiratory difficulty immediately after birth. He had no evidence of congenital infection, immune-related hemolysis or exogenous iron uptake. Postmortem examination revealed abnormal facial features. The organs were of normal weight for his age except a small liver and lungs, and a large spleen. The most prominent changes were in the liver and pancreas. The liver was coarsely nodular and fibrotic. The lobular architecture was totally distorted by innumerable multinucleated giant cells, loss or collapse of the hepatocytes, and diffuse fibrosis. A large amount of hemosiderin was seen in the liver, pancreatic acini and thyroid follicular cells. Scanty amount of hemosiderin was also found in the myocardial fibers and renal tubular cells. The pancreas showed hyperplasia and hypertrophy of the islets. The spleen showed severe congestion and a moderate extramedullary hemopoiesis but no deposits of hemosiderin. This patient had three siblings died in neonatal period, one of which had clinical features of neonatal hemochromatosis.

Key Words : *Newborn, Hemochromatosis, Iron, Family History, Liver*

INTRODUCTION

Neonatal hemochromatosis (NH) is a specific entity in the spectrum of pediatric liver diseases and is characterized clinically by intrauterine growth retardation, preterm birth, hepatic failure in a few hours of postnatal age, rapid progression to death within a few days to weeks , recurrence in siblings, and the absence of an identifiable agent of hepatic injury (Silver et al.,1987 ; Laurendeau et al., 1961; Ehrlich et al., 1955). Pathologically, NH is characterized by hepatic fibrosis with varying degrees of hepatocellular lo-ss and by abundant stainable iron in the liver and many epithelia, with a remarkable sparing of the spleen, lymph-node, and bone marrow (Blisard and Bartow, 1986; Feinberg, 1960). This pattern of iron deposition is abnormal in infancy and is typical of hereditary hemochromosis(HH) manifested in adulthood. Recently we experienced a case of neonatal hemochromatosis in a male infant who had marked hypotonia and respiratory difficulty since birth. To our knowledge, no such case has been reported in the Korean literature.

Address correspondence to : *Dr.Yeon-Lim Suh, Department of Pathology, Inje University Seoul Paik Hospital, 85, 2-ka, Jur-Dong, Chung-Ku, Seoul, 100-032, Korea, (Tel : 02-278-1321 Ext.3203)*

CASE REPORT

The patient was born at full-term after an uneventful pregnancy. The birth weight was 3,000㎎ and Apgar scores after 1 and 5 minutes were 7 to 9, respectively. He had facial anomaly and a mild jaundice. He suffered from severe hypotonia and respiratory diffi-

culty since birth and died 3 hours later. On physical examination his breathing sounds decreased. The heart and abdomen were unremarkable. No enlargement of the liver or spleen was identified. Neurologic examination revealed that Moro reflex was absent.

The leukocyte count was 27,200 /mm3, hemoglobin 9.3 gm/dl, and hematocrit 28 %.

The platelete count was 74,000 /mm3. Laboratory studies documented hypoglycemia(30 mg / dl), hyperphosphatenemia(10 mg/dl), hypocholesterolemia(15 mg/dl), hypoalbuminemia(1.4 gm/dl), elevation of serum alkaline phosphatase(403 U/l) and aspartate aminotransferase(251 U/l), and hyperbilirubinemia (total bilirubin, 1.8 mg/dl; conjugated, 1.2 mg/dl). There was no serologic evidence for maternal-fetal blood group incompatibility.

Both parents were well and the mother was 38 years old. Her parity was 2-1-0-0. The first baby was a premature female with a birth weight of 1,500 gm, who died at 2 days of age. The second baby was a full-term female without perinatal problems, weighing 2,700gm. She presented with jaundice and melena at 5 days of life and jaundice progressed up to 39.3㎎/dl of total bilirubin.

Ascites, splenomegaly and a caput medusae developed and hypocoagulability could not be corrected. Laboratory studies revealed hypoproteinemia, hypocoagulability, hyperbilirubinemia, anemia, and elevated serum alkaline phosphatase and aspartate amino-transferase. Urine showed albumin, bilirubin, and urobilinogen. Serologic tests for TORCH and direct and indirect Coombs' tests were negative. She developed Acinetobacter septicemia and died on 42 postnatal days. The clinial diagnosis was liver cirrhosis of unknown etiology. The third baby died at 10 days of age.

PATHOLOGIC FINDINGS

At autopsy, the patient's body weight and height were appropriate for gestational age. There were generalized petechiae on the body, and abnormal facial features included oblique palpebral fissure, a small beaked nose, and large malformed ears. He had a high arched palate. Internal examination revealed hypoplasia of lungs (22.5gm combined), atrophy of the thymus, a small liver, and a large spleen(55 gm/9.7gm). The liver showed an uniform reduction in size, weighing 61 gm (normal, 140 gm). The capsule was scalloped with coarse nodules. When sectioned, the liver gave a gritty fibrous resistance and showed dark reddish-brown nodules of 0.2 to 0.4 ㎝ in diameter. The right lobe was less nodular than the left. The nodules were widely separated by whitish fibrotic tissue(Fig. 1). Microsopically, the liver showed almost total distortion of the lobular architecture by innumerable multinuclear giant cells, loss of the hepatocytes, and a diffuse increase in fibrous tissue. The giant cells occupied most of the hepatocytic lobules and were extremely irregular in size, shape, and distribution. The giant cells contained 50 or more uniform round nuclei that were arranged in irregular clusters, but often in the shape of floret or Touton-type giant cells. The cytoplasm of the giant cells was deeply pigmented with coarse brown granules and showed a vacuolated or foamy appearance. Active necrosis of the giant cells was noted(Fig 2). In some areas giant cells were scattered in a loose fibrous tissue, whereas in other areas they were surrounded by dense fibrous tissue. Remaining liver parenchyma consisted of tubular liver cells (neocholangioles)(Fig.3). These histological abnormalities of the liver were much more prominent in the left lobe than in the right, where some nodules consisted of a relatively well preserved hepatic lobules and the giant cells were small or medium in size. The right lobe represented residual hepatic parenchyma, not yet transformed into bizzare pattern noted in the left lobe. Intracellular cholestasis was marked in giant cell cytoplasm, and bile plugs filled neocholangioles. Bile ductules showed hyperplasia, but small and large bile ducts appeared normal. There was diffuse extramedullary hemopoiesis of moderate degree in the sinusoids and portal tracts. Prussian blue stain showed a large amount of hemosiderin in the giant cells, and less in degree in bile duct epithelium, Kupffer cells, macrophages, and small liver cells(Fig.

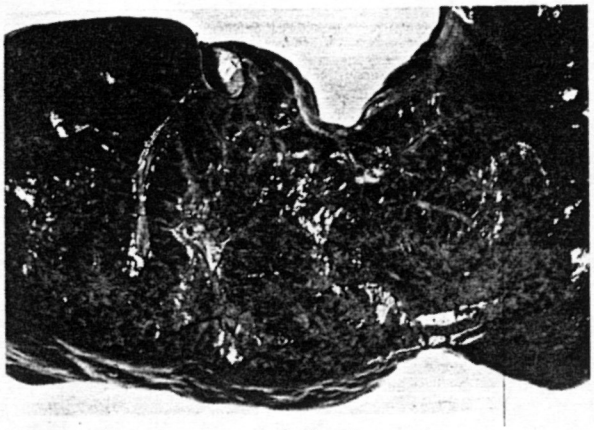

Fig. 1. Cut surface of the liver shows coarse nodules ranging in size from 0.2 to 0.4 cm. These nodules are separated by whitish fibrotic tissue.

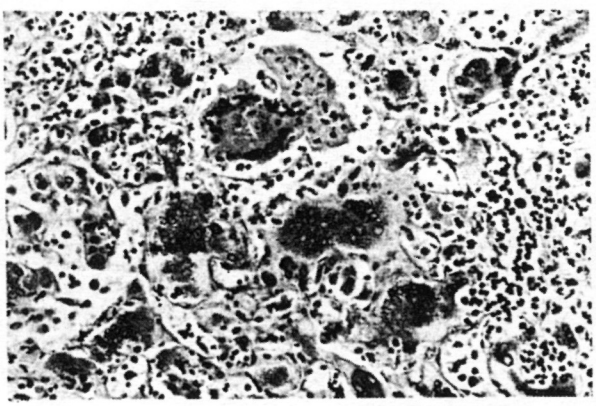

Fig. 2. Multinucleated giant liver cells contain corse brown pigments and some of giants cells undergo necrosis (H&E,x200).

4). Massive iron deposits were also found in the acinar cells of the pancreas and follicular cells of the thyroid(Fig. 5,6). The islets of Langerhans were hypertrophied and hyperplastic. These histologic features of the pancreas were also noted in the heterotopic pancreas in the stomach. A small amount of hemosiderin was encountered in many myocardial fibers and renal tubular epithelial cells. The spleen showed severe congestion and a moderate extramedullary hemopoiesis but no hemosiderin deposits. The heart showed multifocal ischemic necrosis of papillary muscles with fibrosis and dystrophic calcification.

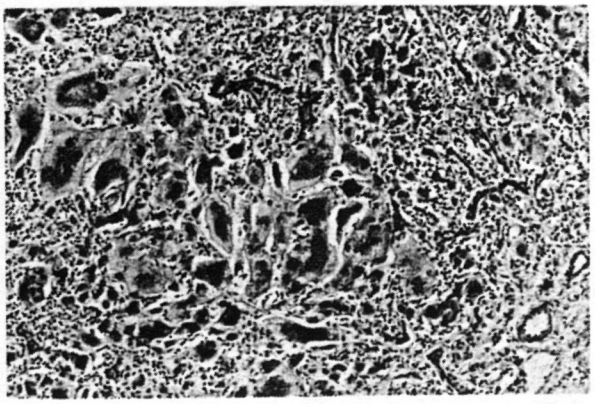

Fig. 3. Many of the liver cell columns have disappeared, and remaining cells frequently transformed into the tubules,the so-called neocholangioles(H&E,x100).

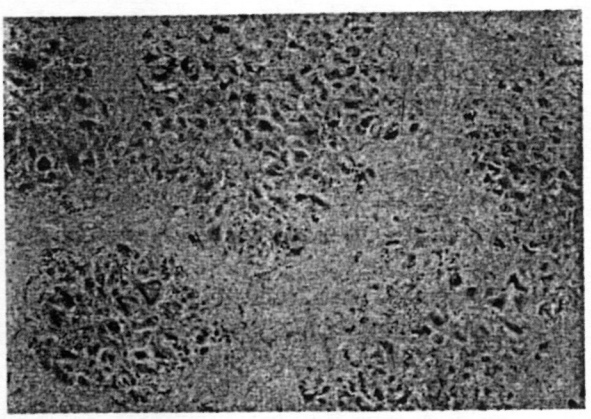

Fig. 4. Liver shows severe distortion of lobular architecture, multinucleated giant cells, and fibrosis. Allmost all of the hemosiderin is confined to the giant cells, with scanty deposits in the Kupffer cells, histiocytes, and bile duct epithelium. (Prussian blue, x10).

DISCUSSION

Hemochromatosis has been defined as an abnormal increase in the amount of parenchymal iron, stored as hemosiderin, associated with tissue injury and dysfunction. This disorder is distinguished from hemosiderosis, in which tissue iron is increased without tissue damage(Garace and Powell, 1974). Neonatal hemochromatosis is characterized by severe hepatic insufficiency of intrauterine onset and by marked organ iron overloading.

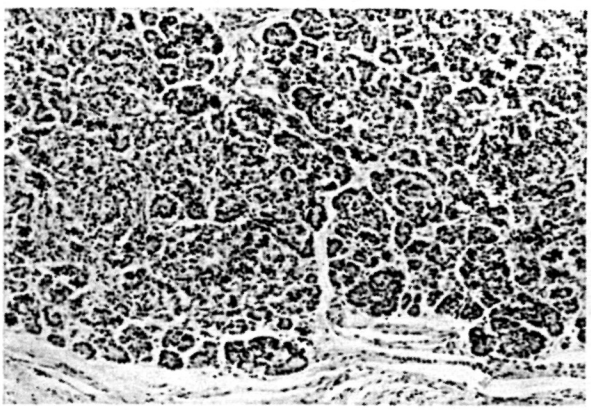

Fig. 5. The pancreas shows hyperplasia and hypertrophy of the Langerhans islets. There is a large amount of hemosiderin in the acini (H&E, x40).

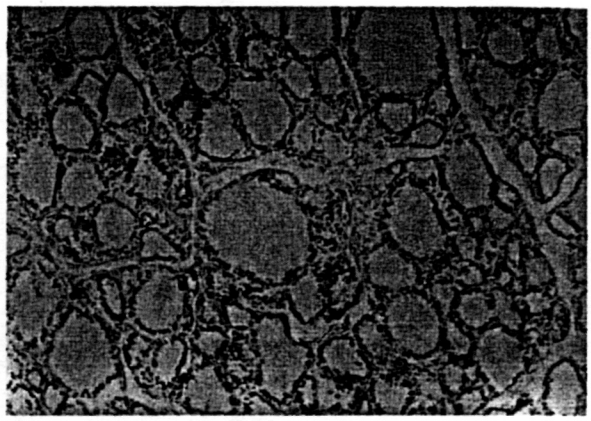

Fig. 6. The thyroid follicular cells are heavily stained with iron pigments (Prussian blue, x100).

Over thirty cases of NH have been reported in the literature and most cases of them have been diagnosed only by autopsy findings; Two children, siblings of autopsydiagnosed cases, appear to have survived episodes of hepatic failure at birth (Jacknow et al., 1983; Glista et al., 1986). A case in a stillborn and a case in the oldest survivor who lived 4 months are recorded (Dible et al., 1954; Goldfischer et al., 1981).

Fienberg(1966) proposes diagnostic criteria for NH. These criteria include the presence of giant liver cell, accompanied by massive deposits of iron in the giant cells and mononuclear liver cells, and iron deposits in the pancreatic acinar cells and infrequently in the islets of Langerhans, and absence or scanty amount of iron in the spleen. Other features are the occurrence in consecutive siblings, the lack of serologic evidence for an isoimmunization phenomenon, the lack of viral isolation, minimal amout of extramedullary hemopoiesis and bile stasis, and patency of the common and hepatic ducts. The patient reported here meet these criteria for NH. This disorder is termed " idiopathic perinatal" or neonatal hemochromatosis " and" neonatal iron storage disease" (Fienberg, 1960; Laurendeau et al, 1961; Blisard and Bartow,1986; Knisely et al., 1987). Silver et al.(1987) propose the term "perinatal hemochromatosis " because the disease clearly begins in utero. The pattern of parenchymal iron deposits characterizes both NH and HH. The A3 alloantigen which is the antigen most closely associated with HH has been detected in several infants with NH (Silver et al., 1987; Knisely et al., 1989). Hypersideremia or HH also have been detected in the parents of some infants with NH, suggesting that NH might represent an unusual form of HH (Knisely et al., 1987 : Laurendeau et al., 1961; Glista et al., 1986). But Hardy(1990) observed no evidence for linkage of NH to HLA serotypes, suggesting that NH and HH are genetically not related. The relationship between two diseases is still unclear.

The hepatic lesion of the present case is mostlikely of intrauterine origin, having resulted from excessive iron deposits. Reduction of the liver weight might be resulted from massive necrosis of the hepatic parenchyma, especially the giant cells containing hemosiderin pigments. The pattern of hepatic fibrosis suggested postnecrotic scarring. The diffuse neocholangioles were in keeping with regeneration after this destructive event. This patient seems to have had a hypoxic insult in perinatal period, accounting for papillary muscle necrosis of the heart. The direct cause of death was respiratory failure due to pulmonary hypoplasia and hepatic insufficiency. Abnormal facial features and associated congenital anomalies were described in few cases of NH. The abnormal facies and odd facial expression were observed only in two infants with familial and

congenital iron overload (Vitale et al.,1969). Associated congenital anomalies, such as polycystic kidney, megalencephaly, and esophageal atresia, and tracheoesophageal fistula were noted (Silver et al., 1987 and Vitale et al., 1967). These anomalies seem to occur as an isolated lesion. The pathologic findings of documented cases showed a constant pattern of advanced siderotic cirrhosis, with diffuse fibrosis, neocholangiolar proliferation, and cholestasis, as well as widespread extrahepatic parenchymal iron deposits. Variable features included hepatic giant cell formation and bile ductular proliferation. The extrahepatic sites of iron accumulation were variable in cases and included parenchymal cells of the endocrine organs (adrenal, thyroid, parathyroid, pancreas, pituitary), thymic epithelia, myocardium, renal tubules, oropharyngeal and upper respiratory tract mucous glands, superficial gastro-duodenal-jejunal mucosa, and gastric crypts (Knisely et al., 1988). These variations of site are likely to be related to age and the accelerated time-course of disease in utero. End-stage cirrosis is rare in NH.

Recently, an abnormal increase of parenchymal iron in neonates dying of various diseases was shown in an autopsy survey by Blisard(1986). The diseases included necrotizing enterocolitis, neonatal infection, hydrops fetalis, congenital heart disease, extrahepatic biliary obstruction, primary liver disease, multiple congenital anomalies, and Reye's syndrome. Therefore, our case should be differentiated from the iron accumulation caused by the above diseases. However, in those diseases the hepatic iron was not significantly increased, and various degrees of iron deposits were also found in the spleen and pulmonary macrophages. The distinguishing feature of NH seems to be the pattern of iron deposits, with the liver and pancreas containing this pigment and little or none in the reticuloendothelial cells. The differential diagnosis from tyrosinemia and Zellweger's syndrome that have cirrhosis and increased tissue iron should also be included. The lack of excessive iron accumulation in the former and presence of neuronal migration defect and polycystic kidney in the latter are helpful. Hepatic fibrosis or cirrhosis is also common in transfusion-related hemochromatosis which has been well described in children with thalassemia who have been regularly transfused(Risdon et al., 1975). In the later stages of transfusion-related hemochromatosis both the epithelial and reticuloendothelial cells contain iron, but the spleen in NH continues to be practically free of iron.

This case is of interest in that all the siblings died in a neonatal period. The cause of death in the first and third siblings was not known but the clinical history of the second sibling was available. She died of hepatic failure. Although the pathologic examination of the liver had not been performed, the above clinical history is similar to that of two siblings described by Knisely et al. (1989). It is possible that she had the same lesion of the liver as this case. This occurrence of NH in the patient's sibling indicates that NH is probably a genetically determined. The etiology of NH is still unknown. Many theories have been suggested and included a recessive genetic defect of iron metabolism, a primary abnormality in fetoplacental cytoferrin metabolism, and a common result of fetal liver disease of various etiology, some of which are not heritable(Laurendeau et al., 1961; Greco et al., 1973; Knisely et al.,1989; Hardy et al.,1990). NH has seldom been diagnosed before death and pertinent clinical parameter, such as serum iron, transferrin, and ferritin levels, and HLA types are not available, although hypertransferrinemia, hyperferrinemina, hypersideremia has been identified in reported cases(Knisely et al.,1989; Silver et al.,1987; Glista et al.,1986). Therefore, NH should be suspected in any infants with severe neonatal liver disease. Only when this disease is more commonly recognized and studied, will information about the pathogenesis and treatment become available.

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